CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213051Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	213051
Priority or Standard	Priority
Submit Date(s)	March 20, 2019
Received Date(s)	March 20, 2019
PDUFA Goal Date	September 20, 2019
Division/Office	DMEP
Reviewer Name(s)	Andreea Ondina Lungu
Review Completion Date	September 18, 2019
Established/Proper Name	Semaglutide
(Proposed) Trade Name	Rybelsus
Applicant	Novo Nordisk
Dosage Form(s)	oral
Applicant Proposed Dosing Regimen(s)	7 mg, 14 mg, orally, once daily
Applicant Proposed Indication(s)/Population(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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Glossary

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
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
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
CRT	clinical review template
CSR	clinical study report
CV	cardiovascular
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DPP-4	Dipeptidyl peptidase-4
DUN	dispensing unit number
EAC	Event Adjudication Committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ER	extended release
FAS	full analysis set

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FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FPG	fasting plasma glucose
GCP	good clinical practice
GLP-1	glucagon-like peptide 1
GLP-1 RA	GLP-1 receptor agonist
GRMP	good review management practice
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HLT	Medical Dictionary for Regulatory Activities High Level Term
ICH	International Council for Harmonization
IGlar	insulin glargine
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
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
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effects model repeated measures
NA	not applicable
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NN	Novo Nordisk
NNMQ	Novo Nordisk MedDRA Query
OAD	oral antidiabetic drug
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OW	once weekly
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment

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PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Medical Dictionary for Regulatory Activities Preferred Term
RA	receptor agonist
REMS	risk evaluation and mitigation strategy
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
Sita	sitagliptin
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	Medical Dictionary for Regulatory Activities System Organ Class
SU	sulfonylurea
T1/2	terminal half-life
TEAE	treatment emergent adverse event
T2DM	type 2 diabetes mellitus
TG	triglycerides
TZD	thiazolidinedione
VAI	voluntary action indicated

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1. Executive Summary

1.1. Product Introduction

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) studied for daily oral administration in patients with type 2 diabetes mellitus (T2DM). Semaglutide is already approved for treatment of T2DM as a once weekly subcutaneous injection under the brand name OZEMPIC. The applicant proposes two therapeutic doses of oral semaglutide for commercialization: 7 mg daily, and 14 mg daily. To minimize gastrointestinal adverse events, a fixed dose escalation regimen was employed in the clinical trials and is proposed for marketing in a similar manner. All patients started treatment with oral semaglutide with a dose of 3 mg daily for 4 weeks. The dose was then increased to 7 mg daily. After an additional 4 weeks, the dose was increased to 14 mg daily for patients randomized to receive 14 mg of semaglutide.

The proposed trade name for oral semaglutide is Rybelsus.

The applicant proposes the following indication for the oral semaglutide:

> *Rybelsus is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus*

1.2. Conclusions on the Substantial Evidence of Effectiveness

The semaglutide phase 3 development program is comprised of 7 multi-national efficacy trials (PIONEER 1-5, and 7, 8) 2 efficacy trials conducted solely in Japan (PIONEER 9 and 10), and one safety trial (a pre-market cardiovascular outcomes trial to rule out excessive cardiovascular [CV] risk) – PIONEER 6.

The clinical trials conducted to support efficacy were conducted on a variety of background therapies. These included use of semaglutide as monotherapy, in combination with metformin (with or without other oral antidiabetic drugs [OADs]), in combination with OADs including sodium-glucose co-transporter 2 (SGLT2) inhibitors, and in combination with insulin. One of the trials evaluated oral semaglutide in patients with renal impairment vs placebo, and one trial evaluated flexible dose of oral semaglutide based on need and tolerability vs sitagliptin. In all the trials, patients treated with semaglutide demonstrated improved glycemic control as shown by a reduction in HbA1c from baseline (comparator-adjusted range: -0.3% to -1.2%). The reduction was generally observed in the first 14 weeks of treatment, and then sustained for the remainder of the study – up to 78 weeks. Three of the multi-national efficacy trials evaluated more than one dose of semaglutide (PIONEER 1, as monotherapy vs placebo, PIONEER 3 vs sitagliptin on a background of metformin/metformin and sulfonylurea (SU), and PIONEER 8 vs

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placebo on a background of insulin. All other multinational trials, including the cardiovascular outcomes trial, only studied the 14 mg daily dose of semaglutide.

In summary, semaglutide, at both 7 and 14 mg dose, is efficacious as a glycemic lowering agent in patients with T2DM.

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1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Diabetes mellitus is a serious disease that affects 22 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. There are currently 12 classes of diabetes medications approved for the treatment of type 2 diabetes mellitus including GLP-1 receptor agonists.

Semaglutide would be the 7th product in the GLP-1 receptor agonist class and would be the 1st oral GLP-1 receptor agonist.

The semaglutide phase 3 development program is comprised of 7 multi-national efficacy trials, one cardiovascular outcomes trial (CVOT) of short duration (safety outcomes trial to rule out excessive CV risk pre-marketing, rather than an efficacy trial), and 2 Japanese safety trials. The development program appears generally adequate to evaluate the efficacy of semaglutide in patients with T2DM as monotherapy and on different antidiabetic background medications (including commonly used therapies, such as metformin, sulfonylureas (SU), and insulin).

In all the efficacy trials, as well as the Japanese trials, semaglutide showed a dose-dependent reduction on HbA1c, sustained over the duration of the trials. This reduction was statistically superior to placebo as monotherapy and on a background of insulin, as well as in patients with renal impairment. Semaglutide was also statistically superior to sitagliptin, both on a background of OADs including metformin, and as a flexible dose. Additionally, semaglutide was statistically superior to empagliflozin, but not to liraglutide. Overall, the clinical program provides evidence that semaglutide is efficacious in improving glycemic control in patients with T2DM.

Overall, the semaglutide safety profile was generally consistent with the known safety profile for GLP-1 RAs, with gastrointestinal adverse events being the most common adverse events. Findings from the development program, particularly the findings from the CVOT, support concluding that there is no increased risk for adverse cardiovascular outcomes with semaglutide. The addition of SNAC as absorption enhancer raised potential concerns of inhibition of mitochondrial transport chain, and clinical events of lactic acidosis were evaluated during the development program. However, there was no imbalance in lactic acidosis events, and no safety concerns new to the drug class have been identified during the review of the oral semaglutide NDA.

The clinical benefits of semaglutide outweigh the risks. The safety profile is similar to other approved GLP-1 Ras.

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I recommend approval of semaglutide for improving glycemic control in patients with T2DM.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2014, the Center for Disease Control estimated that 22 million people in the United States have diabetes. • Diabetes is associated with multiple complications including macrovascular and microvascular complications which may shorten and affect the quality of life of patients. • Studies have shown that improving glycemic control in patients with diabetes improved clinical outcomes (e.g., reduction in retinopathy). • Many diabetic patients also have additional risk factors such as smoking, obesity, hypertension and hyperlipidemia which contribute to their overall health burden.	• Diabetes is a serious condition associated with chronic morbidity and premature death. • Glycemic control of diabetes improves microvascular complications.
Current Treatment Options	• Twelve classes of drugs, including GLP1-RAs, are FDA approved in the United States to improve glycemic control in patients type 2 diabetes.	• There are multiple effective treatment options available for the treatment of type 2 diabetes, including other members of the GLP-1RA class administered via injection.
Benefit	• Semaglutide reduced HbA1c in a dose-dependent manner in all phase 3 trials, across a variety of backgrounds. • Patients on semaglutide were more likely to achieve glycemic targets. • Semaglutide led to sustained weight loss in patients with T2DM.	• The efficacy pertaining to glycemic benefit was seen across all phase 3 trials. • The doses of oral semaglutide proposed for marketing, 7, and 14 mg, improved glycemic control as measured by change from baseline in HbA1c and proportion achieving a HbA1c target. • Additional findings which may be desirable for patients include reduction in weight. • This would be the first oral member of the drug class, with potential for increased

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		patient compliance.
Risk and Risk Management	• The safety database reflects the expected use in the patient population. • Semaglutide safety is overall consistent with the GLP1RA drug class. Gastrointestinal adverse events were more common with semaglutide. Semaglutide by itself does not appear to increase the risk for hypoglycemia, but it is expected to lead to an increased risk for hypoglycemia when used in combination with sulfonylurea or insulin. Increases in serum amylase and lipase were seen but an increase in confirmed pancreatitis events was not seen. Increases in heart rate were seen, but an increase in arrhythmia events was not seen. • Though skin, prostate, lung, colorectal, and thyroid cancers were more common with semaglutide vs comparator in the phase 3a pool but not in the cardiovascular outcomes trial, it is not possible to draw meaningful conclusions due to the small number of events and presence of confounders. • There was no liver signal identified in the semaglutide development program. • Events of lactic acidosis were evaluated as a result of the SNAC component of oral semaglutide but no imbalance not favoring semaglutide was seen. • In the premarket cardiovascular outcomes trial, semaglutide was not associated with increased cardiovascular risk.	• The safety profile of semaglutide is generally consistent with other GLP-1 RAs. • Most of the potential risks associated with oral semaglutide can be adequately managed through labeling. • Since semaglutide and SNAC can potentially be expressed in human milk, a lactation study will be needed to evaluate the potential risk associated with SNAC in this specific situation.

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1.4. Patient Experience Data

Not applicable. Validated patient experience data (e.g., experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition) were not reviewed as part of this review.

2. Therapeutic Context

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)

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- 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. The GLP-1RAs are only available in injectable form. Additionally, progressive β-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

3.1. U.S. Regulatory Actions and Marketing History

Semaglutide is already marketed in the US as weekly subcutaneous injection under the trade name OZEMPIC. Although there are already 7 drugs approved in the GLP-1 RA class of anti-hyperglycemics, they are all in subcutaneous injection form, and oral semaglutide would be the first oral GLP-1 RA drug product.

3.2. Summary of Presubmission/Submission Regulatory Activity

The IND for oral semaglutide was submitted on September 26, 2013. Selected presubmission regulatory activities are summarized below.

June 11, 2015	End of Phase 2 Meeting: Discussion of the phase 3 program as it pertains to the glycemic lowering indication. The FDA

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	expressed concern regarding limited placebo-controlled data [redacted] (b) (4) and that the sponsor includes a placebo arm in the renal impairment trial for better characterization of the effect size in this population. For the renal impairment study, the FDA recommended stratification by eGFR category. The sponsor also proposed a pre-approval CVOT to acquire a minimum of 122 MACE events to rule out 80% excess risk. [redacted] (b) (4) The FDA also asked the Applicant to be specific when defining the background medications in order to better characterize the benefit-risk profile of oral semaglutide in common use settings. In addition to the common background medications used in diabetes trials, because of the specific adverse event profile with SNAC/semaglutide (nausea, vomiting, potential for dehydration), the FDA recommended that the applicant study semaglutide on a background of an SGLT2 inhibitor to further evaluate the potential risk for dehydration and renal impairment. The primary estimand and handling of missing data were also discussed. For safety, because of a few events of CPK elevation, it was agreed upon that CPK will be collected in all studies, and abnormal values will be confirmed with a second measurement. The applicant agreed with the FDA recommendation to adjudicate acidosis and renal impairment. Also, due to the SNAC component of the drug product, the applicant agreed to collect lactate levels in studies, particularly on a background of metformin.
April 11, 2018	Type C Meeting – Discussion of CV assessment strategy
April 23, 2018	Advice/Information request on CV bridging strategy for semaglutide injection and tablets
December 28, 2019	Type B meeting, pre-NDA meeting for oral semaglutide for the T2DM indication. The division and the applicant were in agreement with the way the NDA data was to be submitted, data pooling strategy, immunogenicity assessments.

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3.3. Foreign Regulatory Actions and Marketing History

Semaglutide oral tablet is not currently approved for use in any foreign country.

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

4.1. Office of Scientific Investigations (OSI)

The inspection for this new drug application (NDA) consisted of five domestic and five foreign clinical sites covering three studies (PIONEER 1, 3 and 6). The OSI reviewer concluded that, in general, based on the inspections of the ten clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

Please see OSI review by Dr Cynthia Kleppinger for details regarding the inspections performed and results.

4.2. Product Quality

Semaglutide is a long acting analogue of the endogenous GLP-1 molecule, with 94% structural homology to native GLP-1 with three main modifications:

- Amino acid substitution at position 8 (alanine to alfa-amino isobutyric acid (Aib), a synthetic amino acid). This is expected to make semaglutide less susceptible to DPP-4 degradation.
- Lysine to Arginine at position 34
- Acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain linked to the lysine at position 26. The fatty di-acid chain and the spacer are expected to mediate strong non-covalent binding to albumin, thereby reducing renal clearance and extending half-life of the product.

<u>Drug substance</u>

The chemical name is $N^{\varepsilon 26}$ [(S)-(22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl)] [Aib^{8}, Arg^{34}]GLP-1-(7-37) peptide.

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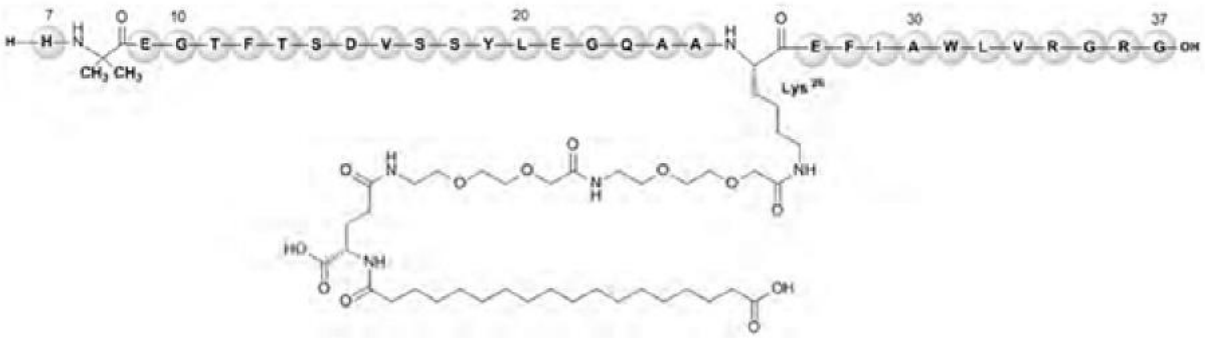
Figure 1 Chemical Structure of Semaglutide



Source: Figure 1 Introduction document

Drug product

Semaglutide is presented as white to yellow oval shaped tablets and available in three doses, 3,7 and 14 mg tablets. Semaglutide is formulated with 300 mg Salcaprozate Sodium (SNAC) as absorption enhancer to facilitate oral absorption of the drug. SNAC is considered a novel excipient and toxicity studies were conducted to assess its safety.

Excipient related information including manufacturing and control information for salcaprazoate was reviewed by drug product reviewer. The review concluded that the manufacturing and control information for SNAC and other excipients are adequate.

Please see Integrated Quality Assessment details regarding the manufacturing of semaglutide.

Immunogenicity

The sponsor also conducted studies to assess the immunogenicity of oral semaglutide. The screening and confirmatory assays used in monitoring the ADA response were validated and found suitable for their intended purpose, however the assay used to assess neutralizing activity was found to lack sensitivity. Please see Immunogenicity review by Dr Mohanraj Manangeeswaran for details.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Non-clinical documentation pertaining to semaglutide was submitted and reviewed as part of the subcutaneous semaglutide NDA 209637 which is FDA approved as Ozempic, and this is considered the basis of the nonclinical qualification of semaglutide.

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SNAC is considered a novel excipient, and a non-clinical program to qualify SNAC had to be conducted for this application.

Per the Pharmacology and Toxicology review, SNAC absorption was evaluated after oral administration in mice, rats, and monkeys. In all test species examined, SNAC was rapidly absorbed, typically reached Cmax in under 2 hours and had a half-life that ranged between 1-3 hours. Although systemic exposure was highly variable, AUC and Cmax values generally increased with increasing dose and female rodents tended to have a higher systemic exposure when compared to male rodents. In dogs and monkeys, the relative oral bioavailability of semaglutide in the presence of SNAC was estimated to range from 0.04 – 4.04%. SNAC absorption was influenced by the fasting state of the animal. Fasted Sprague Dawley rats given a single oral dose of ^{14}C-SNAC had AUC(0-6h) values 1.4 to 3-fold greater than unfasted rats.

Absorption of semaglutide after co-formulation with SNAC has been investigated both in vitro and in vivo (rats, dogs and monkeys). Similar to SNAC absorption, SNAC-facilitated absorption of semaglutide showed very high inter-animal variability in rats, dogs, and monkeys and was influenced by the fasting state of the animal.

SNAC distribution was evaluated in mice and rats, including pregnant female rats. SNAC and its five major metabolites distributed to highly perfused tissues within 1.5 hours in rats. SNAC-related radioactivity present in tissues was considerably higher in females when compared to males up to 12 hours after dosing. Very little distribution of either SNAC or metabolytes was seen in the brain. When pregnant rats were allowed to litter and a single oral ^{14}C-SNAC dose was administered 10 day post-partum, SNAC-related radioactivity was detected in the milk of lactating females for up to 24 hours. Radiolabeled SNAC (500 mg/kg) was present at a milk/plasma ratio of 12 indicating that SNAC and/or its metabolites accumulate in the lipophilic milk of lactating rats.

SNAC had a similar in vitro metabolite profile in humans, monkeys and rats. SNAC quickly undergoes rounds of conjugation into glucuronide metabolites and β-oxidation by phase II enzymes. Glucuronidation reactions were facilitated most efficiently by UGT2B7 with additional contributions by UGT1A8 and UGT1A7 using uridine diphosphate glucuronic acid as a substrate. β-oxidized metabolites (E494 and E506) were at least 10-times less potent inhibitors of ATP biosynthesis in mitochondria and glucuronidated metabolites had minimal effect on cellular respiration indicating that metabolism could be important for detoxification of the parent compound.

SNAC was generally tolerated at doses up to and including 75-500 mg/kg/day, depending on species. As outlined in the Pharmacology and Toxicology review, *SNAC has been shown to inhibit cellular respiration in animals at high concentrations. Though SNAC exposure associated with toxicity in animals was not achieved in Phase 3 studies with semaglutide/SNAC, a risk for higher exposure to SNAC and/or its metabolites is plausible for individuals with weak*

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UGT2B7activity (an enzyme involved in SNAC metabolism) or with compromised hepatic function. Similarly, pediatric patients and breastfed infants may be at greater risk given the immaturity of UGT2B7 in this population and because it is unknown if SNAC and or its metabolites accumulate in milk.

As a result, specific labelling recommendations pertaining to the SNAC component were suggested by the Pharmacology and Toxicology review team, specifically the recommendation to not breastfeed due to the potential accumulation of SNAC in the breastmilk in humans. Please see full Pharmacology and Toxicology review by Dr Elena Braithwhite for details.

4.5. Clinical Pharmacology

The Office of Clinical Pharmacology reviewed the information in this application and found it acceptable to support approval of semaglutide in the T2DM population. All three doses proposed for titration and/or efficacy are supported by clinical pharmacology and clinical trials.

The following is a summary of clinical pharmacokinetics of oral semaglutide:

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

Source: Clinical Pharmacology Review

A total of 30 completed clinical studies conducted in healthy volunteers and T2DM patients assessed the PK and PD of oral semaglutide. The PK of SNAC was also investigated in these studies. Oral semaglutide has not been studied in pediatric patients.

Absorption of oral semaglutide was considerably lower under fed conditions compared to fasting, and exposure increased with post-fasting duration from 15 to 120 minutes. Additionally, semaglutide exposure was lower when administered with 240 mls of water vs 120

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mls of water. As a result, the recommended dosing condition for semaglutide is to be administered with 120 mls of water under fasting conditions, at least 30 minutes before the first food.

SNAC

When administered with semaglutide, SNAC is rapidly absorbed and eliminated. There is no accumulation of SNAC after multiple daily doses of oral semaglutide and the PK of SNAC appears similar after single and multiple dosing. Additionally, the PK of SNAC was comparable between healthy patients and patients with T2DM. Following 10 days of treatment with oral semaglutide (containing 300 mg SNAC) in patients with T2DM, the geometric mean AUC0-24h of SNAC was 1034 ng.hr/mL, Cmax was 1038 ng/mL and median Tmax was 0.3 hr. Five major metabolites of SNAC were identified and quantified in the plasma, accounting for approximately 95% of the AUC, suggesting that SNAC is extensively metabolized. The primary routes of elimination for SNAC are urine (82.31%) and feces (3.76%). Some variability was observed in SNAC exposure when 300 mg SNAC was administered with various doses of semaglutide, and it also appears that SNAC exposure may be lower when SNAC is co-formulated with semaglutide vs with placebo.

PopPK analysis did not identify age, body weight, gender, ethnicity and race to have any clinically relevant impact on the pharmacokinetics of oral semaglutide.

Please see Clinical Pharmacology review for details and drug-drug interactions.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The semaglutide development program included 10 phase 3 clinical trials and enrolled a total of 9543 patients and included a pre-marketing cardiovascular outcomes trial (CVOT).

Semaglutide was investigated vs placebo as monotherapy, add-on to insulin, and in renal impairment patients. Semaglutide was also investigated on a background of metformin, alone in combination with sulfonylurea (SU), SGLT2 inhibitors, and/or other OADs. Active comparator

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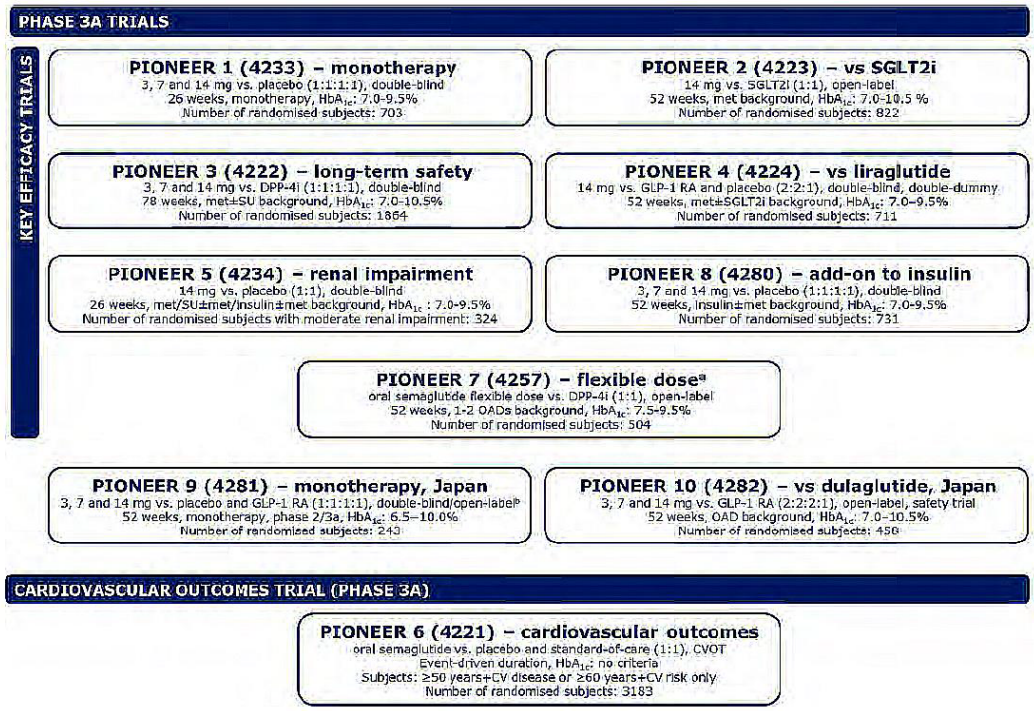
trials include trials against sitagliptin, empagliflozin, and liraglutide. Two studies were performed in Japan, one randomized against liraglutide and placebo, and one open label against dulaglutide. The phase 3 program included a trial in patients with moderate renal impairment, PIONEER 5. An event-driven pre-market cardiovascular outcomes trial (PIONEER 6) compared semaglutide vs placebo on a background ranging from monotherapy to OADs, basal or pre-mixed insulin. This last trial was only for evaluation of cardiovascular outcomes and general safety of semaglutide, not for any glycemic lowering claim.

Figure 2 Semaglutide Phase 3 Development Program



[a] investigates the flexible use of oral semaglutide 3, 7 and 14 mg; includes a 52-week extension that is not part of the NDA (blinded safety data from the extension (deaths, serious adverse events and pregnancies) are, however, included) [b] double-blind vs. placebo; open-label vs. GLP-1 RA. CV: cardiovascular; CVOT: CV outcomes trial; DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1: glucagon-like peptide-1; met: metformin; OAD: oral anti-diabetic drug; RA: receptor agonist; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulphonylurea.

Source: Figure 1-2 Clinical Overview

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An overview of the distribution of the background medications by study is presented below.

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Table 1 Background Therapies

	Metformin only	Insulin ± OADs	SU ± metformin	SGLT2-i ± metformin	TZDs ± metformin	Other	No background medication
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PIONEER 1-10	3057 (32.0)	2785 (29.2)	1911 (20.0)	375 (3.9)	107 (1.1)	314 (3.3)	992 (10.4)
PIONEER 1	0	0	0	0	0	0	703 (100)
PIONEER 2	821 (100)	0	0	0	0	0	0
PIONEER 3	986 (52.9)	0	877 (47.1)	0	0	0	0
PIONEER 4	528 (74.3)	0	0	183 (25.7)	0	0	0
PIONEER 5	77 (23.8)	115 (35.5)	132 (40.7)	0	0	0	0
PIONEER 7	189 (37.5)	1 (0.2)	244 (48.4)	51 (10.1)	13 (2.6)	6 (1.2)	0
PIONEER 8	0	731 (100)[a]	0	0	0	0	0
PIONEER 9	0	0	0	0	0	0	243 (100)
PIONEER 10	0	0	147 (32.1)	78 (17.0)	79 (17.2)	154 (33.6)	0
PIONEER 6	456 (14.3)	1938 (60.9)	511 (16.1)	63 (2.0)	15 (0.5)	154 (4.8)	46 (1.4)

N (%): number (proportion) of subjects in the full analysis set on glucose-lowering background medication. In PIONEER 8, the insulin regimens were basal, basal-bolus and premix insulin. OAD: oral anti-diabetic drug; SGLT2i: sodium-glucose co-transporter 2 inhibitor; SU: sulphonylurea; TZD: thiazolidinedione.

Source: Table 1-1 Clinical Overview

The duration of treatment in the phase 3 trials ranged from 26 to 78 weeks. The CVOT was event-driven, with most patients exposed for up to 79 weeks.

Four of the multinational studies evaluated the highest dose of semaglutide proposed for marketing, 14 mg. Three of the multinational studies evaluated three doses of oral semaglutide, 3, 7, and 14 mg. One study evaluated flexible semaglutide dose based on tolerability. The two Japanese safety trials evaluated the 3, 7, and 14 mg doses of oral semaglutide. To mitigate gastrointestinal side effects, all semaglutide-treated patients followed a fixed dose escalation regimen starting at 3 mg for 4 weeks before escalating to 7 mg as maintenance dose or another 4 weeks before escalating to 14 mg maintenance dose.

Not all trials were blinded. Placebo-controlled trials, as well as trials comparing semaglutide to liraglutide and most trials vs sitagliptin were blinded. PIONEER 2, comparing oral semaglutide to empagliflozin, was open label, and so was the flexible dose trial vs sitagliptin.

Table 2 Listing of Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Controlled Studies to Support Efficacy and Safety						

Reference ID: 4497478

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
PIONEER 1- 4233	Semaglutide vs placebo monotherapy DB	1) Semaglutide (3, 7, and 14 mg) 2) Placebo	Change from baseline in HbA1c	26 weeks	703	Multinational (incl. US); T2DM; diet and exercise only HbA1c 7-9.5%
PIONEER 2 - 4223	Semaglutide vs SGLT2 inhibitor OL	1) Semaglutide 14 mg 2) Empagliflozin 25 mg	Change from baseline in HbA1c	52 weeks	821	Multinational (incl. US); T2DM; inadequately controlled on metformin HbA1c 7-10.5%
PIONEER 3 - 4222	Semaglutide vs DPP-4 inhibitor DB	1) Semaglutide (3, 7, and 14 mg) 2) Sitagliptin 100 mg	Change from baseline in HbA1c	78 weeks	1862	Multinational (incl. US); T2DM; Inadequately controlled on metformin +/-SU
PIONEER 4 - 4224	Semaglutide vs GLP-1 RA DB	1) Semaglutide 14 mg 2) Liraglutide 1.8 mg 3) Placebo	Change from baseline in HbA1c	52 weeks	711	Multinational (incl. US); T2DM; Inadequately controlled on metformin +/- SGLT2i
PIONEER 5 - 4234	Semaglutide vs placebo DB	1) Semaglutide 14 mg 2) Placebo	Change from baseline in HbA1c	26 weeks	324	Multinational (incl. US); T2DM; with moderate renal impairment inadequately controlled on metformin +/- SU, basal insulin alone, or metformin in combination with basal insulin
PIONEER 7 - 4257	Flexible dose vs sitagliptin OL	1) Semaglutide flexible dose 2) Sitagliptin 100 mg	Change from baseline in HbA1c	52 weeks	504	Multinational (incl. US); T2DM; inadequately controlled on 1-2 OADs
PIONEER 8 - 4280	Insulin add-on vs placebo DB for the first 26 weeks	1) Semaglutide (3, 7, and 14 mg) 2) Placebo	Change from baseline in HbA1c	52 weeks	731	Multinational (incl. US); T2DM; background of insulin
Studies to Support Safety						

Reference ID: 4494748

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

Source: Reviewer generated using the tabular listing of clinical trials provided by the applicant

Reference ID: 4494748

5.2. Review Strategy

The applicant submitted seven multi-national efficacy phase 3 trials, one pre-market CVOT, and two Japanese trials as evidence of efficacy and safety in patients with T2DM.

The efficacy review of the semaglutide program was performed by individual trial review (not including the Japanese trials) and by comparisons across trials. For the individual trial review, the reviewer focused on the individual clinical trial reports, protocols and statistical analysis plan; this review is located in sections 6.2 to 6.7. For the review across trials, the reviewer used the summary of clinical efficacy, and clinical overview documents provided in the submission. The integrated review of effectiveness is located in section 7.

The CVOT was not reviewed here for efficacy, as it is not relevant for the glycemic reduction indication, and it will be reviewed under NDA 213182 where the applicant is requesting a CV risk reduction indication for the oral semaglutide product. The safety data from PIONEER 6 will be reviewed in the safety section of this review.

Safety was assessed in individual studies as well as using pools of studies. These pools included:

- Phase 3a pool excluding PIONEER 6
- Placebo pool
- CVOT

A more detailed discussion of the approach to the review of safety is located in section 8.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. PIONEER 1 (4233)

6.1.1. Study Design

Overview and Objective

Study title: A 26-week, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of oral semaglutide vs placebo in patients with type 2 diabetes mellitus treated with diet and exercise only

Primary objective: To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo on glycemic control in patients with type 2 diabetes treated with diet and exercise only.

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Secondary objective:

- To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo on body weight in patients with type 2 diabetes treated with diet and exercise only.
- To compare the safety and tolerability of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo in patients with type 2 diabetes treated with diet and exercise only.

Trial Design

The trial was randomized, double-blind, placebo-controlled multinational, multi-center efficacy and safety trial with a 26-week treatment period (including an 8-week dose escalation period) and a 5- week follow-up period.

A total of 704 adults with T2DM treated with diet and exercise only were planned to be randomized to once-daily treatment with oral semaglutide (3, 7 or 14 mg) or placebo.

Key inclusion/exclusion criteria:

- Inclusion criteria included adult patients with T2DM, HbA1c 7-9.5%, treated with diet and exercise for at least 30 days prior to screening.

- Exclusion criteria included treatment with any glucose lowering agent within 90 days before screening, history of pancreatitis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired renal function (eGFR <60 mL/min/1.73 m2 per MDRD formula), acute coronary or cerebrovascular event within 90 days before randomization, heart failure (New York Heart Association class IV), known proliferative retinopathy or maculopathy.

Dose selection/Study treatments:

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 was to 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.

This type of administration was preserved for all PIONEER trials. The dose escalation, also preserved throughout PIONEER trials, is presented in Table 3 below.

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Table 3 Dose Escalation and Treatment Periods

	Treatment periods		
Treatment arm	**Dose escalation**	**Dose escalation**	**Maintenance dose**
	Week 0 to 4	Week 4 to 8	Week 8 to 26
Oral semaglutide 3 mg	3 mg	3 mg	3 mg
Oral semaglutide 7 mg	3 mg	7 mg	7 mg
Oral semaglutide 14 mg	3 mg	7 mg	14 mg
Placebo	Placebo	Placebo	Placebo

Source: Table 9-1 CSR

Administrative structure:
The trial was monitored by a Novo Nordisk internal safety committee. The safety committee could recommend unblinding of any data for further analysis; in such cases, an independent group was to be established ad hoc to maintain the blinding of trial personnel.

An independent external event adjudication committee (EAC) performed ongoing, blinded evaluation of specific pre-defined events, throughout all PIONEER trials.

Procedures and schedule:
The patients had in person visits at screening, randomization, weeks 4, 8, 12, 14, 20, 26 (end of treatment), and 31 (follow-up). A phone visit occurred at week 2.

The patients were to attend most visits in a fasting state, defined as no food or liquid intake within the last 8 hours before sampling; water was allowed up until 2 hours before blood sampling. Trial product was not to be taken until after blood sampling. Other oral medication could be taken 30 minutes after trial product and injectable medications could be administered after blood sampling.

Eye examination was to be performed at screening and end of treatment. ECGs were performed at randomization, end of treatment, and follow up.

Please see study protocol for study procedures details.

Concurrent medications:
The patients were treatment naïve, no other antidiabetic medications were allowed except for rescue medication.

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Treatment compliance
Compliance was assessed by monitoring of drug accountability.

Rescue medications
Patients with unacceptable hyperglycemia on the trial product alone or who had trial product discontinued could start other antidiabetic medications at the discretion of the investigator, after week 8. GLP-receptor agonists, DPP-IV inhibitors and pramlintide were not allowed as rescue medication.

There were no set criteria for the use of rescue medication in PIONEER 1.

Use of antidiabetic medications for ≤21 days was not considered additional antidiabetic medication by the applicant.

Patient completion, discontinuation, or withdrawal
The trial product had to be discontinued in case of safety concern related to the trial product or unacceptable tolerability, violation of any inclusion/exclusion criteria, pregnancy or intention to become pregnant, calcitonin >100ng/dL, and simultaneous participation in another clinical trial.

If the trial product was discontinued prematurely, it was not to be re-initiated.

A trial completer was defined as a patient who attended the final scheduled visit.

Study Endpoints

Primary endpoint:
- Change from baseline in HbA1c to week 26.

Confirmatory secondary endpoint:
- Change in body weight from baseline to week 26[1]

A multitude of other efficacy and safety supportive endpoints were predefined by the sponsor, but not included in the testing hierarchy. The results will not be discussed in detail in this review as they are not relevant to approval and/or labelling for the current application.

Statistical Analysis Plan

Per the applicant, the sample size calculation was based on the primary endpoint and allowed for at least 90% power to confirm superiority of semaglutide vs placebo. Per this calculation,

[1] Secondary endpoint with control for type 1 error

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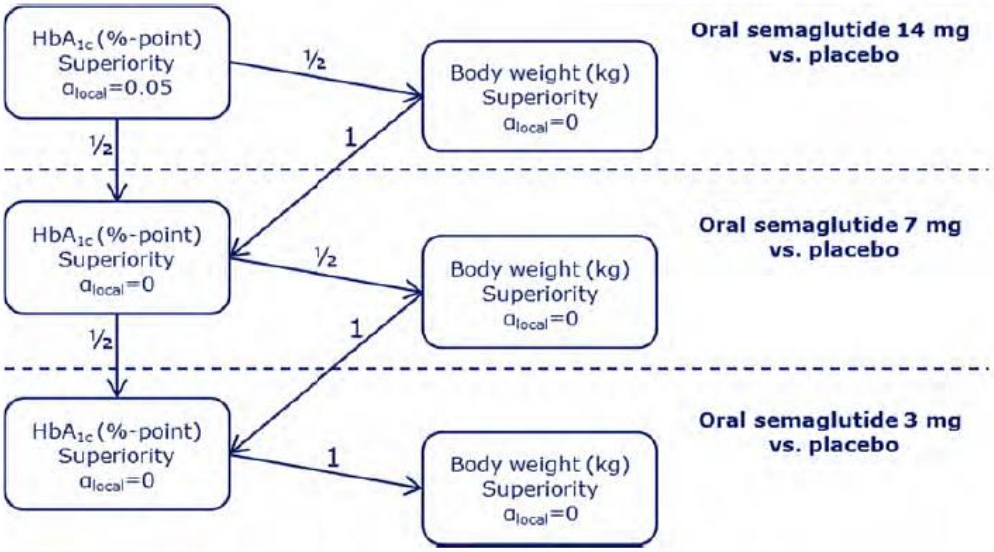
176 patients/treatment group were needed, amounting to 704 patients planned to be randomized to the 4 treatment arms.

The testing hierarchy tested for superiority for the primary endpoint, followed by testing for superiority for the confirmatory secondary endpoint, for each of the semaglutide doses in turn.

Table 4 Statistical Testing Hierarchy



The total significance level of α = 0.05 (two-sided) was initially allocated to the hypothesis of superiority of oral semaglutide 14 mg vs placebo on change from baseline at week 26 in HbA_{1c}; if that hypothesis was confirmed, the local significance level (α-local) was reallocated to the other hypotheses in the testing strategy according to the indicated weight (½ or 1) of the arrows. Each hypothesis was tested at its updated local significance level (α-local) until all hypotheses had been confirmed or until no hypothesis could be confirmed.

Source: Figure 9-7 CSR PIONEER 1

<u>Definition of the analysis sets</u>

- Full analysis set (FAS) included all randomized patients.
- Safety analysis set (SAS) included all randomized patients who had received at least one dose of randomized semaglutide or placebo.

<u>Definition of observation periods</u>

- 'In-trial' observation period represents the period after randomization until the final scheduled visit, including any period after initiation of rescue medication or premature discontinuation
- 'On-treatment' observation period includes the period when the patients were expected to be treated and exposed to the trial product.
- 'On-treatment without rescue medication' period included observations recorded from the first dose of trial product until the occurrence of initiation of rescue medication

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Missing data:

The treatment policy estimand was used to evaluate efficacy, with missing data at week 26 imputed using pattern-mixture models.

Protocol Amendments

There were three substantial amendments to the protocol (2 local amendments, and 1 global amendment). The global amendment referred mainly to the introduction of eye examinations and additional data collection for diabetic retinopathy.

I reviewed the protocol amendments and they are not likely to have impacted the results of the study.

6.1.2. Study Results

Compliance with Good Clinical Practices

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

Financial Disclosure

The applicant submitted adequate financial disclosures for the investigators that participated in this trial.

There was a total of 529 investigators, out of which 9 reported financial disclosures. See Appendix 13.3 for details.

Patient Disposition

Of the 1006 patients screened, 303 were screening failures, thus 703 patients were randomized at a 1:1:1:1 ratio to receive semaglutide (3, 7 or 14 mg) or placebo. Most of the screen failures – 240 patients, failed due to non-fulfillment of HbA1c inclusion criterion. All randomized patients received trial product. A total of 630 patients (89.6%) completed the treatment with the trial product, and 663 (94.3%) completed the trial, with no major differences across treatment groups.

A total of 5.7% of all patients withdrew from the trial; more patients in the oral semaglutide 7 mg (8.0%) and 14 mg (6.9%) groups withdrew from the trial than from the oral semaglutide 3 mg (3.4%) and placebo (4.5%) groups. The proportion of patients who completed treatment without receiving rescue medication was greater with oral semaglutide (85.1−87.4%) than with placebo (75.3%). A higher proportion of discontinuations due to AEs was observed with

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semaglutide (2.3-7.4 % vs 2.2%) vs placebo, and this was dose dependent.

Table 5 Patient Disposition PIONEER 1

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N (%)
Screened					1006
Screening failures					303 (30.1)
Randomised	175	175	175	178	703
Exposed	175 (100)	175 (100)	175 (100)	178 (100)	703 (100)
Analysis sets					
Full analysis set	175 (100)	175 (100)	175 (100)	178 (100)	703 (100)
Safety analysis set	175 (100)	175 (100)	175 (100)	178 (100)	703 (100)
Treatment completers [1]	163 (93.1)	157 (89.7)	151 (86.3)	159 (89.3)	630 (89.6)
Without rescue medication	152 (86.9)	153 (87.4)	149 (85.1)	134 (75.3)	588 (83.6)
With rescue medication	11 (6.3)	4 (2.3)	2 (1.1)	25 (14.0)	42 (6.0)
Premature trial product discont.	12 (6.9)	18 (10.3)	24 (13.7)	19 (10.7)	73 (10.4)
- primary reason					
Adverse event(s)	4 (2.3)	7 (4.0)	13 (7.4)	4 (2.2)	28 (4.0)
Pregnancy	0	0	0	0	0
Participation in another clinical trial[2]	1 (0.6)	0	1 (0.6)	0	2 (0.3)
Subject withdrawal from trial	0	5 (2.9)	5 (2.9)	3 (1.7)	13 (1.8)
Violation of in-/excl. crit.	2 (1.1)	1 (0.6)	0	0	3 (0.4)
Exclusion criteria 2	1 (0.6)	0	0	0	1 (0.1)
Exclusion criteria 7	1 (0.6)	0	0	0	1 (0.1)
Exclusion criteria 13	0	1 (0.6)	0	0	1 (0.1)
Other	5 (2.9)	5 (2.9)	5 (2.9)	12 (6.7)	27 (3.8)
Trial completers [3]	169 (96.6)	161 (92.0)	163 (93.1)	170 (95.5)	663 (94.3)
Withdrawal from trial	6 (3.4)	14 (8.0)	12 (6.9)	8 (4.5)	40 (5.7)
- primary reason					
Withdrawal by subject	0	5 (2.9)	5 (2.9)	4 (2.2)	14 (2.0)
Lost to follow-up	5 (2.9)	7 (4.0)	5 (2.9)	2 (1.1)	19 (2.7)
Other	1 (0.6)	2 (1.1)	2 (1.1)	2 (1.1)	7 (1.0)
Died	0	0	1 (0.6)	0	1 (0.1)

'[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product; N: number of subjects; %: proportion of randomised subjects except for screening failures where it is proportion of screened subjects. For exclusion criteria see the protocol (Appendix 16.1.1, Section 6.3)

Source: Table 10-1 CSR PIONEER 1

Protocol Violations/Deviations

Protocol deviations (PDs) were categorized as important or non-important and according to project-wide PD categories and subcategories. A PD was categorized as important if the PD could significantly impact the completeness, accuracy or reliability of the trial results or if the PD could significantly affect the rights, safety or well-being of the patient(s).

In total there were 142 important PDs; the PDs comprised one trial-level PD, one country-level

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PD as well as 17 site-level PDs and 123 patient-level PDs.

The trial-level PD belonged to the 'Assessment deviation (incl. lab)' category and concerned the reporting of body weight measurements with precisions less than the one specified in the trial protocol (0.1 kg/pounds) at some trial sites due to use of scales with a precision of 0.5 kg/pound or due to rounding off to the nearest half or whole kg/pound by the site staff.

The one important country-level PD was reported from the US after the database lock. The PD belonged to the 'Other' category and concerned a 2-day delay in the delivery of a SUSAR report from Novo Nordisk to the investigators.

The distribution of site and patient-level PDs is outlined in the table below. Only 5PDs which were related to eligibility criteria led to withdrawal of the patients from the trial. None of the other deviations led to exclusion of patients or data points from the statistical analyses.

Table 6 Summary of Important Site-Level and Patient-Level Protocol Deviations PIONEER 1

Category	Site-level PDs (n)	Subject-level PDs (n)					
		Screening failures	Oral sema 3 mg	Oral sema 7 mg	Oral sema 14 mg	Placebo	Total no of subject-level PDs
Informed consent	3	9	3	3	9	6	30
Inclusion/exclusion/ randomisation criteria	-	-	6	4	2	2	14
Trial product handling	-	-	-	7	3	4	14
Treatment compliance	-	-	5	3	10	2	20
Assessment deviations	-	-	6	11	10	7	34
Other	14	-	3	2	1	4	10
Total	17	9	23	30	35	25	122

n: number of PDs; PD: protocol deviation; sema: semaglutide. Summary includes important protocol deviations closed by database lock.

Source: Table 10-5 CSR PIONEER 1

I evaluated details provided by the applicant regarding these deviations, and I agree that it is unlikely that they impacted the outcome of the trial.

Patient Demographics and Other Baseline Characteristics

The demographic and baseline characteristics were generally similar across treatment groups. The population was evenly distributed between male and female patients with a mean age of

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around 55 years. The mean weight and waist circumference were similar across groups. Most patients had a BMI >25 kg/m2 and the mean BMI was 31.8 kg/m2. T2DM was relatively recently diagnosed, with an overall mean duration of 3.5 years (SD 4.9). The mean HbA1c was 8.0%, similar between treatment groups.

Renal function (based on baseline eGFR) was normal for 73.7% of the patients; 25.5% had mild renal impairment and 0.9% had moderate renal impairment. Compared with the other groups, slightly more patients in the oral semaglutide 7 mg group had mild renal impairment. The mean estimated GFR was 98 mL/min/1.73 m^2 and was similar across treatment groups.

Table 7 Demographics and Baseline Characteristics – Continuous Variables, PIONEER 1

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N(%)
Number of subjects	175	175	175	178	703
Age (years)					
N	175	175	175	178	703
Mean (SD)	55 (11)	56 (11)	54 (11)	54 (11)	55 (11)
HbA1c (%)					
N	175	175	175	178	703
Mean (SD)	7.9 (0.7)	8.0 (0.6)	8.0 (0.7)	7.9 (0.7)	8.0 (0.7)
Duration of diabetes (years)					
N	175	175	175	178	703
Mean (SD)	3.8 (5.3)	3.6 (5.1)	3.4 (4.4)	3.4 (4.6)	3.5 (4.9)
Body weight (kg)					
N	175	175	175	178	703
Mean (SD)	86.9 (21.0)	89.0 (21.8)	88.1 (22.1)	88.6 (23.4)	88.1 (22.1)
Median	84.2	86.7	87.1	83.7	85.5
Min; Max	41.2 ; 140.8	44.2 ; 173.3	47.7 ; 153.2	46.8 ; 210.9	41.2 ; 210.9
eGFR (mL/min/1.73 m^2)					
N	175	175	175	178	703
Mean (SD)	99 (14)	95 (16)	97 (16)	100 (15	98 (15)

The eGFR was estimated using the CKD-EPI formula.'Baseline': defined as the latest assessment at or prior to the randomisation visit; eGFR: estimated glomerular filtration rate; CKD_EPI; N: number of subjects; SD: standard deviation.

Source: Modified from Table 10-2 CSR PIONEER 1

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Table 8 Demographics and Baseline Characteristics for Categorical Variables – PIONEER 1

	Sema 0.5 mg	Sema 1.0 mg	Placebo	Total
Number of subjects	128	130	129	387
Age (years)				
N	128	130	129	387
Mean (SD)	54.6 (11.1)	52.7 (11.9)	53.9 (11.0)	53.7 (11.3)
HbA1c (%)				
N	128	130	129	387
Mean (SD)	8.09 (0.89)	8.12 (0.81)	7.95 (0.85)	8.05 (0.85)
Fasting plasma glucose (mg/dL)				
N	125	129	127	381
Mean (SD)	174.1 (49.89)	178.5 (44.99)	174.4 (49.85)	175.7 (48.19)
Duration of Diabetes (years)				
N	127	129	129	385
Mean (SD)	4.85 (6.11)	3.65 (4.89)	4.06 (5.48)	4.18 (5.52)
Body mass index (kg/m2)				
N	128	130	129	387
Mean (SD)	32.46 (7.62)	33.92 (8.43)	32.40 (6.86)	32.93 (7.68)
MDRD GFR 'estimated' (mL/min/1.73 m^2)				
N	128	130	129	387
Mean (SD)	95.91 (26.23)	100.9 (27.74)	100.2 (24.97)	99.02 (26.37)

Notes: The baseline value is defined as the latest pre-dosing value.
Body mass index is calculated based on baseline measurement of body weight and height.
Abbreviations: N: Number of subjects, SD: Standard deviation, CV: Coefficient of variation, MDRD: Modification of diet in renal disease, GFR: glomerular filtration rate

Source: Modified from Table 10-3 CSR PIONEER 1

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

The most frequent and clinically relevant concomitant illnesses for all treatment groups were; dyslipidemia (24.7–30.9%), obesity (20.6–23%), gastrointestinal disorders (11.4–18.3%), hepatic steatosis (9.7–12.6%) and hypothyroidism (1.7–8.0%), neoplasms (3.4–8.0%), vascular disorders (1.7–8.0%), psychiatric disorders (8.0–11.4%), which included depression (1.1–6.9%). All were balanced between treatment groups.

The most frequently reported histories of cardiovascular disease were ischemic heart disease (7.4%, 10.3%, 8.0% and 8.4%) and hypertension (60.6%, 57.7%, 51.4% and 55.1%) for oral semaglutide 3 mg, 7 mg and 14 mg, and placebo, respectively.

Most patients did not have diabetic retinopathy at baseline with no clinically relevant differences across treatment groups observed for history of diabetes retinopathy; the proportions of patients with diabetic retinopathy were 8.0%, 5.7%, 8.0% and 4.5% for oral semaglutide 3 mg, 7 mg and 14 mg, and placebo, respectively (all reported as nonproliferative diabetic retinopathy).

Other diabetic complications included diabetic neuropathy (8.6%, 6.9%, 8.0% and 5.1%) and

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diabetic nephropathy (2.3%, 5.7%, 5.1% and 3.4%) for oral semaglutide 3 mg, 7 mg and 14 mg, and placebo, respectively.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were 20 patient-level deviations for treatment compliance, 2 of them because the patient did not take more than 50% of the scheduled doses (one on semaglutide and one on placebo). The remaining deviations (15 on semaglutide and one on placebo) were filed because the patients reported a treatment pause of more than 10 days.

At baseline, the reported use of concomitant medications was similar across the treatment groups with no clinically relevant differences. The most frequently used concomitant medications were HMG CoA reductase inhibitors, ACE inhibitors and platelet aggregation inhibitors excluding heparin.

The proportion of patients receiving additional anti-diabetic medications was lower with semaglutide compared to placebo, as expected.

Table 9 Additional Anti-Diabetic Medication and Rescue Medication PIONEER 1

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	175	175	175	178	703
ADDITIONAL ANTI-DIABETIC MEDICATION					
Number of subjects	**16 (9.1)**	**8 (4.6)**	**7 (4.0)**	**35 (19.7)**	**66 (9.4)**
BIGUANIDES	12 (6.9)	6 (3.4)	6 (3.4)	25 (14.0)	49 (7.0)
SULFONYLUREAS	2 (1.1)	1 (0.6)	2 (1.1)	8 (4.5)	13 (1.8)
INSULINS,FAST-ACTING	1 (0.6)	0	0	0	1 (0.1)
INSULINS,IN.MED-ACTING	0	0	0	1 (0.6)	1 (0.1)
INSULINS,LONG-ACTING	4 (2.3)	0	0	3 (1.7)	7 (1.0)
SGLT2 INHIBITORS	1 (0.6)	1 (0.6)	0	2 (1.1)	4 (0.6)
DPP-4 INHIBITORS	0	0	0	2 (1.1)	2 (0.3)
RESCUE MEDICATION (subset of additional anti-diabetic medication)					
Number of subjects	**13 (7.4)**	**4 (2.3)**	**2 (1.1)**	**27 (15.2)**	**46 (6.5)**
BIGUANIDES	9 (5.1)	2 (1.1)	2 (1.1)	20 (11.2)	33 (4.7)
SULFONYLUREAS	2 (1.1)	1 (0.6)	0	7 (3.9)	10 (1.4)
INSULINS,LONG-ACTING	3 (1.7)	0	0	2 (1.1)	5 (0.7)
INSULINS,IN.MED-ACTING	0	0	0	1 (0.6)	1 (0.1)
SGLT2 INHIBITORS	1 (0.6)	1 (0.6)	0	2 (1.1)	4 (0.6)
THIAZOLIDINEDIONES	1 (0.6)	0	0	0	1 (0.1)

Source: Table 10-4 CSR PIONEER 1

Efficacy Results

Primary and Confirmatory Secondary Endpoint

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Superiority of oral semaglutide (all doses) vs placebo was confirmed for the primary endpoint of change from baseline in HbA1c at week 26 (treatment policy estimand, in-trial observation period). Superiority of the confirmatory secondary endpoint (change in weight) was only confirmed for the 14 mg of semaglutide.

Table 10 Primary and Confirmatory Secondary Endpoints – Primary Statistical Analyses – Treatment Policy Estimand, PIONEER 1

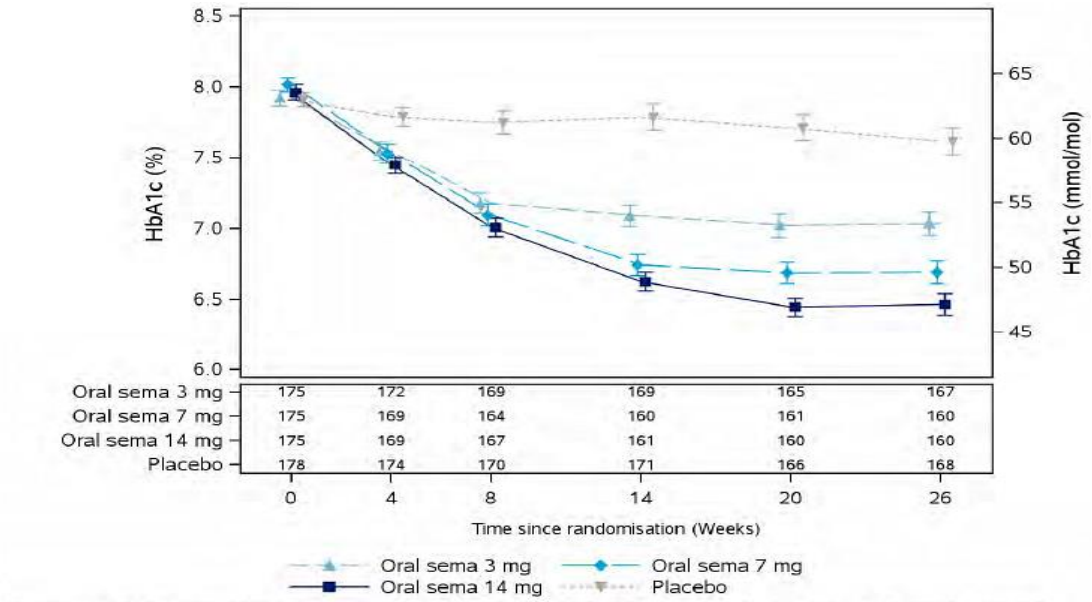
Endpoint	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoint: Change from baseline at week 26 in HbA1c (%-points)					
Oral sema 14 mg - Placebo	-1.1 [-1.3 ; -0.9]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-0.9 [-1.1 ; -0.6]	<0.0001		Superiority	Confirmed
Oral sema 3 mg - Placebo	-0.6 [-0.8 ; -0.4]	<0.0001		Superiority	Confirmed
Confirmatory secondary endpoint: Change from baseline at week 26 in body weight (kg)					
Oral sema 14 mg - Placebo	-2.3 [-3.1 ; -1.5]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-0.9 [-1.9 ; 0.1]	0.0866	0.025	Superiority	Not confirmed
Oral sema 3 mg - Placebo	-0.1 [-0.9 ; 0.8]	0.8692	0.025	Superiority	Not confirmed

'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval; 'p-value': unadjusted two-sided p-value for test of no difference from 0.

Source: Table 11-1 CSR PIONEER 1

HbA1C decreased from baseline to week 20 with all semaglutide doses, while not much change was seen on placebo. The observed changes from baseline were −0.9, −1.3 and −1.5 %-points with oral semaglutide 3, 7 and 14 mg, respectively, and −0.3 %-points with placebo.

Figure 3 Mean HbA1c by Week – Mean Plot – PIONEER 1



Observed data from the in-trial observation period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel represent the number of subjects contributing to the means.

Source: Figure 11-2 CSR PIONEER 1

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Sensitivity analyses were supportive of the primary endpoint results. Please see Biometrics review by Dr Robert Abugov for details on the FDA statistical evaluation.

Data Quality and Integrity

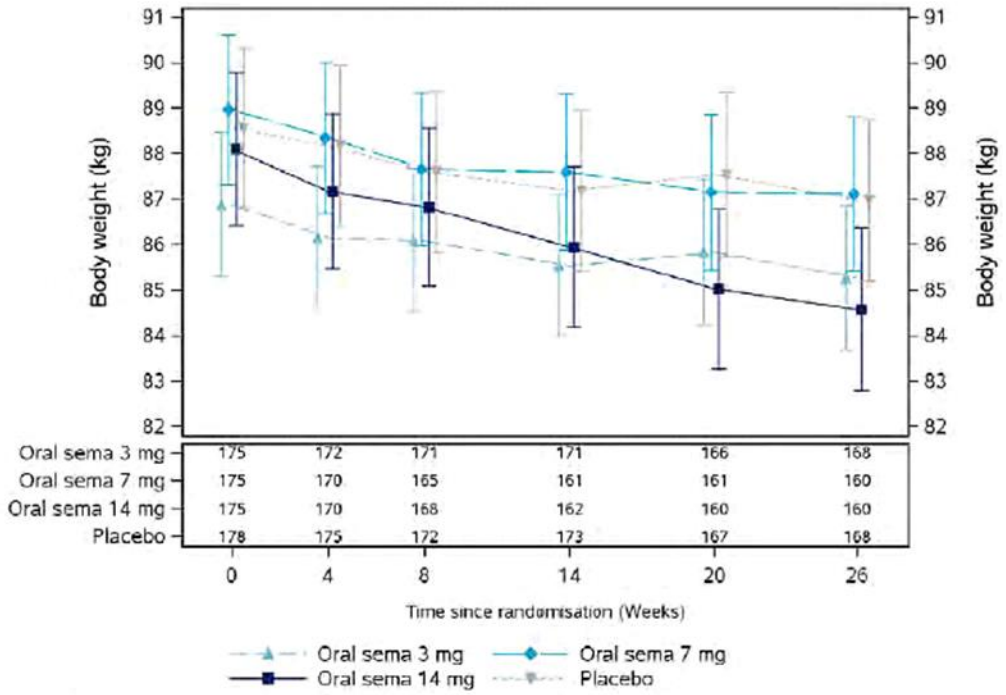
Datasets and study documents appear adequate; I did not identify any issues.

Efficacy Results – Secondary and other relevant endpoints

Change in body weight

At baseline, weight was similar between treatment groups (86.9-89 Kg). Body weight decreased in all treatment arms by week 26. The estimated decrease from baseline were -1.5, -2.3, -3.7 kg with semaglutide 3, 7, and 14 mg respectively, and -1.4 Kg with placebo.

Figure 4 Mean Body Weight Over Time PIONEER 1



Observed data from the in-trial observation period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel represent the number of subjects contributing to the means.

Source: Figure 11-1 CSR PIONEER 1

HbA1c treatment targets

A higher proportion of patients achieved a target HbA1c ≤6.5% after 30 weeks with either of the semaglutide doses (semaglutide 3 mg – 35.9%, semaglutide 7 mg – 47.5%, semaglutide 14 mg – 63.8%) compared to placebo (17.9%). Similarly, a higher proportion of patients on

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semaglutide achieved a HbA1c target of <7% (semaglutide 3 mg – 55.1%, semaglutide 7 mg – 68.8%, semaglutide 14 mg – 76.9%) compared to placebo (31%).

An HbA1c<7% without severe or BG-confirmed symptomatic hypoglycemia and no weight gain was more likely in patients exposed to semaglutide 3 mg (37.1%), semaglutide 7 mg (56.9%) and semaglutide 14 mg (68.8%) when compared with placebo (23.2%).

Dose/Dose Response

The placebo-adjusted HbA1C reduction was greater with semaglutide 14 mg compared to 7 mg, and 3 mg, and a clear dose-response was seen for efficacy.

Durability of Response

Most of the effect on HbA1c and weight was observed in the first 20 weeks of treatment and was sustained for the duration of the study (week 26). This study was not of sufficient duration to assess the durability of response.

Persistence of Effect

Not applicable. The effect after discontinuation of study drug was not assessed.

Additional Analyses Conducted on the Individual Trial

Sensitivity analyses are discussed above in the context of the primary analysis for the primary and secondary endpoints. They were generally consistent with the results of the primary analysis.

6.2. PIONEER 2 (4223)

6.2.1. Study Design

Overview and Objective

Study title: A 52-week randomized, open-label, active-controlled trial to investigate the efficacy and safety of oral semaglutide versus empagliflozin in patients with type 2 diabetes mellitus

Primary objective: To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on glycemic control in patients with type 2 diabetes mellitus.

Secondary objective:

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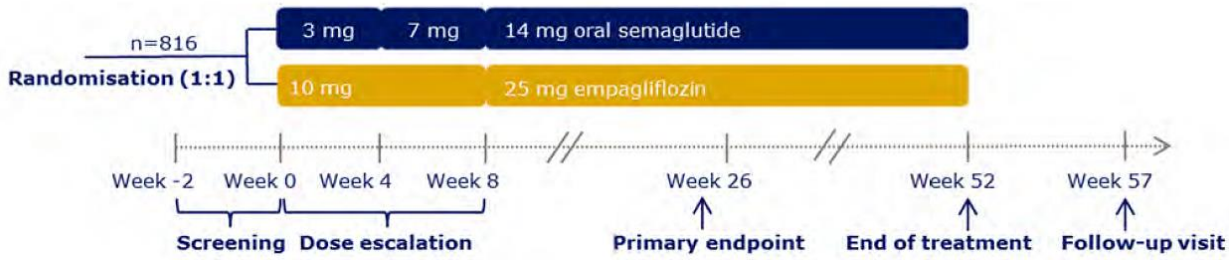
- To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on body weight in patients with type 2 diabetes mellitus.
- To compare the safety and tolerability of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, in patients with type 2 diabetes mellitus.

Trial Design
This was a multinational, multi-center, randomized, open-label, active-controlled efficacy and safety trial with a 52-week treatment period (including an 8-week dose escalation period) and a 5-week follow-up period. The applicant states that the trial was open label because manufacturing placebo tablets resembling empagliflozin was not feasible.

The trial was conducted at 108 sites in 12 countries.

Figure 5 PIONEER 2 Trial Design



Source: Figure 9-1 CSR PIONEER 2

Key inclusion/exclusion criteria:
Patients with T2DM treated with metformin only at a stable dose for at least 90 days with a maximum HbA1c of 7-10.5%, both inclusive. Otherwise, the inclusion/exclusion criteria were similar to PIONEER 1.

Dose selection/Study treatments:
Dose escalation of semaglutide was similar to PIONEER 1, with the difference that only the highest dose of semaglutide was to be studied against the highest approved dose of empagliflozin.

Empagliflozin treatment was started at 10 mg daily for 8 weeks, followed by increase to 25 mg daily from week 8 on.

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 tablet could be taken with up to

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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 oral semaglutide could be taken 30 minutes after administration of the tablet.

Randomization was 1:1.

Dose modification/discontinuation:
Similar to PIONEER 1.

Administrative structure:
Similar to PIONEER 1 with an internal safety committee and an event adjudication committee.

Procedures and schedule:
The patients had in person visits at screening, randomization, weeks 4, 8, 14, 20, 26, 32, 38, 45, 52 (end of treatment), and 57 (follow up). One phone visit occurred at week 2.

Of note, fundoscopy or fundus photography was to be performed at randomization, and end of treatment.

Detailed study proceedings can be found in the study protocol submitted as part of this NDA.

Concurrent medications:
Patients were to continue their background anti-diabetic medication (metformin) throughout the entire trial, preferably at the same dose unless rescue medication was needed or a safety concern related to use of metformin arose.

Treatment compliance
Compliance was assessed by monitoring of drug accountability.

Rescue medications
Similar to PIONEER 1.

Patient completion, discontinuation, or withdrawal
Similar to PIONEER 1.

Study Endpoints

The primary endpoint was change from baseline to week 26 in HbA1c (%-points).

The confirmatory secondary endpoint was change from baseline to week 26 in body weight (kg).

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A variety of supportive endpoints were described by the sponsor, but they are not relevant for this review as they are not included in the prescribing information.

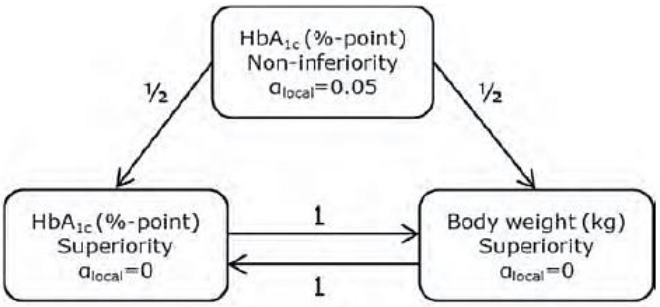
Statistical Analysis Plan

The sample size was calculated to ensure a statistical power of at least 90% to confirm superiority on change from baseline to week 26 in HbA1c for the treatment policy estimand of oral semaglutide 14 mg vs empagliflozin 25 mg.

Based on the applicant predictions, 408 patients to each of the two arms would provide a ≥90% statistical power to confirm HbA1c superiority and a ≥85% statistical power to confirm body weight superiority of oral semaglutide 14 mg versus empagliflozin 25 mg. In total 2×408 = 816 patients were planned to be randomized.

The first hypothesis to be tested was non-inferiority on HbA1c of oral semaglutide 14 mg vs empagliflozin 25 mg. The hypothesis was tested at %5 overall significance level. If the hypothesis was confirmed, the significance level was reallocated as specified in the figure below.

Figure 6 Statistical Testing Strategy, PIONEER 2



The total significance level of α = 0.05 (two-sided) was initially allocated to the hypothesis of non-inferiority of oral semaglutide 14 mg vs empagliflozin on change from baseline in HbA_{1c}. If that hypothesis was confirmed, the local significance level (α-local) was reallocated to the other hypotheses in the testing strategy according to the indicated weight (½) of the arrows. Each hypothesis was tested at its updated local significance level (α-local) until all hypotheses had been confirmed or until no hypothesis could be confirmed.

Source: Figure 9-7 CSR PIONEER 2

<u>Analysis populations</u>

The following analysis sets were specified:

- The full analysis set (FAS) comprises all randomized patients.
- Per protocol (PP) analysis set comprises all patients in the FAS who have not violated any inclusion criteria, have not fulfilled any exclusion criteria, have a valid baseline

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HbA1c measurement and were exposed to trial product and have at least one valid HbA1c measurement while on treatment without rescue medication at or after week 14.
- The safety analysis set (SAS) comprises all randomized patients who received at least one dose of trial product.

The FAS was used for the evaluation of the efficacy endpoints

Observation periods

For the efficacy and safety evaluations, three different observation periods were defined:
- The in-trial observation period – the time period from when a patient was randomized until the final scheduled visit, including any period after initiation of rescue medication or premature discontinuation of trial product
- The on-treatment observation period – the time period when a patient was on treatment with trial product, including any period after initiation of rescue medication
- The on-treatment without rescue medication observation period – the time period when a patient was on treatment with trial product, excluding any period after initiation of rescue medication

The definitions of additional antidiabetic-therapy, rescue therapy, and trial completers were the same as for PIONEER 1.

Protocol Amendments

There was one substantial amendment to the protocol, which was global. The changes introduced by the amendment were as follows:
- Introduction of additional eye examinations and additional data collection on diabetic retinopathy
- Added text to highlight the investigator's responsibility in ensuring evaluation and management of certain risk factors and complications
- Clarification of the criteria for completion, withdrawal and lost to follow-up
- Other minor corrections and clarifications

Overall this is unlikely to have impacted the results of the study.

Data Quality and Integrity: Sponsor's Assurance

The trial was conducted in accordance with ICH good clinical practice (GCP) per the applicant.

Investigators had to be trained in GCP, and all principal investigators provided written assurances of compliance with GCP. The trial was monitored by Novo Nordisk via on-site visits, telephone calls, and regular inspection of the eCRFs.

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6.2.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with ICH GCP.

Financial Disclosure

The applicant submitted adequate financial disclosure documents.

Of the 427 total investigators that participated in the trial, 5 had financial disclosures. See Appendix 13.3 for details.

Patient Disposition

In total, 1122 patients were screened and 300 patients failed screening; thus, 822 patients were randomized to receive either oral semaglutide 14 mg (412 patients) or empagliflozin 25 mg (410 patients). Of the randomized patients, one patient in each group was not exposed to trial product; thus, there were more patients in the FAS than in the SAS for each treatment group.

One patient (patient ID: (b) (6)) was a duplicate patient, already enrolled in the trial at another site, 704 patients (85.6%) completed the treatment with trial product and 787 patients (95.7%) completed the trial. The proportion of patients completing treatment was lower with oral semaglutide 14 mg (82.3%) than with empagliflozin 25 mg (89.0).

The proportion of randomized patients completing the treatment without receiving rescue medication was slightly lower with oral semaglutide 14 mg (75.2%) than with empagliflozin 25 mg (78.5%).

A total of 118 patients (14.4%) discontinued trial product prematurely for the following reasons: adverse events (7.9%), violation of inclusion or exclusion criteria (0.2%), participation in another clinical trial (0.4%), patient withdrawal from trial (1.6%), and 'Other' reasons (4.0%). The proportion of patients who prematurely discontinued trial product due to AEs was larger with oral semaglutide 14 mg (10.9%) than with empagliflozin 25 mg (4.9%). With oral semaglutide 14 mg, gastrointestinal AEs were the event type that most frequently led to premature trial product discontinuation (8% for oral semaglutide 14 mg and 0.7% with empagliflozin 25 mg); with empagliflozin 25 mg, infections and infestations were the event type that most frequently led to premature trial product discontinuation (no patients with oral semaglutide 14 mg and 1.2% with empagliflozin 25 mg).

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Table 11 Patient Disposition PIONEER 2

	Oral sema 14 mg N (%)	Empa 25 mg N (%)	Total N (%)
Screened			1122
Screening failures			300 (26.7)
Randomised	412	410	822
Exposed	411 (99.8)	409 (99.8)	820 (99.8)
Analysis sets			
Full analysis set	411 (99.8)	410 (100)	821 (99.9)
Safety analysis set	410 (99.5)	409 (99.8)	819 (99.6)
Per protocol analysis set	362 (87.9)	384 (93.7)	746 (90.8)
Treatment completers [1]	339 (82.3)	365 (89.0)	704 (85.6)
Without rescue medication	310 (75.2)	322 (78.5)	632 (76.9)
With rescue medication	29 (7.0)	43 (10.5)	72 (8.8)
Premature trial product discontinuation - primary reason	73 (17.7)	45 (11.0)	118 (14.4)
Exposed			
Adverse event(s)	45 (10.9)	20 (4.9)	65 (7.9)
Violation of inclusion and/or exclusion criteria	0	2 (0.5)	2 (0.2)
Intention of becoming pregnant	0	0	0
Participation in another clinical trial [2]	3 (0.7)	0	3 (0.4)
Calcitonin value >= 100 ng/L	0	0	0
Subject withdrawal from trial	6 (1.5)	7 (1.7)	13 (1.6)
Pregnancy	0	0	0
Other	18 (4.4)	15 (3.7)	33 (4.0)
Not exposed			
Violation of inclusion and/or exclusion criteria	0	1 (0.2)	1 (0.1)
Other	1 (0.2)	0	1 (0.1)
Trial completers [3]	400 (97.1)	387 (94.4)	787 (95.7)
Withdrawal from trial - primary reason	12 (2.9)	23 (5.6)	35 (4.3)
Lost to follow-up	4 (1.0)	10 (2.4)	14 (1.7)
Withdrawal by subject	8 (1.9)	12 (2.9)	20 (2.4)
Other	0	1 (0.2)	1 (0.1)
Died	0	1 (0.2)	1 (0.1)

'[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'primary reason': according to the end-of-trial form; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product; N: number of subjects; %: proportion of randomised subjects except for screening failures where it is proportion of screened subjects.

Source: Table 10-1 study report

Out of the 300 patients who failed screening, the majority (212 patients, 70.7%) failed due to nonfulfillment of HbA1c inclusion criterion 4. Other reasons for screen failures included: impaired renal function, 12.7% of all screening failures.

Protocol Violations/Deviations

In total, there were 379 important PDs reported as follows: 2 trial level PDs, 42 site-level PDs and 335 patient-level PDs.

<u>Trial-level PDs</u>

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One PD belonged to the 'Assessment deviation (incl. lab)' category and concerned the reporting of body weight measurements with precisions less than the one specified in the trial protocol (0.1 kg/pound) at some trial sites. This occurred due to use of scales with a precision of 0.5 kg/pound or rounding off to the nearest half or whole kg/pound by the site staff. The PD was not considered to have had any impact on the data interpretation.

The second PD belonged to the 'Other' category and concerned a deviation from the predefined process for compilation of adjudication packages, which could have led to unblinding of some EAC members when events were sent for adjudication at the EAC. The trial treatment assignment, dose or administration route was not consistently redacted from the adjudication packages by the vendor responsible for the event adjudication which could have unblinded the EAC. As a result, 7 previously adjudicated events underwent re-adjudication in PIONEER 2 by uncompromised EAC members. Additionally, staff training and preventive measures were also instituted.

The other protocol deviations are summarized in the table below.

Table 12 Important Site and Patient-Level Protocol Deviations, PIONEER 2

Category	Site-level PDs (n)	Subject-level PDs (n)			
		Screening failures	Oral semaglutide 14 mg	Empagliflozin 25 mg	Total no of subject-level PDs
Informed consent	16	13	53	54	120
Inclusion/exclusion/ randomisation criteria	-	-	6	8	14
Trial product handling	6	-	8	16	24
Treatment compliance	1	-	11	13	24
Assessment deviations	5	-	63	53	116
Other	14	2	16	19	37
Total	42	15	157	163	335

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

Source: Table 10-5 study report

Six of the PDs (all related to the eligibility criteria) led to prematurely discontinuation from the trial product.

While the trial protocol deviation which led to unblinding of the EAC is concerning, it is unlikely to have impacted efficacy findings. Additionally, the events were readjudicated by independent

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committee members, and, in the safety section, I reviewed all events send for adjudication, whether they were confirmed or not.

Table of Demographic Characteristics

The population was evenly distributed between male and female patients with a mean age of 58 years. The T2DM had an overall mean duration of 7.4 years (SD 6.1), and the mean HbA1c was 8.1%.

Generally, the baseline demographic characteristics were matched between the treatment groups. The renal function (based on baseline eGFR) was normal for 66.5% of the patients; 32.6% had mild renal impairment and 0.9% had moderate renal impairment. The mean estimated eGFR was 95 mL/min/1.73 m2 and was similar across treatment groups.

Table 13 Baseline Characteristics and Demographics – Continuous Variables PIONEER 2

	Oral sema 14 mg	Empa 25 mg	Total
Number of subjects	411	410	821
Age (years)			
N	411	410	821
Mean (SD)	57 (10)	58 (10)	58 (10)
HbA1c (%)			
N	411	410	821
Mean (SD)	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)
Duration of diabetes (years)			
N	411	410	821
Mean (SD)	7.2 (5.8)	7.7 (6.3)	7.4 (6.1)
Body weight (kg)			
N	411	410	821
Mean (SD)	91.9 (20.5)	91.3 (20.1)	91.6 (20.3)
eGFR (mL/min/1.73 m^2)			
N	411	410	821
Mean (SD)	96 (15)	95 (15)	95 (15)

The eGFR was estimated using the CKD-EPI formula.
'Baseline': defined as the latest assessment at or prior to the randomisation visit; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; N: number of subjects; SD: standard deviation.

Source: Modified from Table 10-2 CSR PIONEER 2

Reference ID: 4494348

Table 14 Baseline Characteristics and Demographics – Categorical Variables – PIONEER 2

	Oral sema 14 mg N (%)	Empa 25 mg N (%)	Total N (%)
Number of subjects	411	410	821
Age group (years)			
N	411 (100)	410 (100)	821 (100)
18 <= to < 65	306 (74.5)	300 (73.2)	606 (73.8)
65 <= to < 75	92 (22.4)	98 (23.9)	190 (23.1)
75 <= to < 85	13 (3.2)	12 (2.9)	25 (3.0)
85 <=	0	0	0
Sex			
N	411 (100)	410 (100)	821 (100)
Female	205 (49.9)	201 (49.0)	406 (49.5)
Male	206 (50.1)	209 (51.0)	415 (50.5)
Region			
N	411 (100)	410 (100)	821 (100)
Europe	221 (53.8)	204 (49.8)	425 (51.8)
North America	115 (28.0)	127 (31.0)	242 (29.5)
South America	52 (12.7)	61 (14.9)	113 (13.8)
Asia	23 (5.6)	18 (4.4)	41 (5.0)
Race			
N	411 (100)	410 (100)	821 (100)
White	355 (86.4)	353 (86.1)	708 (86.2)
Black or African American	26 (6.3)	33 (8.0)	59 (7.2)
Asian	28 (6.8)	21 (5.1)	49 (6.0)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	2 (0.5)	3 (0.7)	5 (0.6)
Ethnicity			
N	411 (100)	410 (100)	821 (100)
Hispanic or Latino	91 (22.1)	108 (26.3)	199 (24.2)
Not Hispanic or Latino	320 (77.9)	302 (73.7)	622 (75.8)
Not applicable	0	0	0
Renal function, eGFR (mL/min/1.73 m^2)			
N	411 (100)	410 (100)	821 (100)
Normal (90 <=)	278 (67.6)	268 (65.4)	546 (66.5)
Mild RI (60 <= to < 90)	130 (31.6)	138 (33.7)	268 (32.6)
Moderate RI (30 <= to < 60)	3 (0.7)	4 (1.0)	7 (0.9)
Severe RI (15 <= to < 30)	0	0	0
End-stage renal disease (< 15)	0	0	0

NA: for ethnicity values recorded as 'missing', 'not done', or 'not-available'; 'Baseline': defined as the latest assessment at or prior to the randomisation visit; 'Smoking': defined as smoking at least one cigarette or equivalent daily; The renal function categories are based on the eGFR as per CKD-EPI; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; RI: renal impairment; N: number of subjects; %: proportion of subjects.

Source: Modified from Table 10-3 CSR PIONEER 2

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

The most frequent and clinically relevant concomitant illnesses for oral semaglutide 14 mg and empagliflozin 25 mg were, respectively; obesity (26.3% and 28.5%), dyslipidemia (23.6% and 23.2%), hepatic steatosis (10.0% and 10.2%) and hypothyroidism (7.1% and 9.0%). These comorbidities were generally evenly distributed between the treatment groups.

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No clinically relevant differences across treatment groups were observed for histories of cardiovascular disease. The most frequently reported histories and risk factors of cardiovascular disease were ischemic heart disease (13.9% and 11.2%) and hypertension (72.5% and 74.4%) for oral semaglutide 14 mg and empagliflozin 25 mg, respectively.

The proportions of patients with diabetic retinopathy were 7.8% and 11.2% for oral semaglutide 14 mg, and empagliflozin 25 mg, respectively (the majority reported as non-proliferative diabetic retinopathy). At screening, the proportion of patients that had normal fundoscopy findings were similar with oral semaglutide 14 mg (left eye: 72.1% and right eye: 71.9%) and empagliflozin 25 mg (left eye: 72.5% and right eye: 71.6%). The proportions of patients with 'abnormal, not clinically significant' and 'abnormal, clinically significant' were similar across treatment groups at screening. Other diabetic complications included diabetic neuropathy (12.9% and 15.6%) and diabetic nephropathy (4.1% and 3.7%) for oral semaglutide 14 mg and empagliflozin 25 mg, respectively.

Gallbladder and GI disorders were also balanced between the treatment groups at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was monitored throughout the trial through monitoring of drug accountability. Semaglutide plasma concentrations were measured three times during the trial (weeks 4, 26, and 52).

At baseline, the reported use of concomitant medications was similar across the treatment groups with no clinically relevant differences. The most frequently used concomitant medications were HMG CoA reductase inhibitors, ACE inhibitors and platelet aggregation inhibitors excluding heparin.

A comparable number of patients had initiated rescue medication at week 26, whereas at week 52, more patients on empagliflozin 25 mg (44 patients) had initiated rescue medication compared to oral semaglutide 14 mg (31 patients).

Reference ID: 4494748

Table 15 Additional Anti-Diabetic Medication and Rescue Medication at week 26 and 52 – PIONEER 2

	Oral sema 14 mg N (%)		Empa 25 mg N (%)	
	Additional anti-diabetic medication	Rescue medication	Additional anti-diabetic medication	Rescue medication
Number of subjects in FAS	411		410	
Week 26	17 (4.1)	8 (1.9)	13 (3.2)	5 (1.2)
Sulfonylureas	8 (1.9)	3 (0.7)	5 (1.2)	2 (0.5)
Metformin	2 (0.5)	2 (0.5)	3 (0.7)	2 (0.5)
DPP-4 inhibitors	2 (0.5)		2 (0.5)	1 (0.2)
Insulins	7 (1.7)	3 (0.7)	1 (0.2)	
SGLT-2 inhibitors			3 (0.7)	
GLP-1 analogues			2 (0.5)	1 (0.2)
Week 52	52 (12.7)	31 (7.5)	56 (13.7)	44 (10.7)
Sulfonylureas	34 (8.3)	21 (5.1)	41 (10.0)	36 (8.8)
Metformin	3 (0.7)	3 (0.7)	9 (2.2)	8 (2.0)
DPP-4 inhibitors	5 (1.2)		5 (1.2)	3 (0.7)
Insulins	14 (3.5)	7 (1.7)	3 (0.7)	1 (0.2)
SGLT-2 inhibitors	3 (0.7)	1 (0.2)	4 (1.0)	
GLP-1 analogues	1 (0.2)		3 (0.7)	1 (0.2)
Thiazolininediones			1 (0.2)	

Source: Table 10-4 CSR PIONEER 2

Efficacy Results - Primary Endpoint

Change in HbA1c

At baseline, mean HbA1c levels were similar for the two treatment groups (8.1%). Superiority of oral semaglutide 14 mg vs empagliflozin 25 mg was confirmed for the primary endpoint of change from baseline in HbA1c at week 26 (treatment policy estimand).

Reference ID: 4494748

Table 16 Primary and Confirmatory Secondary Endpoints – PIONEER 2

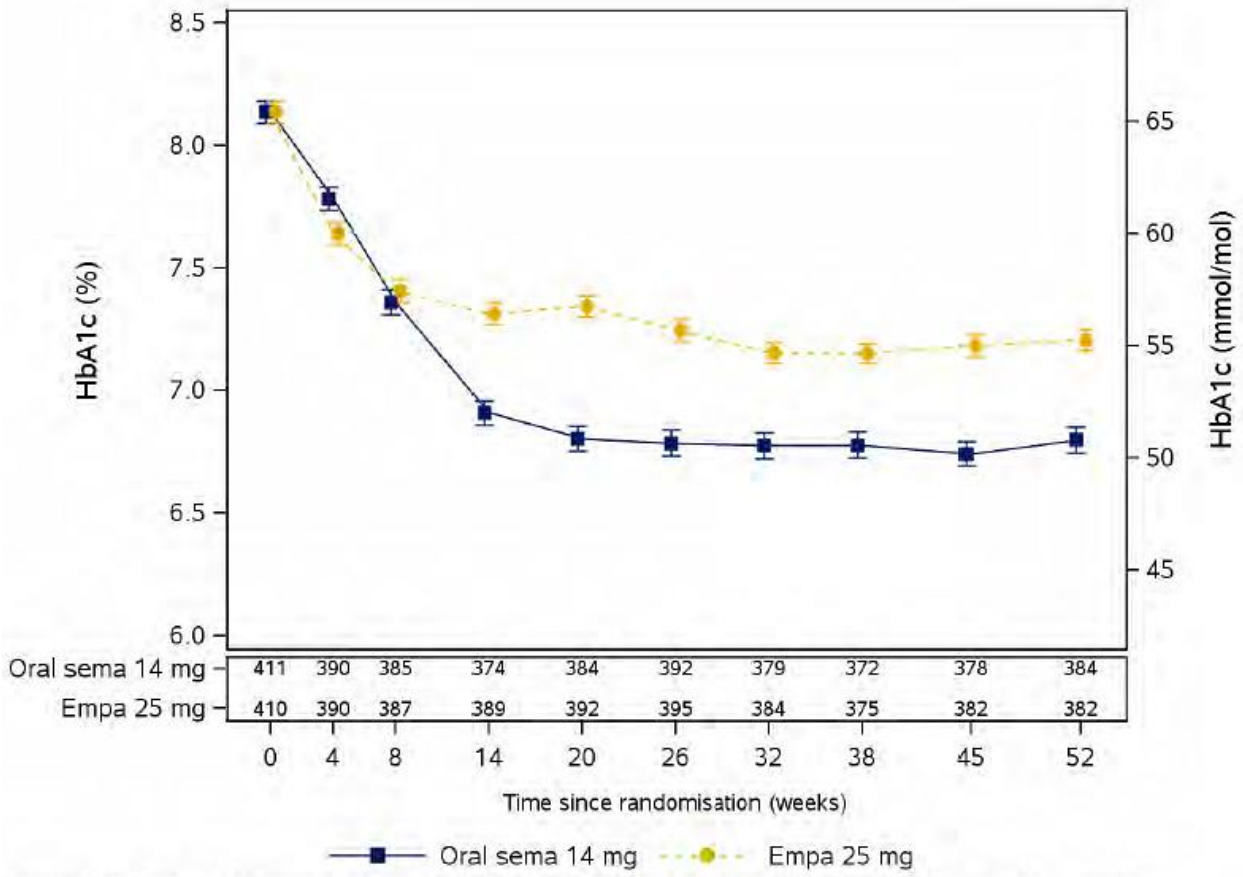
Endpoint	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoint: Change from baseline at week 26 in HbA1c (%-points)					
Oral sema 14 mg - Empa 25 mg	-0.4 [-0.6 ; -0.3]	<0.0001		Non-inferiority	Confirmed
Oral sema 14 mg - Empa 25 mg	-0.4 [-0.6 ; -0.3]	<0.0001		Superiority	Confirmed
Other confirmatory endpoints: Change from baseline at week 26 in body weight (kg)					
Oral sema 14 mg - Empa 25 mg	-0.1 [-0.7 ; 0.5]	0.7593	0.05	Superiority	Not confirmed

'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval 'p-value': unadjusted two-sided p-value for test of no difference from 0 (superiority) or for test of no difference from the non-inferiority margin (non-inferiority).

Source: Table 11-1 CSR PIONEER 2

HbA1c levels decreased from baseline to week 8 in both treatment group. From week 8 through weeks 20-26 the HbA1c levels decreased additionally with oral semaglutide 14 mg; while with empagliflozin 25 mg a plateau was reached.

Figure 7 HbA1c (% and mmol/mol) by Week – PIONEER 2



Observed data from the in-trial observation period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel represent the number of subjects contributing to the means.

Source: Figure 11-2 CSR PIONEER 2

Reference ID: 4494348

The estimated changes from baseline in HbA1c at week 26 were −1.3% with oral semaglutide 14 mg, and −0.9% with empagliflozin 25 mg.

Please see Biometrics review by Dr Robert Abugov for details regarding the FDA analyses.

Data Quality and Integrity - Reviewers' Assessment

Datasets and study documents appear adequate; I did not identify any issues.

Efficacy Results - Secondary and other relevant endpoints

Change in body weight
At baseline, the mean body weight was similar in the oral semaglutide and empagliflozin groups, 91.9 kg and 91.3 kg, respectively. The body weight decreased in both treatment groups at week 26. The observed mean reductions in body weight at week 26 were similar with oral semaglutide 14 mg (−3.9 kg) and empagliflozin 25 mg (−3.8 kg).

HbA1c treatment targets
At weeks 26 and 52, the proportions of patients who reached the AACE (≤6.5%) or ADA (<7.0%) HbA1c treatment targets were greater with oral semaglutide than with empagliflozin.

For HbA1c <7%, the proportion of patients reaching target at week 26 was 66.8% with semaglutide vs 40 % with empagliflozin, and at 52 weeks it was 66.1% and 43.2%, respectively. Similar results were obtained for HbA1C <6.5%. with 47.4% of patients on semaglutide and 17.2% of patients on empagliflozin achieving this endpoint at week 26. At week 52, 47.4% of patients on semaglutide and 21.7% of patients on empagliflozin achieved this target.

Various other secondary endpoints were explored by the applicant, but I will not discuss them in this review as they are not relevant for the prescribing information.

Dose/Dose Response

Not applicable as only one dose of semaglutide was studied.

Durability of Response

While most of the response was noticed in the first 14 weeks, the results were sustained for the remaining of the study.

Persistence of Effect

Not applicable.

Reference ID: 4494748

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.3. PIONEER 3 (4222)

6.3.1. Study Design

Overview and Objective

Study title: Efficacy and long-term safety of oral semaglutide versus sitagliptin in patients with type 2 diabetes

Primary objective: To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on glycemic control in patients with T2DM.

Secondary objectives:

- To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on body weight in patients with T2DM.

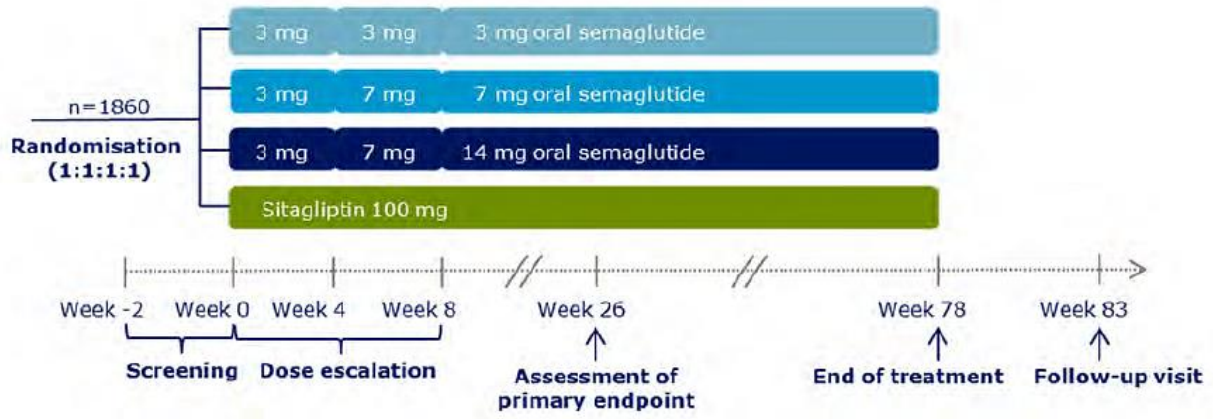
- To compare the long-term safety and tolerability of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, in patients with T2DM.

Trial Design

The trial was a 78-week, randomized, double-blind, double-dummy, active-controlled, trial with four arms comparing efficacy and safety of oral semaglutide 3 mg, 7 mg and 14 mg once-daily with sitagliptin 100 mg once-daily.

Reference ID: 4494748

Figure 8 Trial Design PIONEER 3



Source: Figure 9-1 CSR PIONEER 3

A total of 1860 adult male and female patients with T2DM were planned for enrolment.

Key Inclusion/Exclusion Criteria:
Similar to PIONEER 2 with the following difference:

- Background medication was stable daily dose of metformin (≥1500 mg or maximum tolerated dose as documented in the patient medical record) alone or in combination with SU (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in the patient medical record) within 90 days prior to the day of screening.

Dose selection/Study treatments:
Patients were randomized 1:1:1:1 to receive once-daily treatment for 78 weeks with oral semaglutide 3 mg, 7 mg or 14 mg or with sitagliptin 100 mg. The semaglutide titration and details of administration were the same for all PIONEER trials.

Dose modification/discontinuation:
Similar to PIONEER 2.

Administrative structure:
Similar to PIONEER 2.

Procedures and schedule:
Similar to PIONEER 2. The patients had in person visits at screening, randomization, weeks 4, 8, 14, 29, 26, 32, 38, 45, 52, 59, 66, 72, 78 (end of treatment), and 83 (follow-up). A telephone visit occurred at week 2.

Reference ID: 4494748

Eye examinations occurred at screening, week 52, and end of treatment.

For detailed procedures please see study protocol.

Concurrent medications:
Details of any concomitant medication were to be recorded at the first visit (screening). Changes in concomitant medication were to be recorded at each visit as they occurred. If a change was due to an AE, this was to be reported.

Upon inclusion, patients were to continue anti-diabetic pre-trial background medication throughout the entire trial. The background medication was to be maintained at the stable, pre-trial dose and frequency during the whole treatment period unless rescue medication was needed.

Treatment compliance
Compliance was assessed by monitoring of drug accountability.

Rescue medications
Rescue medication criteria based on FPG and HbA1c were applied to ensure acceptable glycemic control in all treatment groups. Patients with persistent and unacceptable hyperglycemia were to be offered treatment intensification from week 8 onwards.

FPG criteria for rescue:
- 14.4 mmol/L (260 mg/dL) from week 8 to end of week 13
- 13.3 mmol/L (240 mg/dL) from week 14 to end of week 25
- 11.1 mmol/L (200 mg/dL) from week 26 to end of treatment

In addition, a patient was to be offered rescue medication if:
- HbA1c >8.5% (69.4 mmol/mol) from week 26 to end of treatment

The rescue medication was at the investigator's discretion according to professional guidelines, with the exception that GLP-1 RAs, DPP-4 inhibitors and pramlintide were not allowed.

Patient completion, discontinuation, or withdrawal
Similar to PIONEER 2.

Study Endpoints

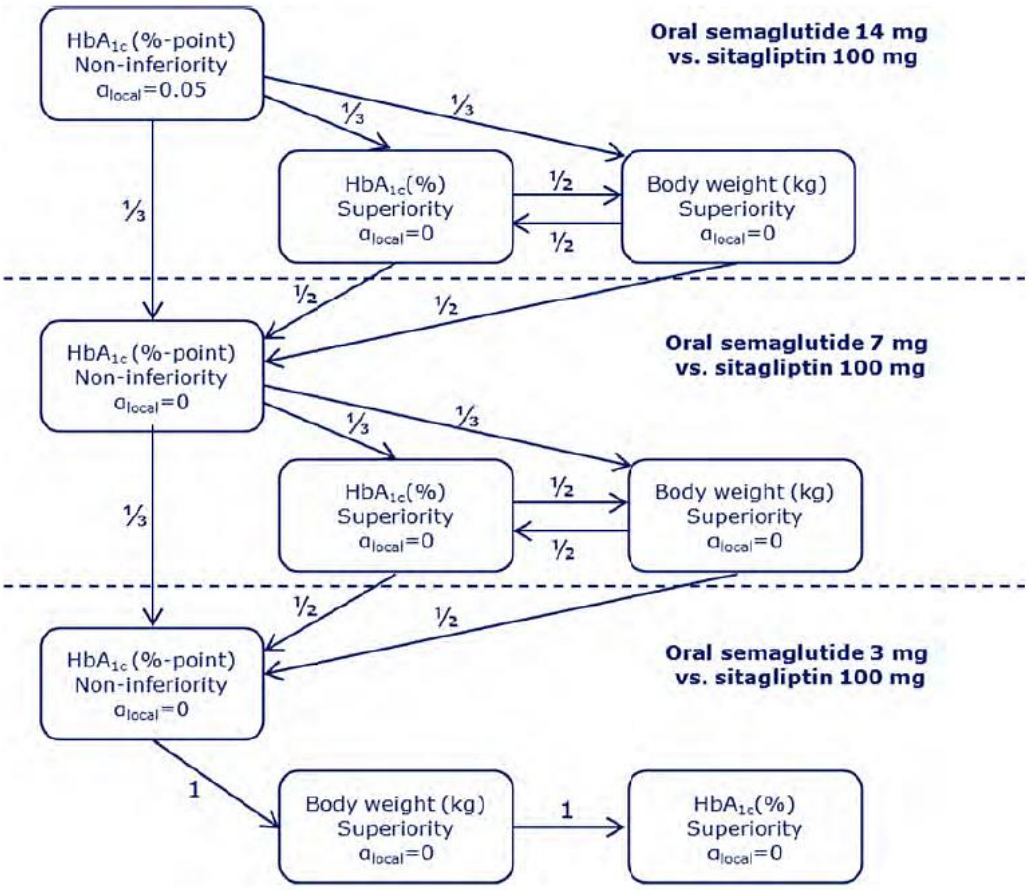
Primary and confirmatory secondary endpoints were the same as for PIONEER 2.

Statistical Analysis Plan

Reference ID: 4494748

The sample size was calculated to ensure a statistical power of at least 90% to jointly confirm HbA1c superiority of oral semaglutide 14 mg vs sitagliptin 100 mg, HbA1c superiority of oral semaglutide 7 mg vs sitagliptin 100 mg and HbA1c non-inferiority of oral semaglutide 3 mg vs sitagliptin 100 mg. All nine pre-specified confirmatory tests were assumed to be independent. Because some of the tests were expected to be positively correlated, the assumption of independence is conservative. The testing strategy is outlined in the figure below.

Figure 9 Statistical Testing Strategy PIONEER 3



The overall significance level of α = 0.05 (two-sided) was initially allocated to the hypothesis of non-inferiority of oral semaglutide 14 mg vs sitagliptin 100 mg on HbA_{1c}. If that hypothesis was confirmed, the local significance level (α-local) was reallocated to the other hypotheses in the testing strategy according to the weight (1/3, 1/2 or 1) as indicated arrows. Each hypothesis was tested at its updated local significance level (α-local) until all hypotheses had been confirmed or until no hypothesis could be confirmed.

Source: Figure 9-7 CSR PIONEER 3

Analysis sets and observation periods were the same as for the other PIONEER trials.

Protocol Amendments

Reference ID: 4494348

There were 5 amendments to the protocol as seen below.

Table 17 Amendments to the Protocol PIONEER 3

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes (for changes issued after FSFV)
1	10-Nov-2015	Before	Global	The cut off level for repeat testing of increased levels of aminotransferases has been updated from ALT/AST >10x ULN to >5x ULN. The rationale is to prompt follow-up of potential clinically significant aminotransferase levels. In addition several sections have been updated to add clarity, i.e. stratification, drug accountability, ECG reporting, antibodies and safety reporting.
2	22-Jan-2016	Before	France	Addition of two new sites and withdrawal of one site.
3	03-Mar-2016	After	France	Addition of one new site and update of investigators at two other sites.
4	02-May-2016	After	France	Addition of sub-investigators to four sites
5	14-Nov-2016	After	Global	Eye examinations and additional data collection for diabetic retinopathy were introduced along with additional minor clarifications.

First subject first visit (FSFV) took place 15-Feb-2016

Source: Table 9-13 CSR PIONEER 3

Data Quality and Integrity: Sponsor's Assurance

The investigators were required to have been trained in ICH GCP. Training of the investigators in the protocol was carried out through training sessions at the investigator meetings as well as an e-learning session, to ensure compliance and standardize performance across the trial. All principal investigators provided written commitments to comply with ICH GCP and conduct the trial per the protocol, prior to participation in the trial. The trial was monitored by Novo Nordisk by on-site visits, telephone calls and regular inspection of the eCRFs.

6.3.2. Study Results

Compliance with Good Clinical Practices

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

Financial Disclosure

Of the 261 investigators, 12 had disclosable information. See Appendix 13.3 for details.

Patient Disposition

Reference ID: 4494748

In total, 2463 patients were screened for the trial and 599 patients were screening failures, and 1864 patients were randomized to receive either oral semaglutide 3 mg (466 patients), 7 mg (466 patients), 14 mg (465 patients), or sitagliptin 100 mg (467 patients). Out of the 599 patients who failed screening, the majority (388 patients, 64.8%) failed due to nonfulfillment of HbA1c inclusion criterion.

In total, 1863 patients contributed to the FAS, and 1861 patients contributed to the SAS. In total, 1566 patients (84.0%) completed the treatment with trial product and 1758 patients (94.3%) completed the trial. A total of 5.7% of patients withdrew from the trial for the following reasons; lost to follow-up, withdrawal by patient and other reasons (including death). More patients in the oral semaglutide groups withdrew from the trial; oral semaglutide 3 mg (7.1%), oral semaglutide 7 mg (6.4%) and oral semaglutide 14 mg (5.8%) compared to 3.4% in the sitagliptin 100 mg group.

The proportions of patients who completed the treatment without receiving rescue medication were 52.1%, 64.6% and 72.0% with oral semaglutide 3 mg, 7 mg and 14 mg, respectively, and 60.6% with sitagliptin 100 mg.

A total of 298 patients (16.0%) discontinued trial product prematurely, primarily due to the following reasons: adverse events (5.4−11.6%), patient withdrawal from trial (0.4−2.6%), violation of inclusion or exclusion criteria (0.6−1.1%) and ‘Other’ reasons (4.9−7.3%).

Reference ID: 4494748

Table 18 Patient Disposition Summary PIONEER 3

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Sita 100 mg N (%)	Total N (%)
Screened					2463
Screening failures					599 (24.3)
Randomised	466	466	465	467	1864
Exposed	466 (100)	464 (99.6)	465 (100)	466 (99.8)	1861 (99.8)
Analysis sets					
Full analysis set	466 (100)	465 (99.8)	465 (100)	467 (100)	1863 (99.9)
Safety analysis set	466 (100)	464 (99.6)	465 (100)	466 (99.8)	1861 (99.8)
Per protocol analysis set	426 (91.4)	430 (92.3)	422 (90.8)	440 (94.2)	1718 (92.2)
Treatment completers [1]	388 (83.3)	396 (85.0)	376 (80.9)	406 (86.9)	1566 (84.0)
Without rescue medication	243 (52.1)	301 (64.6)	335 (72.0)	283 (60.6)	1162 (62.3)
With rescue medication	145 (31.1)	95 (20.4)	41 (8.8)	123 (26.3)	404 (21.7)
Premature trial product discont.					
- primary reason	78 (16.7)	70 (15.0)	89 (19.1)	61 (13.1)	298 (16.0)
Exposed					
Adverse event(s)	26 (5.6)	28 (6.0)	54 (11.6)	25 (5.4)	133 (7.1)
Violation of in-/excl. crit.	5 (1.1)	5 (1.1)	3 (0.6)	3 (0.6)	16 (0.9)
Intension of becoming pregnant	0	1 (0.2)	0	0	1 (0.1)
Participation in another CT [2]	0	1 (0.2)	0	1 (0.2)	2 (0.1)
Calcitonin value >= 100 ng/L	0	0	1 (0.2)	0	1 (0.1)
Subject withdrawal from trial	12 (2.6)	6 (1.3)	8 (1.7)	2 (0.4)	28 (1.5)
Pregnancy	1 (0.2)	0	0	0	1 (0.1)
Other	34 (7.3)	27 (5.8)	23 (4.9)	29 (6.2)	113 (6.1)
Not exposed					
Violation of in-/excl. crit.	0	1 (0.2)	0	1 (0.2)	2 (0.1)
Other	0	1 (0.2)	0	0	1 (0.1)
Trial completers [3]	433 (92.9)	436 (93.6)	438 (94.2)	451 (96.6)	1758 (94.3)
Completed treatment	387 (83.0)	395 (84.8)	374 (80.4)	405 (86.7)	1561 (83.7)
Discontinued trial product	46 (9.9)	41 (8.8)	64 (13.8)	46 (9.9)	197 (10.6)
Withdrawal from trial					
- primary reason	33 (7.1)	30 (6.4)	27 (5.8)	16 (3.4)	106 (5.7)
Lost to follow-up	9 (1.9)	7 (1.5)	7 (1.5)	5 (1.1)	28 (1.5)
Withdrawal by subject	18 (3.9)	18 (3.9)	17 (3.7)	8 (1.7)	61 (3.3)
Other	6 (1.3)	5 (1.1)	3 (0.6)	3 (0.6)	17 (0.9)
Died	5 (1.1)	4 (0.9)	1 (0.2)	3 (0.6)	13 (0.7)

'[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'primary reason': according to the end-of-trial form; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product; N: number of subjects; %: proportion of randomised subjects except for screening failures where it is proportion of screened subjects.

Source: Table 10-1 CSR PIONEER 3

Reference ID: 4494348

The proportion of patients who prematurely discontinued trial product due to AEs was greater with oral semaglutide 14 mg (11.6%) than with oral semaglutide 3 mg (5.6%), oral semaglutide 7 mg (6.0%) and sitagliptin 100 mg (5.4%). Gastrointestinal AEs were the most frequently reported events which led to premature trial product discontinuation, and more patients discontinued trial product due to gastrointestinal AEs with oral semaglutide 14 mg (6.9%) than with oral semaglutide 3 mg (2.4%), oral semaglutide 7 mg (3.4%) and sitagliptin 100 mg (2.6%).

Protocol Violations/Deviations

In total, 907 important PDs were disclosed; the PDs comprised 2 trial-level PDs, 2 country-level PDs, 77 site-level PDs and 826 patient-level PDs.

One trial-level deviation belonged to the 'Assessment deviation (incl. lab)' category and concerned the reporting of body weight measurements with precisions less than the one specified in the trial protocol (0.1 kg/pound) at some trial sites. This occurred due to use of scales with a precision of 0.5 kg/pound or rounding off to the nearest half or whole kg/pound by the site staff. The PD was not considered to have had any impact on the data interpretation.

The second trial-level PD belonged to the 'Incl./Excl./Rand. Criteria' category and concerned violation of stratification criteria. This occurred due to an IWRS system error which led to incorrect stratification of 8 patients. These patients were randomized according to the strata decided at screening, instead of the eligibility criteria information available before the randomization.

One country level PD belonged to the 'Informed consent' category and concerned an error in the patient information and informed consent form for United Kingdom. It was incorrectly stated that blood samples instead of urine were to be used for pregnancy testing. During the study, all pregnancy tests were conducted using urine samples.

The second country-level PD belonged to the 'Other' category and concerned late distribution of the Council for International Organizations of Medical Sciences safety reports. Due to an administrative error, 3 safety reports were sent late to the active sites in the USA. No safety concerns were reported because of this.

Site and patient-level deviations are summarized in the table below:

Reference ID: 4494748

Table 19 Summary of Important Site and Patient-Level Protocol Deviations PIONEER 3

Category	Site-level PDs (n)	Subject-level PDs (n)					
		Screening failures	Oral sema 3 mg	Oral sema 7 mg	Oral sema 14 mg	Sitagliptin 100 mg	Total no of subject-level PDs
Informed consent	11	42	37	45	44	58	226
Inclusion/exclusion/ randomisation criteria	1	3	16	22	15	15	71
Trial product handling	12	-	22	15	25	30	92
Treatment compliance	1	-	32	22	35	21	110
Assessment deviations	4	-	45	36	47	33	161
Discontinuation criteria	-	-	1	1	-	1	3
Other	48	4	37	34	47	41	163
Total	77	49	190	175	213	199	825

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

Source: Table 10-5 study report

No significant differences were observed between the treatment arms regarding PDs.

Considering that this was a relatively large study, it is unlikely that these PDs impacted the trial results, or patient safety.

Table of Demographic Characteristics

The demographic and baseline characteristics were generally similar across treatment groups. The mean age was around 58 years and more males were represented (52.8%) compared to females (47.2%). All patients had T2DM with an overall mean duration of 8.6 years. The overall mean HbA1c was 8.3%. The trial was conducted in 14 countries; the countries with most sites and patients were United States (538 patients) and Japan (207 patients). Most patients were White (71.1%) and the treatment groups were similar with regards to race and ethnicity.

The mean eGFR was 96 mL/min/1.73 m2 and eGFR values were similar across treatment groups; 70.5% of the patients had normal renal function; 28.3% had mild renal impairment and 1% had moderate renal impairment.

Reference ID: 4494348

Table 20 Demographics and Baseline Characteristics for Continuous Variables – PIONEER 3

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Sita 100 mg N (%)	Total N(%)
Number of subjects	466	465	465	467	1863
Age (years)					
N	466	465	465	467	1863
Mean (SD)	58 (10)	58 (10)	57 (10)	58 (10)	58 (10)
HbA_{1c} (%)					
N	466	465	465	467	1863
Mean (SD)	8.3 (1.0)	8.4 (1.0)	8.3 (0.9)	8.3 (0.9)	8.3 (0.9)
Duration of diabetes (years)					
N	466	465	465	467	1863
Mean (SD)	8.4 (6.1)	8.3 (5.8)	8.7 (6.1)	8.8 (6.0)	8.6 (6.0)
Body weight (kg)					
N	466	465	465	467	1863
Mean (SD)	91.6 (22.0)	91.3 (20.8)	91.2 (21.7)	90.9 (21.0)	91.2 (21.4)
eGFR (mL/min/1.73 m^2)					
N	466	465	465	467	1863
Mean (SD)	96 (15)	96 (16)	95 (16)	96 (15)	96 (16)

The eGFR was estimated using the CKD-EPI formula.'Baseline': defined as the latest assessment at or prior to the randomisation visit; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; N: number of subjects; SD: standard deviation.

Source: Adapted from Table 10-2 CSR PIONEER 3

Reference ID: 4494348

Table 21 Demographics and Baseline Characteristics for Categorical Variables – PIONEER 3

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Sita 100 mg N (%)	Total N(%)
Number of subjects	466	465	465	467	1863
Age group (years)					
N	466 (100)	465 (100)	465 (100)	467 (100)	1863 (100)
18 <= to < 65	339 (72.7)	335 (72.0	342 (73.5)	346 (74.1)	1362 (73.1)
65 <= to < 75	107 (23.0)	113 (24.3)	109 (23.4)	106 (22.7)	435 (23.3)
75 <= to < 85	20 (4.3)	17 (3.7)	14 (3.0)	15 (3.2)	66 (3.5)
85 <=	0	0	0	0	0
Sex					
N	466 (100)	465 (100)	465 (100)	467 (100)	1863 (100)
Female	212 (45.5)	220 (47.3)	218 (46.9)	229 (49.0)	879 (47.2)
Male	254 (54.5)	245 (52.7)	247 (53.1)	238 (51.0)	984 (52.8)
Region					
N	466 (100)	465 (100)	465 (100)	467 (100)	1863 (100)
Europe	185 (39.7)	186 (40.0)	181 (38.9)	186 (39.8)	738 (39.6)
North America	139 (29.8)	134 (28.8)	134 (28.8)	131 (28.1)	538 (28.9)
South America	57 (12.2)	56 (12.0)	56 (12.0)	67 (14.3)	236 (12.7)
Africa	33 (7.1)	37 (8.0)	43 (9.2)	31 (6.6)	144 (7.7)
Asia	52 (11.2)	52 (11.2)	51 (11.0)	52 (11.1)	207 (11.1)
Race					
N	466 (100)	465 (100)	465 (100)	467 (100)	1863 (100)
White	344 (73.8)	330 (71.0)	317 (68.2)	333 (71.3)	1324 (71.1)
Black or African American	38 (8.2)	38 (8.2)	45 (9.7)	39 (8.4)	160 (8.6)
Asian	56 (12.0)	69 (14.8)	61 (13.1)	59 (12.6)	245 (13.2)
American Indian or Alaska Native	4 (0.9)	3 (0.6)	5 (1.1)	6 (1.3)	18 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	0	0	1 (<0.1)
Other	13 (2.8)	11 (2.4)	20 (4.3)	12 (2.6)	56 (3.0)
NA*	10 (2.1)	14 (3.0)	17 (3.7)	18 (3.9)	59 (3.2)
Ethnicity					
N	466 (100)	465 (100)	465 (100)	467 (100)	1863 (100)
Hispanic or Latino	76 (16.3)	77 (16.6)	75 (16.1)	93 (19.9)	321 (17.2)
Not Hispanic or Latino	385 (82.6)	378 (81.3)	377 (81.1)	366 (78.4)	1506 (80.8)
NA**	5 (1.1)	10 (2.2)	13 (2.8)	8 (1.7)	36 (1.9)
Renal function, eGFR (mL/min/1.73 m^2)					
N	466 (100)	465 (100)	465 (100)	467 (100)	1863 (100)
Normal (90 <=)	329 (70.6)	326 (70.1)	324 (69.7)	335 (71.7)	1314 (70.5)
Mild RI (60 <= to < 90)	130 (27.9)	134 (28.8)	133 (28.6)	131 (28.1)	528 (28.3)
Moderate RI (30 <= to < 60)	7 (1.5)	5 (1.1)	6 (1.3)	1 (0.2)	19 (1.0)
Severe RI (15 <= to < 30)	0	0	1 (0.2)	0	1 (<0.1)
End-stage renal disease (< 15)	0	0	1 (0.2)	0	1 (<0.1)

NA*: race is recorded as 'NA' for Brazil and France; NA**: ethnicity is recorded as 'NA' for France. NA: for ethnicity values recorded as 'missing', 'not done', or 'not-available'; 'Baseline': defined as the latest assessment at or prior to the randomisation visit; 'Smoking': defined as smoking at least one cigarette or equivalent daily; The renal function categories are based on the eGFR as per CKD-EPI; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; RI: renal impairment; N: number of subjects; %: proportion of subjects.
Source: Adapted from Table 10-3 CSR PIONEER 3

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

Medical history and concomitant illnesses were relatively balanced between the treatment groups.

Reference ID: 4494748

The most frequent and clinically relevant concomitant illnesses for all treatment groups were; dyslipidemia (28.4–30.2%), obesity (25.6–30.5%), gastrointestinal disorders (17.6–20.6%), eye disorders (21.2–27.7%), hepatic steatosis (10.1–12.0%), hypothyroidism (6.2–7.7%), neoplasms (5.2–6.5%), vascular disorders (8.8–13.1%) and psychiatric disorders (16.3–17.6%) of which depression constituted 6.9–10.1%.

At baseline, diabetic retinopathy was present in 15.7–17.3% of patients, with no relevant differences across treatment groups. Other diabetic complications included diabetic neuropathy (21.9–27.6%) and diabetic nephropathy (8.6–11.2%), with no relevant differences across treatment groups.

The most frequently reported cardiovascular diseases were: hypertension (70.5–76.8%), ischemic heart disease (15.7–17.3%) and heart failure (7.1–9.0%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

At baseline, 100% of patients were on metformin and 46.9−47.3% of patients were on metformin + SU.

Other most frequently used concomitant medications ongoing at time of randomization were HMG-CoA reductase inhibitors (51.0−53.4%), angiotensin-converting-enzyme (ACE) inhibitors (28.4−36.6%), platelet aggregation inhibitors excluding heparin (27.5−33.1%), beta blockers (17.6−20.8%) and angiotensin II antagonists (17.6−20.2%).

Additional and rescue diabetes medication use is outlined in the table below.

Reference ID: 4494748

Table 22 Additional Concomitant Anti-Diabetic Medication and Rescue Medication at Weeks 26, 52 and 78

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Sita 100 mg N (%)	Total N (%)
Number of subjects	466	465	465	467	1863
WEEK 26					
ADD. ANTI-DIABETIC MEDICATION	33 (7.1)	20 (4.3)	15 (3.2)	20 (4.3)	88 (4.7)
RESCUE MEDICATION	25 (5.4)	11 (2.4)	5 (1.1)	13 (2.8)	54 (2.9)
WEEK 52					
ADD. ANTI-DIABETIC MEDICATION	137 (29.4)	86 (18.5)	51 (11.0)	111 (23.8)	385 (20.7)
RESCUE MEDICATION	121 (26.1)	73 (15.7)	31 (6.7)	94 (20.1)	319 (17.1)
WEEK 78					
ADD. ANTI-DIABETIC MEDICATION	179 (38.4)	119 (25.6)	75 (16.1)	148 (31.7)	521 (28.0)
RESCUE MEDICATION	160 (34.3)	103 (22.2)	47 (10.1)	129 (27.6)	439 (23.6)

'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product. N: number of subjects; %: proportion of subjects; ADD: additional.

Source: Table 10-4 CSR PIONEER 3

Efficacy Results - Primary Endpoint

Change in HbA1c

At baseline, the HbA1c levels were similar between the semaglutide and sitagliptin arms. The results of the primary and confirmatory secondary endpoints are summarized below. At week 26, the superiority of the 7 and 14 mg doses of semaglutide vs sitagliptin were confirmed for both HbA1c and weight.

Reference ID: 4494748

Table 23 Primary and confirmatory secondary endpoints – PIONEER 3

Endpoint	Estimate [95% CI]	p-value	Hypothesis	Conclusion
Primary endpoint: HbA_{1c} (%-points) change from baseline at week 26				
Oral sema 14 mg - Sita 100 mg	-0.5 [-0.6 ; -0.4]	<0.0001	Non-inferiority	Confirmed
Oral sema 14 mg - Sita 100 mg	-0.5 [-0.6 ; -0.4]	<0.0001	Superiority	Confirmed
Oral sema 7 mg - Sita 100 mg	-0.2 [-0.4 ; -0.1]	<0.0001	Non-inferiority	Confirmed
Oral sema 7 mg - Sita 100 mg	-0.3 [-0.4 ; -0.1]	<0.0001	Superiority	Confirmed
Oral sema 3 mg - Sita 100 mg	0.2 [0.1 ; 0.3]	0.0856*	Non-inferiority	Not confirmed
Oral sema 3 mg - Sita 100 mg	0.2 [0.0 ; 0.3]	0.0080	Superiority	Not tested
Other confirmatory endpoints: Body weight (kg) change from baseline at week 26				
Oral sema 14 mg - Sita 100 mg	-2.5 [-3.0 ; -2.0]	<0.0001	Superiority	Confirmed
Oral sema 7 mg - Sita 100 mg	-1.6 [-2.0 ; -1.1]	<0.0001	Superiority	Confirmed
Oral sema 3 mg - Sita 100 mg	-0.6 [-1.1 ; -0.1]	0.0185	Superiority	Not tested

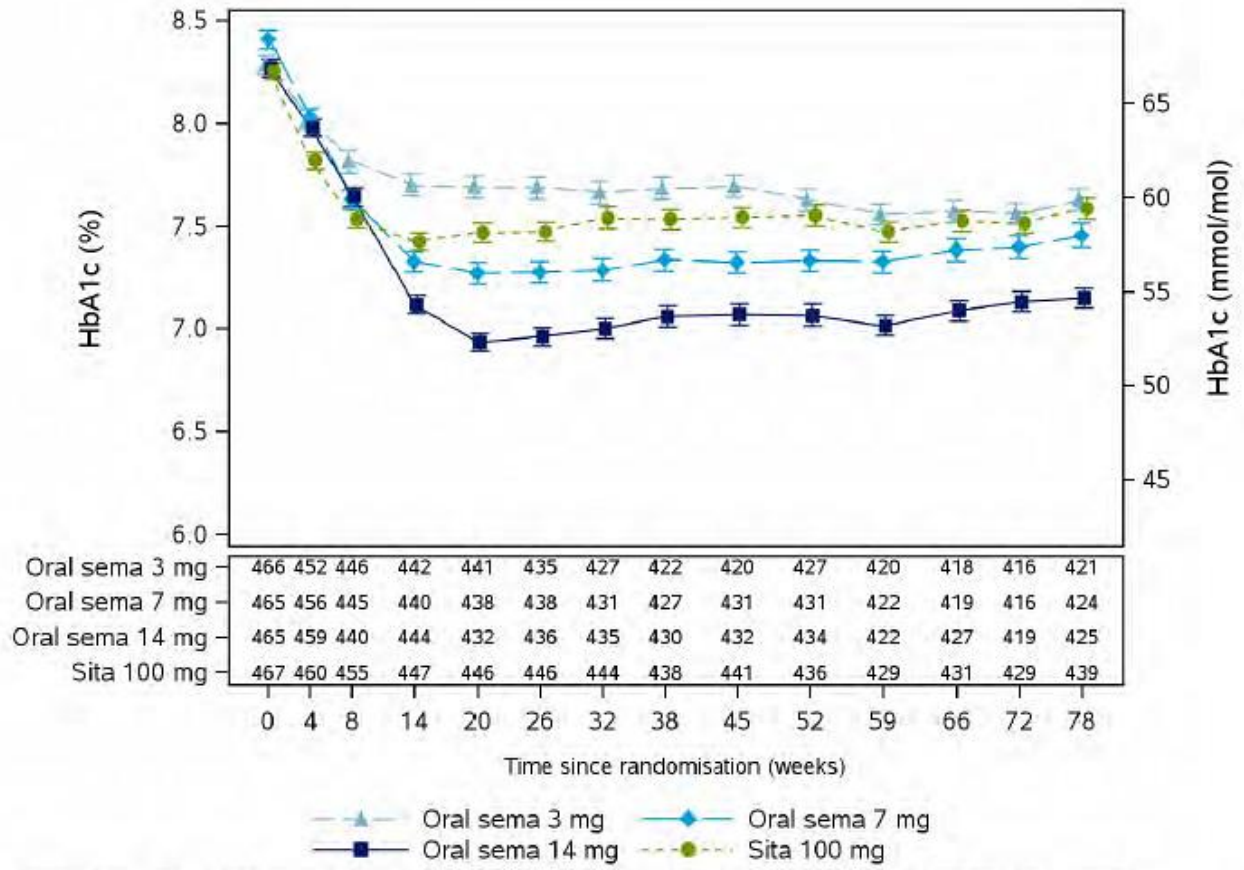
'alpha': *0.05 local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval 'p-value': unadjusted two-sided p-value for test of no difference from 0 (superiority) or for test of no difference from the non-inferiority margin (non-inferiority).

Source: Table 11-1 CSR PIONEER 3

The observed changes from baseline at week 26 were −0.6, −1.1 and −1.3 % with oral semaglutide 3 mg, 7 mg and 14 mg, respectively, and −0.8 % with sitagliptin 100 mg. HbA1c levels decreased from baseline through to week 14 in all treatment groups, and then the changes were sustained for the remaining of the trial.

Reference ID: 4494748

Figure 10 HbA1c (% and mmol/mol) by Week – PIONEER 3



Observed data from the in-trial observation period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel represent the number of subjects contributing to the means.

Source: Figure 11-1 CSR PIONEER 3

The applicant also performed sensitivity analyses, and the results were supportive of the primary analysis.

Data Quality and Integrity - Reviewers' Assessment

The datasets and the study documents were adequate. I did not identify any quality or integrity issues.

Efficacy Results - Secondary and other relevant endpoints

<u>Change in body weight</u>

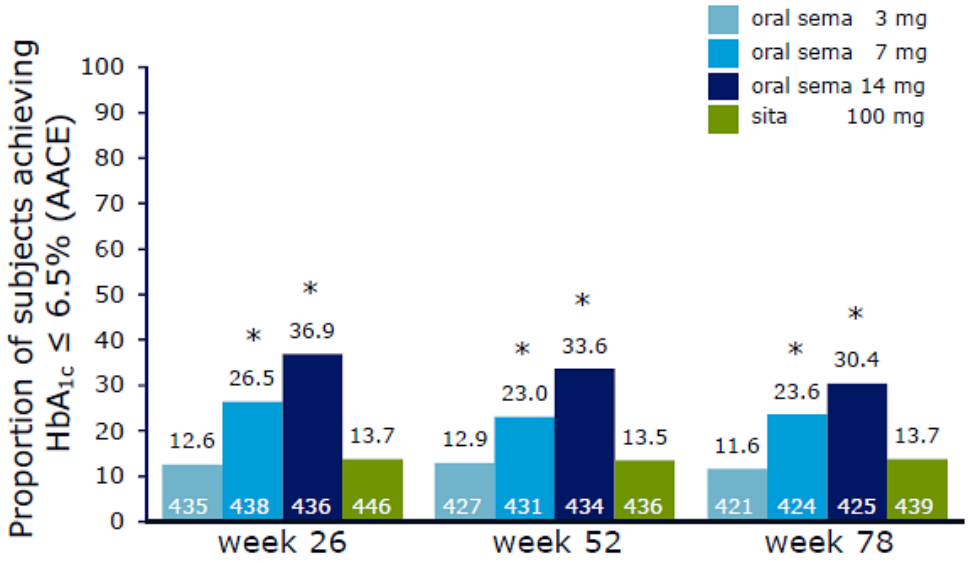
At baseline, body weight was similar between the treatment groups. The mean body weight decreased for all treatment groups at week 26 and was sustained for the remainder of the trial. The estimated changes from baseline for body weight at week 26 were −1.2, −2.2 and −3.1 kg with oral semaglutide 3 mg, 7 mg and 14 mg, respectively, and −0.6 kg with sitagliptin.

Reference ID: 4494748

HbA1c targets

The observed proportions of patients achieving the AACE HbA1c treatment target (≤ 6.5%) were greater with oral semaglutide 7 mg and 14 mg than with sitagliptin week 26, 52 and 78. The same was true of the ADA target of HbA1C <7%.

Figure 11 Proportion of Patients Achieving HbA1c ≤ 6.5% at Week 26, 52 and 78 – PIONEER 3

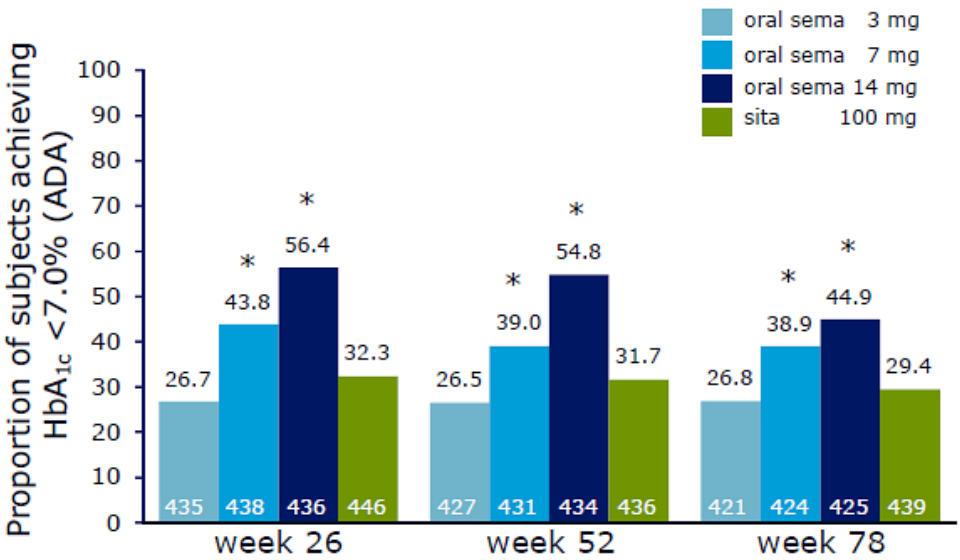


Observed data for the in-trial observation period. The odds were statistically significantly in favour of oral semaglutide (*) at a 5% significance level. Numbers shown in bottom of bar charts represent the number of subjects contributing to the proportions. AACE: American Association of Clinical Endocrinologists.

Source: Figure 11-9 CSR PIONEER 3

Reference ID: 4494348

Figure 12 Proportion of Patients Achieving HbA1c < 7.0% at Week 26, 52 and 78 – PIONEER 3



Observed data for the in-trial observation period. The odds were statistically significantly in favour of oral semaglutide (*) at a 5% significance level. Numbers shown in bottom of bar charts represent the number of subjects contributing to the proportions. ADA: American Diabetes Association.

Source: Figure 11-10 CSR PIONEER 3

Dose/Dose Response

A dose-response for HbA1c reduction was seen for semaglutide in this trial.

Durability of Response

In all treatment arms, HbA1c decreased from baseline until weeks 14, and was sustained for the remainder of the trial.

Persistence of Effect

Not applicable. Effect after discontinuation of study drug was not assessed.

Additional Analyses Conducted on the Individual Trial

The applicant conducted various sensitivity analyses, all supportive of the primary analysis.

6.4. PIONEER 4 (4224)

6.4.1. Study Design

Overview and Objective

Reference ID: 4494748

Title: Efficacy and safety of oral semaglutide versus liraglutide and versus placebo in patients with type 2 diabetes mellitus.

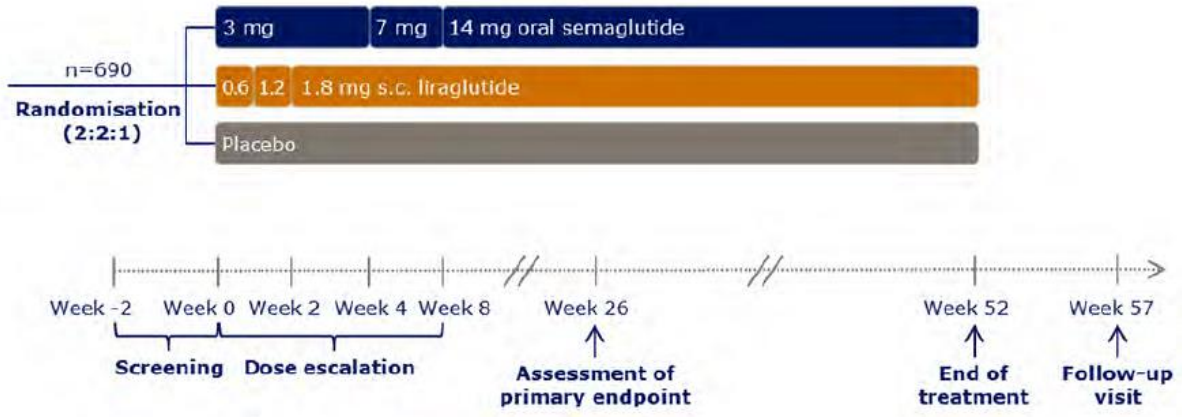
Primary objective
To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a SGLT-2 inhibitor, on glycemic control in patients with T2DM.

Secondary objective
- To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a SGLT-2 inhibitor, on body weight in patients with T2DM.
- To compare the safety and tolerability of once-daily dosing of 14 mg oral semaglutide versus 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a SGLT-2 inhibitor, in patients with T2DM.

Trial Design

This was a multinational, multi-center, randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group efficacy and safety trial comprised of a 52-week treatment period (including an 8-week dose escalation period) and a 5-week follow-up period.

Figure 13 Trial Design PIONEER 4



Source: Figure 9-1 CSR PIONEER 4

A total of 690 patients were planned for enrollment.

Key inclusion/exclusion criteria:
Similar to PIONEER 2 with the following differences:

- HbA1C 7-9.5 both inclusive

Reference ID: 4494348

- Stable daily dose of metformin (≥1500 mg or maximum tolerated dose as documented in the patient medical record) alone or in combination with a stable daily dose of a SGLT-2 inhibitor for at least 90 days prior to the day of screening (fixed-dose combinations are allowed).

Dose selection/Study treatments:
Patients were randomized 2:2:1 to receive once-daily treatment for 52 weeks with oral semaglutide 14 mg, liraglutide 1.8 mg (s.c. injection) or placebo, respectively. The trial included dose escalation for both oral semaglutide and liraglutide. Semaglutide administration details were the same in all PIONEER trials.

Dose modification/discontinuation:
Similar to PIONEER 2

Administrative structure:
Similar to PIONEER 2.

Procedures and schedule:
The patients had in person visits at screening, randomization, weeks 4, 8, 14, 20, 26, 32, 38, 45, 52 (end of treatment), and 57 (follow up). One phone visit occurred at week 2.

Of note, fundoscopy or fundus photography was to be performed at randomization, and end of treatment.

Detailed study proceedings can be found in the study protocol submitted as part of this NDA.

Rescue medication:
The following rescue criteria were set for the study, from week 8 onward.

- FPG values (including SMPG; at central laboratory) exceeding 240 mg/dL from week 8 to end of week 13
- FPG values (including SMPG; at central laboratory) exceeding 200 mg/dL from week 14 to end of treatment
- HbA1c (at central laboratory) >8.5 % from week 26 to end of treatment

Rescue medication was to be prescribed at the investigator's discretion according to guidelines. GLP-1 RAs, DPP-4 inhibitors and amylin analogues were not allowed as rescue medication.

Treatment compliance:
Patient compliance was assessed by monitoring of drug accountability.

Reference ID: 4494748

Study Endpoints

The primary and secondary confirmatory endpoint were the same as for PIONEER 1.

Statistical Analysis Plan

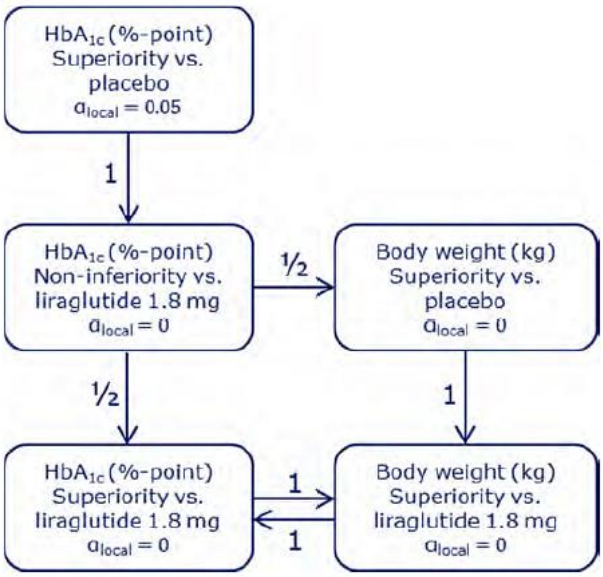
The sample size was calculated to ensure a statistical power of at least 90% to confirm four out of the five pre-specified confirmatory hypotheses, namely:

- HbA1c superiority of oral semaglutide 14 mg vs. placebo
- HbA1c non-inferiority of oral semaglutide 14 mg vs. liraglutide 1.8 mg (margin 0.4%)
- Body weight superiority of oral semaglutide 14 mg vs. placebo
- Body weight superiority of oral semaglutide 14 mg vs. liraglutide 1.8 mg

A total of 690 patients were planned to be randomized.

The testing strategy is outlined in the figure below.

Figure 14 Testing Strategy PIONEER 4



The overall significance level of α = 0.05 (two-sided) was initially allocated to the hypothesis of superiority of oral semaglutide 14 mg vs. placebo on change from baseline at week 26 in HbA_{1c}. If a hypothesis was confirmed, the local significance level (α-local) was reallocated to the other hypotheses in the testing strategy according to the indicated weight (½ or 1) of the arrows. Each hypothesis was tested at its updated local significance level (α-local) until all hypotheses had been confirmed or until no hypothesis could be confirmed.
Source: Figure 9-7 CSR PIONEER 4

Please see Biometrics review by Dr Robert Abugov for comments and the FDA's statistical analyses.

Reference ID: 4494348

The analysis populations and treatment periods were the same as for the previously reviewed PIONEER trials.

Protocol Amendments

There was one substantial amendment to the protocol, with the following changes:

- Introduction of additional eye examinations and additional data collection on diabetic retinopathy
- Added bicarbonate as a part of the biochemistry laboratory assessment
- Added text to highlight investigator's responsibility in ensuring evaluation and management of certain risk factors and complications
- Clarification of the criteria for completion, withdrawal and lost to follow-up
- Other minor corrections and clarifications

Data Quality and Integrity: Sponsor's Assurance

The investigators were trained in GCP. The trial was monitored as an internal safety committee performed ongoing safety surveillance throughout the trial.

6.4.2. Study Results

Compliance with Good Clinical Practices

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

Financial Disclosure

Of the 381 investigators participating in the trial, 13 had disclosable financial information. See Appendix 13.3 for details.

Patient Disposition

In total, 950 patients were screened, and 239 patients failed screening; thus, 711 patients were randomized 2:2:1 to receive once-daily oral semaglutide 14 mg (285 patients), liraglutide 1.8 mg (284 patients), or placebo (142 patients), respectively. All randomized patients were exposed to trial product; thus, the FAS and SAS are identical. Of the 239 patients who failed screening, the majority (158 patients, 66.1%) failed due to nonfulfillment of HbA1c inclusion criterion.

In total, 614 patients (86.4%) completed the treatment with trial product and 685 patients (96.3%) completed the trial. The proportion of patients completing treatment was lower but somewhat similar with oral semaglutide (84.6%) compared with liraglutide (87.3%) and placebo (88.0%).

Reference ID: 4494748

The proportion of patients completing the treatment without receiving rescue medication was higher in the oral semaglutide (78.2%) and liraglutide (81.3%) groups compared with the placebo group (58.5%).

Table 24 Patients Disposition PIONEER 4

	Oral sema 14 mg N (%)	Lira 1.8 mg N (%)	Placebo N (%)	Total N (%)
Screened				950
Screening failures				239 (25.2)
Randomised	285	284	142	711
Exposed	285 (100)	284 (100)	142 (100)	711 (100)
Analysis sets				
Full analysis set	285 (100)	284 (100)	142 (100)	711 (100)
Safety analysis set	285 (100)	284 (100)	142 (100)	711 (100)
Per protocol analysis set	259 (90.9)	261 (91.9)	130 (91.5)	650 (91.4)
Treatment completers [1]	241 (84.6)	248 (87.3)	125 (88.0)	614 (86.4)
Without rescue medication	223 (78.2)	231 (81.3)	83 (58.5)	537 (75.5)
With rescue medication	18 (6.3)	17 (6.0)	42 (29.6)	77 (10.8)
Premature trial product discontinuation - primary reason	44 (15.4)	36 (12.7)	17 (12.0)	97 (13.6)
Exposed				
Adverse event(s)	33 (11.6)	27 (9.5)	6 (4.2)	66 (9.3)
Violation of inclusion and/or exclusion criteria	1 (0.4)	0	0	1 (0.1)
Intention of becoming pregnant	0	0	0	0
Participation in another clinical trial [2]	0	1 (0.4)	0	1 (0.1)
Calcitonin value >=100 ng/L	0	0	0	0
Subject withdrawal from trial	3 (1.1)	3 (1.1)	3 (2.1)	9 (1.3)
Pregnancy	0	0	0	0
Other	7 (2.5)	5 (1.8)	8 (5.6)	20 (2.8)
Trial completers [3]	277 (97.2)	274 (96.5)	134 (94.4)	685 (96.3)
Completed treatment	241 (84.6)	248 (87.3)	124 (87.3)	613 (86.2)
Discontinued trial product	36 (12.6)	26 (9.2)	10 (7.0)	72 (10.1)
Withdrawal from trial - primary reason	8 (2.8)	10 (3.5)	8 (5.6)	26 (3.7)
Lost to follow-up	0	1 (0.4)	4 (2.8)	5 (0.7)
Withdrawal by subject	5 (1.8)	5 (1.8)	3 (2.1)	13 (1.8)
Other	3 (1.1)	4 (1.4)	1 (0.7)	8 (1.1)
Died	3 (1.1)	4 (1.4)	1 (0.7)	8 (1.1)

'[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'primary reason': according to the end-of-trial form; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product; N: number of subjects; %: proportion of randomised subjects except for screening failures where it is proportion of screened subjects.

Source: Table 10-1 CSR PIONEER 4

Premature trial product discontinuation in the oral semaglutide and liraglutide groups mainly occurred during the dose escalation period.

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The proportion of patients who prematurely discontinued trial product due to AEs was larger with oral semaglutide (11.6%) compared with liraglutide (9.5%) and placebo (4.2%). GI AEs were the event type that most frequently led to premature trial product discontinuation; the proportion of patients who prematurely discontinued trial product due to GI AEs was larger with oral semaglutide (7.7%) compared with liraglutide (6.0%) and placebo (2.1%).

Protocol Violations/Deviations

There were 310 important PDs in total; the PDs comprised 2 trial-level PDs, 3 country-level PDs 37 site-level PDs and 268 patient-level PDs.

One trial-level PD concerned the reporting of body weight measurements with precisions less than that specified in the trial protocol (0.1 kg/pounds) at some trial sites. This occurred due to use of scales with a precision of 0.5 kg/pound or due to rounding off to the nearest half or whole kg/pound by the site staff. The PD was not considered to have had any impact on the data interpretation.

The other trial-level PD concerned incorrectly performed bicarbonate testing which resulted in reporting of bicarbonate results below the normal range. The central lab inadvertently analyzed bicarbonate after the last biochemistry analyte in a separate step that included reopening of the tube lid. Bicarbonate dissipates from the tube and therefore should have been measured as the first analyte after opening the tube lid. All bicarbonate samples analyzed after the last biochemistry testing were considered invalid.

Two important country-level PDs were reported. One PD belonged to the category 'Other' and was related to late submission of Polish label of urine dip-stick test to the Central Ethics Committee. The other PD belonged to the category 'Informed consent' and was related to the late distribution of updated SI/IC to the sites, resulting in a delay in re-consenting.

Important site and patient-level deviations are summarized in the table below:

Reference ID: 4494748

Table 25 Summary of Important Site-Level and Patient-Level Protocol Deviations

Category	Site-level PDs (n)	Subject-level PDs (n)				
		Screening failures	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	Total no of subject-level PDs
Informed consent	4	12	24	19	5	60
Inclusion/exclusion/ randomisation criteria	-	-	3	2	4	9
Discontinuation criteria	-	-	1	-	-	1
Trial product handling	11	-	18	23	3	44
Treatment compliance	-	-	13	18	7	38
Assessment deviations	2	3	22	37	23	85
Other	20	-	12	9	8	29
Total	37	15	93	108	50	266

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

Source: Table 10-5 CSR PIONEER 4

Review of the information available regarding these PDs did not raise any concerns regarding the integrity of the efficacy or safety results.

Table of Demographic Characteristics

The demographic characteristics were similar between the treatment groups. Details are presented in the tables below.

The population was evenly distributed between male and female patients with a mean age of 56 years. All patients had T2DM with an overall mean duration of 7.6 years (SD 5.5). The overall mean HbA1c was 8.0%. The mean baseline body weight was slightly higher in the liraglutide group (95.5 kg) compared with the oral semaglutide (92.9 kg) and placebo (93.2 kg) groups. The proportions of patients per region were similar across the three treatment groups. The majority of patients were white (73.0%) and there was no difference between treatment groups in terms of race and ethnicity.

Renal function at baseline (based on eGFR) was normal for 70.2% of the patients; 29.1% of patients had mild renal impairment. Compared with the active treatment groups, slightly more patients in the placebo group had mild renal impairment.

Reference ID: 4494348

Table 26 Baseline Characteristics and Demographics – Continuous Variables – PIONEER 4

	Oral sema 14 mg	Lira 1.8 mg	Placebo	Total
Number of subjects	285	284	142	711
Age (years)				
N	285	284	142	711
Mean (SD)	56 (10)	56 (10)	57 (10)	56 (10)
HbA1c (%)				
N	285	284	142	711
Mean (SD)	8.0 (0.7)	8.0 (0.7)	7.9 (0.7)	8.0 (0.7)
Duration of diabetes (years)				
N	285	284	142	711
Mean (SD)	7.8 (5.7)	7.3 (5.3)	7.8 (5.5)	7.6 (5.5)
Body weight (kg)				
N	285	284	142	711
Mean (SD)	92.9 (20.6)	95.5 (21.9)	93.2 (20.0)	94.0 (21.0)
eGFR (mL/min/1.73 m^2)				
N	285	284	142	711
Mean (SD)	96 (15)	96 (15)	95 (15)	96 (15)

The eGFR was estimated using the CKD-EPI formula.
'Baseline': defined as the latest assessment at or prior to the randomisation visit; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; N: number of subjects; SD: standard deviation.

Source: Adapted from Table 10-2 CSR PIONEER 4

Reference ID: 4494748

Table 27 Demographics and Baseline Characteristics for Categorical Variables – PIONEER 4

	Oral sema 14 mg N (%)	Lira 1.8 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	285	284	142	711
Age group (years)				
N	285 (100)	284 (100)	142 (100)	711 (100)
18 <= to < 65	232 (81.4)	220 (77.5)	109 (76.8)	561 (78.9)
65 <= to < 75	48 (16.8)	56 (19.7)	27 (19.0)	131 (18.4)
75 <= to < 85	5 (1.8)	8 (2.8)	6 (4.2)	19 (2.7)
85 <=	0	0	0	0
Sex				
N	285 (100)	284 (100)	142 (100)	711 (100)
Female	138 (48.4)	135 (47.5)	68 (47.9)	341 (48.0)
Male	147 (51.6)	149 (52.5)	74 (52.1)	370 (52.0)
Region				
N	285 (100)	284 (100)	142 (100)	711 (100)
Europe	151 (53.0)	148 (52.1)	82 (57.7)	381 (53.6)
North America	75 (26.3)	76 (26.8)	28 (19.7)	179 (25.2)
Africa	23 (8.1)	17 (6.0)	12 (8.5)	52 (7.3)
Asia	36 (12.6)	43 (15.1)	20 (14.1)	99 (13.9)
Race				
N	285 (100)	284 (100)	142 (100)	711 (100)
White	208 (73.0)	212 (74.6)	99 (69.7)	519 (73.0)
Black or African American	12 (4.2)	9 (3.2)	8 (5.6)	29 (4.1)
Asian	39 (13.7)	36 (12.7)	19 (13.4)	94 (13.2)
American Indian or Alaska Native	0	1 (0.4)	1 (0.7)	2 (0.3)
Native Hawaiian or other Pacific Islander	0	1 (0.4)	0	1 (0.1)
Other	3 (1.1)	8 (2.8)	3 (2.1)	14 (2.0)
NA*	23 (8.1)	17 (6.0)	12 (8.5)	52 (7.3)
Ethnicity				
N	285 (100)	284 (100)	142 (100)	711 (100)
Hispanic or Latino	17 (6.0)	18 (6.3)	5 (3.5)	40 (5.6)
Not Hispanic or Latino	268 (94.0)	266 (93.7)	137 (96.5)	671 (94.4)
Renal function, eGFR (mL/min/1.73m^2)				
N	285 (100)	284 (100)	142 (100)	711 (100)
Normal (90 <=)	205 (71.9)	200 (70.4)	94 (66.2)	499 (70.2)
Mild RI (60 <= to < 90)	78 (27.4)	81 (28.5)	48 (33.8)	207 (29.1)
Moderate RI (30 <= to < 60)	2 (0.7)	2 (0.7)	0	4 (0.6)
Severe RI (15 <= to < 30)	0	1 (0.4)	0	1 (0.1)
End-stage renal disease (< 15)	0	0	0	0

NA*: race is recorded as 'NA' for South Africa; 'Baseline': defined as the latest assessment at or prior to the randomisation visit; 'Smoking': defined as smoking at least one cigarette or equivalent daily; The renal function categories are based on the eGFR as per CKD-EPI; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; RI: renal impairment; N: number of subjects; %: proportion of subjects.

Source: Adapted from Table 10-3 CSR PIONEER 4

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

Medical history and concomitant illnesses

There were no clinically relevant differences in medical history and concomitant illnesses between the treatment groups. Frequent and clinically relevant medical history for oral semaglutide 14 mg, liraglutide 1.8 mg and placebo were, respectively: infections and

Reference ID: 4497478

infestations (7.4%, 4.9%, and 8.5%), gastrointestinal disorders (6.3%, 5.6%, and 4.9%), neoplasms (4.2%, 7.4%, and 5.6%), renal and urinary disorders (3.2%, 1.4%, and 4.9%), eye disorders (1.8%, 3.9%, and 4.9%), cardiac disorders (1.4%, 0.4%, and 1.4%), and metabolism and nutrition disorders (0.7%, 0, and 1.4%). The most frequent clinically relevant concomitant illnesses for oral semaglutide, liraglutide, and placebo were, respectively: obesity (25.3%, 23.9%, and 29.6%), dyslipidemia (18.9%, 26.1%, and 25.4%), gastrointestinal disorders (16.8%, 19.0%, and 13.4%), psychiatric disorders (15.4%, 20.1%, and 14.8%; of which depression constituted 7.7%, 10.9%, and 6.3%), hepatic steatosis (14.4%, 13.7%, and 12.0%), vascular disorders (11.2%, 13.0%, and 14.1%), renal and urinary disorders (10.2%, 9.2%, and 14.1%), cardiac disorders (9.5%, 9.9%, and 8.5%), hypothyroidism (8.1%, 8.1%, and 10.6%) and neoplasms (3.2%, 3.5%, and 5.6%).

No clinically relevant differences across treatment groups were observed for histories of diabetic retinopathy and other diabetes complications. The proportions of patients with diabetic retinopathy were 9.8%, 8.8%, and 9.9% for oral semaglutide, liraglutide, and placebo, respectively (the majority reported as non-proliferative diabetic retinopathy). Other diabetic complications included diabetic neuropathy (18.2%, 18.7%, and 22.5%) and diabetic nephropathy (8.1%, 7.4%, and 9.9%) for oral semaglutide, liraglutide, and placebo, respectively.

The most frequently reported histories and risk factors of cardiovascular disease were hypertension (77.9%, 75.7%, and 68.3%) and ischemic heart disease (13.3%, 11.3%, and 8.5%) for oral semaglutide, liraglutide, and placebo, respectively.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patient compliance was assessed by monitoring of drug accountability. As seen in the protocol deviations section, only a small proportion of patients were reported with compliance issues.

<u>Rescue medications:</u>

The proportions of patients receiving additional anti-diabetic medication, including rescue medication, differed at weeks 26 and 52 for the three treatment groups, and were higher for all groups at week 52 compared to week 26. A higher proportion of patients on placebo had initiated additional anti-diabetic medication or rescue medication at weeks 26 and 52 compared with oral semaglutide and liraglutide.

Reference ID: 4494748

Table 28 Additional Anti-Diabetic Medication and Rescue Medication PIONEER 4

	Oral sema 14 mg N (%)		Lira 1.8 mg N (%)		Placebo N (%)	
	Additional anti-diabetic medication	Rescue medication	Additional anti-diabetic medication	Rescue medication	Additional anti-diabetic medication	Rescue medication
Number of subjects in FAS	285		284		142	
Week 26	20 (7.0)	10 (3.5)	16 (5.6)	9 (3.2)	12 (8.5)	11 (7.7)
Sulfonylureas	8 (2.8)	5 (1.8)	8 (2.8)	6 (2.1)	5 (3.5)	5 (3.5)
SGLT-2 inhibitors	7 (2.5)	3 (1.1)	3 (1.1)	2 (0.7)	1 (0.7)	1 (0.7)
Metformin	4 (1.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Insulins	2 (0.7)	1 (0.4)	0	0	3 (2.1)	2 (1.4)
DPP-4 inhibitors	0	0	5 (1.8)	1 (0.4)	0	0
GLP-1 analogues	2 (0.7)	0	0	0	0	0
Thiazolininediones	0	0	0	0	1 (0.7)	1 (0.7)
Alpha glucosidase inhibitors	0	0	0	0	2 (1.4)	2 (1.4)
Mitiglinide calcium	1 (0.4)	0	0	0	0	0
Week 52	39 (13.7)	20 (7.0)	29 (10.2)	18 (6.3)	46 (32.4)	43 (30.3)
Sulfonylureas	19 (6.7)	12 (4.2)	16 (5.6)	13 (4.6)	24 (16.9)	23 (16.2)
SGLT-2 inhibitors	9 (3.2)	4 (1.4)	5 (1.8)	2 (0.7)	11 (7.7)	11 (7.7)
Metformin	7 (2.5)	2 (0.7)	1 (0.4)	1 (0.4)	4 (2.8)	4 (2.8)
Insulins	3 (1.1)	2 (0.7)	3 (1.1)	3 (1.1)	5 (3.5)	3 (2.1)
DPP-4 inhibitors	4 (1.4)	0	6 (2.1)	1 (0.4)	0	0
GLP-1 analogues	3 (1.1)	0	1 (0.4)	0	0	0
Thiazolininediones	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (1.4)	2 (1.4)
Alpha glucosidase inhibitors	0	0	0	0	3 (2.1)	3 (2.1)
Mitiglinide calcium	1 (0.4)	0	0	0	0	0

'Insulins' includes insulins and analogues for injection, including long-acting, fast-acting, and intermediate- or long-acting combined with fast-acting.

Source: Table 10-4 CSR PIONEER 4

Efficacy Results - Primary Endpoint

At baseline, mean HbA1c levels were similar across treatment groups (7.9–8.0%). The estimated changes from baseline in HbA1c at week 26 were −1.2% with semaglutide, −1.1% with liraglutide, and −0.2%-points with placebo;

HbA1c decreased from baseline through weeks 14-26 for the oral semaglutide and liraglutide groups. From week 26 to week 52, HbA1c levels remained relatively stable in the oral semaglutide group, while a modest increase was observed with liraglutide. HbA1c levels remained relatively stable with placebo until week 8 after which a small decrease was observed

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through week 52. Oral semaglutide 14 mg was superior to placebo and non-inferior to liraglutide for the primary endpoint, however, superiority to liraglutide was not demonstrated.

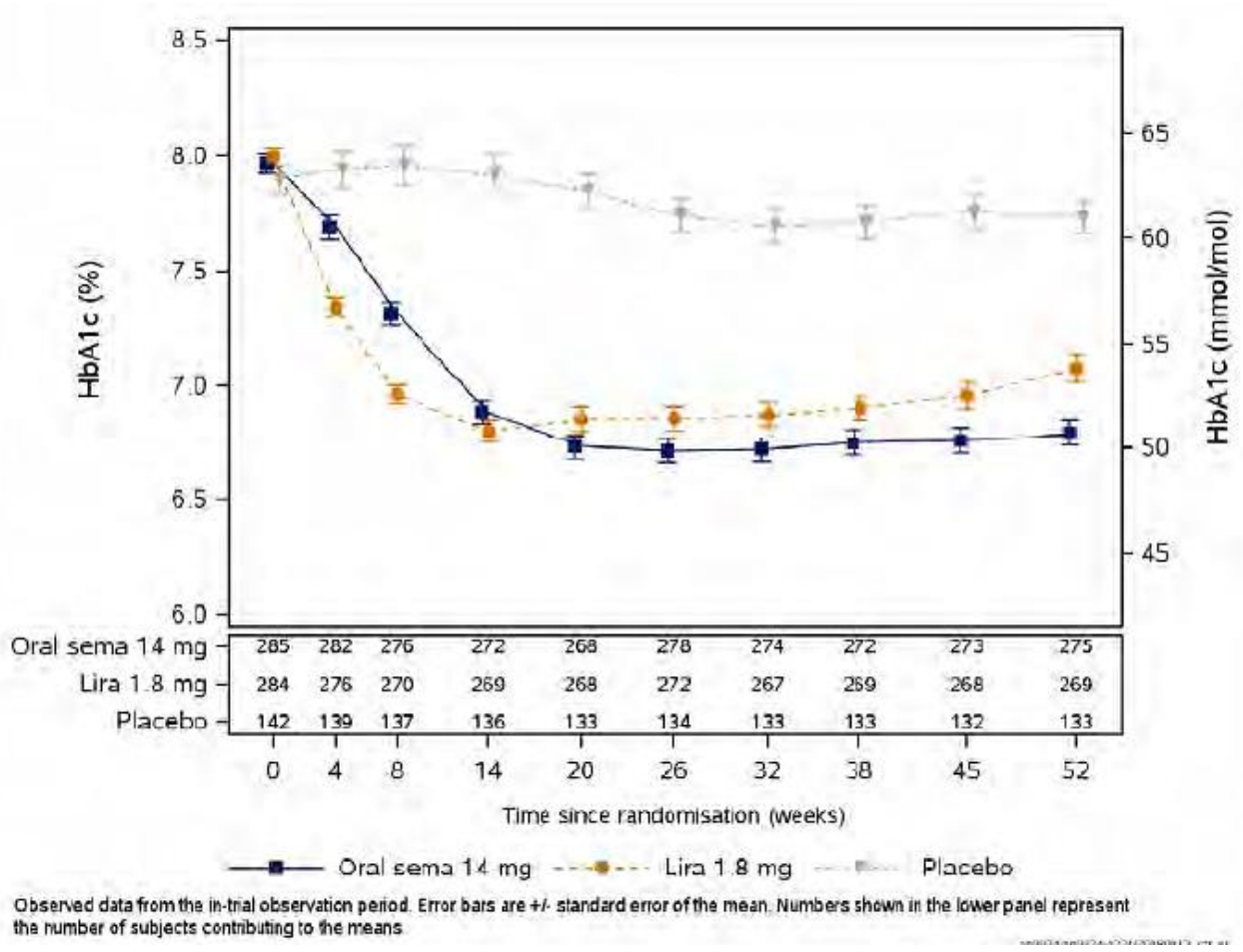
Table 29 HbA1c – Primary Statistical Analysis – FAS – PIONEER 4

Endpoint	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoint: Change from baseline at week 26 in HbA1c (%-points)					
Oral sema 14 mg - Placebo	-1.1 [-1.2 ; -0.9]	<0.0001		Superiority	Confirmed
Oral sema 14 mg - Lira 1.8 mg	-0.1 [-0.3 ; 0.0]	<0.0001		Non-inferiority	Confirmed
Oral sema 14 mg - Lira 1.8 mg	-0.1 [-0.3 ; 0.0]	0.0645	0.05	Superiority	Not confirmed
Other confirmatory endpoints: Change from baseline at week 26 in body weight (kg)					
Oral sema 14 mg - Placebo	-3.8 [-4.7 ; -3.0]	<0.0001		Superiority	Confirmed
Oral sema 14 mg - Lira 1.8 mg	-1.2 [-1.9 ; -0.6]	0.0003		Superiority	Confirmed

'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval

Source: Table 11-1 CSR PIONEER 4

Figure 15 HbA1c (% and mmol/mol) by Week – Mean Plot – PIONEER 4



Source: Figure 11-1 CSR PIONEER 4

Reference ID: 4494348

Data Quality and Integrity - Reviewers' Assessment

I did not identify any issues with the data submitted by the applicant.

Efficacy Results - Secondary and other relevant endpoints

Change in body weight

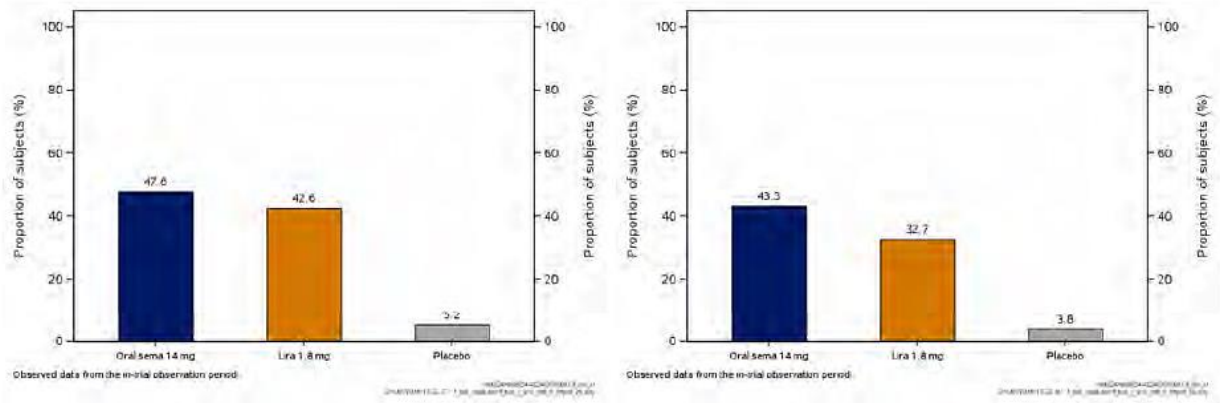
At baseline, the mean body weight in the semaglutide group was 92.9 kg, compared with 95.5 kg in the liraglutide group and 93.2 kg in the placebo group. The observed change in body weight at week 26 was greater with semaglutide (−4.4 kg) vs liraglutide (−3.2 kg) or placebo (−0.6 kg). Of note, the observed maximal weight loss was not achieved at week 26. From weeks 26 through 38, body weight levels decreased further in all treatment groups, and thereafter increased modestly in all treatment groups through week 52.

For the secondary endpoint, change in body weight at week 26, semaglutide was statistically superior to both placebo and liraglutide.

HbA1c treatment targets

For the in-trial observation period, at weeks 26 and 52, the observed proportions of patients who achieved the AACE (≤6.5%; Figure 11-9) and ADA (<7.0%; Figure 11-10) HbA1c treatment targets were greater with oral semaglutide than with liraglutide or placebo, however this was an exploratory endpoint.

Figure 16 Proportion of Patients who Reached the HbA1c ≤6.5% Treatment Target at Week 26 (Left Panel) and at Week 52 (Right Side Panel) – PIONEER 4



Source: Figure 11-9 CSR PIONEER 4

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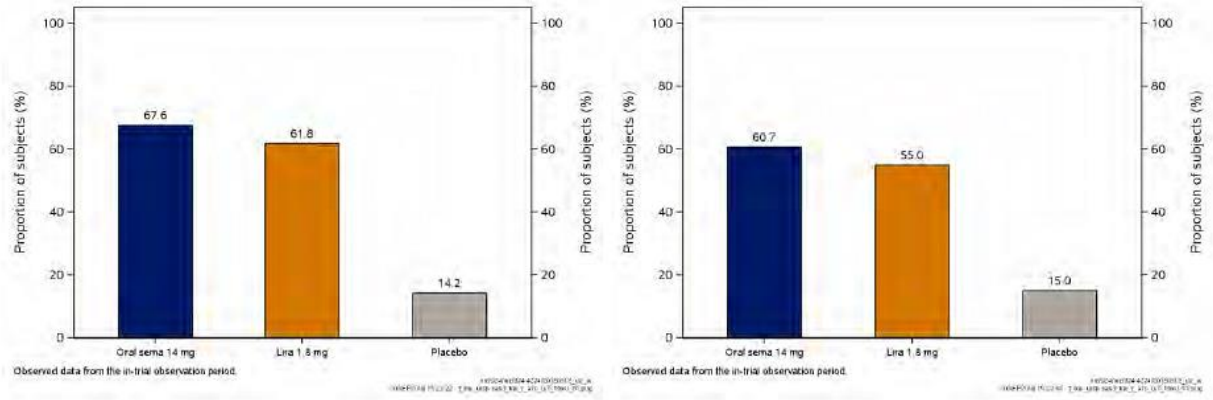
Reference ID: 4494748

Figure 17 Proportion of Patients who Reached the HbA1c <7.0% Treatment Target at Week 26 (Left Side Panel) and at Week 52 (Right Side Panel) – PIONEER 4



Source: Figure 11-10 CSR PIONEER 4

Dose/Dose Response

Not applicable as only one dose of semaglutide was evaluated.

Durability of Response

It appears that the HbA1c lowering persisted for the duration of the trial.

Persistence of Effect

Not applicable. Effect after discontinuation of study drug was not assessed.

Additional Analyses Conducted on the Individual Trial

Sensitivity analyses for the primary endpoint were generally supportive of the primary analysis,

6.5. PIONEER 5 (4234)

6.5.1. Study Design

Overview and Objective

Study title: Efficacy and Safety of Oral Semaglutide Versus Placebo in Patients with Type 2 Diabetes and Moderate Renal Impairment

Primary objective:
To compare the effect of once daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in

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combination with basal insulin on glycemic control in patients with type 2 diabetes mellitus and moderate renal impairment.

Secondary objectives

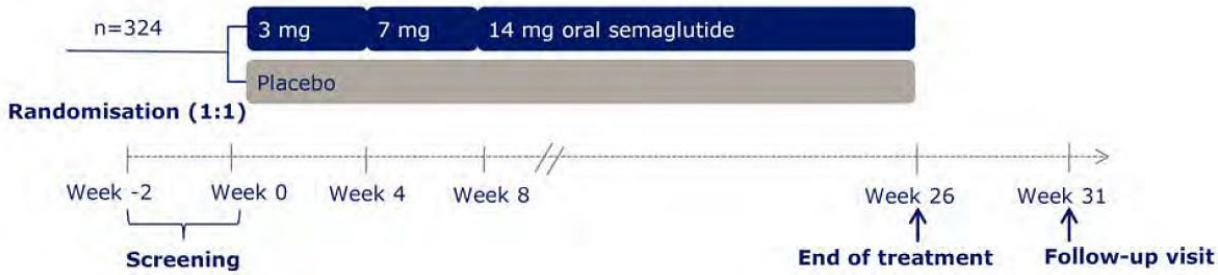
- To compare the effect of once daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin on body weight in patients with type 2 diabetes mellitus and moderate renal impairment.
- To compare the safety and tolerability of once daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin in patients with type 2 diabetes mellitus and moderate renal impairment.

Trial Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational trial with a 26-week treatment period (including an 8-week dose escalation period).

A total of 324 adults with T2DM were planned for randomization.

Figure 18 Trial Design PIONEER 5



Source: Figure 9-1 CSR PIONEER 5

Key inclusion/exclusion criteria:

Similar to other PIONEER trials except for the following:

- HbA1c of 7.0–9.5%
- Moderate renal impairment defined as estimated glomerular filtration rate of 30-59 mL/min/1.73 m2
- Stable daily dose(s) within 90 days prior to the day of screening of any of the following treatment regimens:
    - 1–2 of the following oral anti-diabetic drugs:
        - Metformin ≥ 1500 mg or maximum tolerated dose documented in the patient medical record),

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    - Sulfonylurea (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in patient medical record)
- Basal insulin alone (20% change in total daily dose of insulin glargine, insulin detemir, insulin degludec or NPH insulin) or
    - Metformin (≥ 1500 mg or maximum tolerated dose documented in the patient medical record) in combination with basal insulin (20% change in total daily dose of insulin glargine, insulin detemir, insulin degludec or NPH insulin)

Please see full inclusion and exclusion criteria in the study protocol.

Dose selection/Study treatments:
Patients were randomized 1:1 to receive once-daily treatment for 26 weeks with oral semaglutide 14 mg, or with placebo. The trial product regimens, including the dose escalation approach for oral semaglutide 14 mg, were the same as for other PIONEER trials. Semaglutide dosing and administration details were also the same across all PIONEER trials.

Dose modification/discontinuation:
Same as other PIONEER trials. Patients on basal insulin were to reduce their total daily insulin dose by 20% at randomization and to continue to measure SMPG values regularly throughout the trial. After having reached the maximum dose of oral semaglutide (14 mg), basal insulin could be up-titrated by the investigator from week 10 to week 16 based on the lowest of three fasting pre-breakfast SMPG values.

Administrative structure:
Same as other PIONEER trials.

Procedures and schedule:

The patients attended in-person visits at screening, randomization, 4, 8, 14, 20, 26 (end of treatment), and 31 weeks (follow-up). Additionally, telephone visits were scheduled for weeks 2, and 16. For patients on basal insulin, additional phone visits occurred at weeks 10, 11, 12, 13.

Eye examinations were performed at screening and end of treatment.

See study protocol for a full schedule of events.

Treatment compliance:
Similar to other PIONEER trials.

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Rescue medications:
FPG-based rescue medication criteria were applied to ensure acceptable glycemic control in both treatment groups. Patients with persistent and unacceptable hyperglycemia (as judged by the investigator) were to be offered treatment intensification. To allow time for dose escalation of trial product, dose adjustment of basal insulin, and to observe the expected effect of treatment on glycemic parameters, rescue criteria were to be used from week 12 and onwards. The choice of rescue medication was at the investigator's discretion, with the exception that GLP-1 RAs, DPP-4 inhibitors or amylin analogues were not allowed as rescue medication. For patients with basal insulin as part of their background medication, increase of basal insulin dose was to be first choice.

Study Endpoints

The primary and confirmatory secondary endpoints were the same as for the previously reviewed PIONEER studies.

Statistical Analysis Plan

The sample size was calculated to ensure a statistical power of at least 90% to confirm superiority on change from baseline at week 26 in HbA1c for the treatment policy estimand of oral semaglutide vs placebo. 324 patients were planned to be randomized.

The testing strategy involved testing for superiority for the HbA1c endpoint semaglutide vs placebo, followed by superiority testing for body weight at week 26.

Analysis sets were FAS and SAS, defined as for all other PIONEER trials.
Observation periods were the same as for the other PIONEER trials.

Protocol Amendments

There were 2 amendments to the protocol, as outlined in the table below.

Table 30 Amendments to the Protocol PIONEER 5

Reference ID: 4494748

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes
No 1-SE	10-Jun-2016	Before FSFV	Sweden	Local substantial amendment requested by the Medical Products Agency: • Changed definition of adequate contraception measures
No 2- Global	14-Nov-2016	After FSFV	All	Global substantial amendment based upon feedback from FDA regarding retinopathy. • Additional eye examinations and fundus photography or dilated fundoscopy at end of trial and after premature discontinuation of trial product • Fundoscopy requires pharmacological dilation of both pupils • Eye examination category added as supportive secondary endpoint • Diabetic retinopathy and related complications added as adverse events requiring additional data collection • Addition of 'Diabetic retinopathy complications' subsection to "Benefit-risk assessment of the trial" section of the protocol.

Source: Table 9-11 CSR PIONEER 5

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

Data Quality and Integrity: Sponsor's Assurance

The trial was monitored by Novo Nordisk using on-site visits, telephone calls and regular inspection of the eCRFs.

6.5.2. Study Results

Compliance with Good Clinical Practices

The sponsor stated that the trial was conducted in accordance with ICH GCP.

Financial Disclosure

Of the 538 investigators that participated in the trial, 13 had disclosable financial interests. See Appendix 13.3 for details.

Patient Disposition

Reference ID: 4494748

In total, 721 patients were screened, 397 failed screening; and 324 patients were randomized to receive either oral semaglutide (163 patients) or placebo (161 patients).

Out of the 397 patients who failed screening, the majority (256 patients, 64.5% of all screening failures) failed due to non-fulfilment of inclusion criterion 5: moderate impaired renal function (defined as estimated glomerular filtration rate [eGFR] of 30-59 mL/min/1.73m2

In total, 273 patients (84.3%) completed the treatment with trial product and 314 patients (96.9%) completed the trial. The proportion of patients completing treatment was lower with oral semaglutide 14 mg (81.0%) than with placebo (87.6%), whereas the proportion of patients completing the trial was identical across treatment groups (96.9%). A total of 3.1% (10 patients) of all patients withdrew from the trial, 3.1% in each treatment group.

A total of 50 patients (15.4%) discontinued trial product prematurely. This occurred mainly during the dose escalation period in the oral semaglutide 14 mg group whereas trial product was discontinued throughout the course of the trial with less clear time dependency in the placebo group. Trial product was prematurely discontinued for the following reasons: AEs (10.5%), violation of inclusion and/or exclusion criteria (1.2%), patient withdrawal from trial (0.6%) and 'other' reasons (3.1%).

Reference ID: 4494748

Table 31 Patient Disposition PIONEER 5

	Oral sema 14 mg N (%)	Placebo N (%)	Total N (%)
Screened			721
Screening failures			397 (55.1)
Randomised	163	161	324
Exposed	163 (100)	161 (100)	324 (100)
Analysis sets			
Full analysis set	163 (100)	161 (100)	324 (100)
Safety analysis set	163 (100)	161 (100)	324 (100)
Treatment completers [1]	133 (81.6)	141 (87.6)	274 (84.6)
Without rescue medication	127 (77.9)	127 (78.9)	254 (78.4)
With rescue medication	6 (3.7)	14 (8.7)	20 (6.2)
Premature trial product discontinuation - primary reason	30 (18.4)	20 (12.4)	50 (15.4)
Adverse event(s)	24 (14.7)	10 (6.2)	34 (10.5)
Violation of inclusion and/or exclusion criteria	1 (0.6)	3 (1.9)	4 (1.2)
Intention of becoming pregnant	0	0	0
Participation in another clinical trial [2]	0	0	0
Calcitonin value >=100 ng/L	0	0	0
Subject withdrawal from trial	0	2 (1.2)	2 (0.6)
Pregnancy	0	0	0
Other	5 (3.1)	5 (3.1)	10 (3.1)
Trial completers [3]	158 (96.9)	156 (96.9)	314 (96.9)
Completed treatment	132 (81.0)	141 (87.6)	273 (84.3)
Discontinued trial product	26 (16.0)	15 (9.3)	41 (12.7)
Withdrawal from trial - primary reason	5 (3.1)	5 (3.1)	10 (3.1)
Lost to follow-up	3 (1.8)	1 (0.6)	4 (1.2)
Withdrawal by subject	1 (0.6)	2 (1.2)	3 (0.9)
Other	1 (0.6)	2 (1.2)	3 (0.9)
Died	1 (0.6)	2 (1.2)	3 (0.9)

'[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'primary reason': according to the end-of-trial form; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product; N: number of subjects; %: proportion of randomised subjects except for screening failures where it is proportion of screened subjects.

Source: Table 10-1 CSR PIONEER 5

Protocol Violations/Deviations

In total, there were 147 important PDs; the PDs comprised 1 trial-level PD (Section 10.5.2), 21 site-level PDs and 125 patient-level PDs (Section 10.5.4). No important country-level PDs were reported. The one trial level PD was common with the other PIONEER trials, and it belonged to the 'Assessment deviation (incl. lab)' category and concerned the reporting of body weight measurements with precisions less than the one specified in the trial protocol (0.1 kg/pound) at some trial sites. This occurred due to use of scales with a precision of 0.5 kg/pound or rounding off to the nearest half or whole kg/pound by the site staff. The PD was not considered to have had any impact on the data interpretation.

Reference ID: 4494748

Important site-level and patient-level PDs are summarized below by category.

Table 32 Summary of important site-level and patient-level protocol deviations

Category	Site-level PDs (n)	Subject-level PDs			
		Screening failures	Oral semaglutide 14 mg	Placebo	Total no of subject-level PDs
Informed consent	1	20	10	10	40
Inclusion/exclusion/ randomisation criteria	1	0	3	11	14
Trial product handling	1	0	3	3	6
Treatment compliance	0	0	5	8	13
Assessment deviations	2	1	13	19	33
Other	16	0	13	6	19
Total	21	21	47	57	125

n: number of PDs; PD: protocol deviation
Source: Table 10-16 CSR PIONEER 5

There were no relevant differences across treatment groups in the number of PDs for any PD category or subcategory.

Table of Demographic Characteristics

The demographic and baseline characteristics were generally similar across treatment groups. The population was evenly distributed between male and female patients with a mean age of 70 years. All patients had T2DM with an overall mean duration of 14.0 years (SD 8.0). The overall mean HbA1c was 8.0%. The mean body weight in the oral semaglutide group was 91.3 kg compared to 90.4 kg in the placebo group. The mean estimated eGFR was 48 mL/min/1.73 m2 and was similar across treatment groups.

Reference ID: 4494748

Table 33 Selected Demographics and Baseline Characteristics for Continuous Variables - PIONEER 5

	Oral sema 14 mg	Placebo	Total
Number of subjects	163	161	324
Age (years)			
N	163	161	324
Mean (SD)	71 (8)	70 (8)	70 (8)
HbA1c (%)			
N	163	161	324
Mean (SD)	8.0 (0.7)	7.9 (0.7)	8.0 (0.7)
Duration of diabetes (years)			
N	163	161	324
Mean (SD)	14.1 (8.6)	13.9 (7.4)	14.0 (8.0)
Body weight (kg)			
N	162	161	323
Mean (SD)	91.3 (17.8)	90.4 (17.5)	90.8 (17.6)
eGFR (mL/min/1.73 m^2)			
N	163	161	324
Mean (SD)	47 (10)	48 (10)	48 (10)
Median	47	48	48
Min; Max	24 ; 80	26 ; 77	24 ; 80
Urinary albumin to creatinine ratio (mg/g)			
N	162	156	
Geom. Mean (CV)	3.5 (500.7)	2.8 (619.9)	

The eGFR was estimated using the CKD-EPI formula. 'Baseline': defined as the latest assessment at or prior to the randomisation visit; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; N: number of subjects; SD: standard deviation; Geom.: geometric; CV: coefficient of variation

Source: Modified from Table 10-2 CSR PIONEER 5

Reference ID: 4494348

Table 34 Selected Demographics and Baseline Characteristics for Categorical Variables - PIONEER 5

	Oral sema 14 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	163	161	324
Age group (years)			
N	163 (100)	161 (100)	324 (100)
18 <= to < 65	26 (16.0)	39 (24.2)	65 (20.1)
65 <= to < 75	79 (48.5)	73 (45.3)	152 (46.9)
75 <= to < 85	51 (31.3)	48 (29.8)	99 (30.6)
85 <=	7 (4.3)	1 (0.6)	8 (2.5)
Sex			
N	163 (100)	161 (100)	324 (100)
Female	80 (49.1)	88 (54.7)	168 (51.9)
Male	83 (50.9)	73 (45.3)	156 (48.1)
Region			
N	163 (100)	161 (100)	324 (100)
Europe	120 (73.6)	110 (68.3)	230 (71.0)
North America	43 (26.4)	51 (31.7)	94 (29.0)
Race			
N	163 (100)	161 (100)	324 (100)
White	158 (96.9)	152 (94.4)	310 (95.7)
Black or African American	4 (2.5)	9 (5.6)	13 (4.0)
Asian	1 (0.6)	0	1 (0.3)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Ethnicity			
N	163 (100)	161 (100)	324 (100)
Hispanic or Latino	7 (4.3)	14 (8.7)	21 (6.5)
Not Hispanic or Latino	156 (95.7)	147 (91.3)	303 (93.5)
Not applicable	0	0	0
Urinary albumin to creatinine ratio (mg/g)			
N	163 (100)	161 (100)	324 (100)
Normal to mildly increased (< 30)	96 (58.9)	105 (65.2)	201 (62.0)
Moderately increased (30 <= to <= 300)	44 (27.0)	25 (15.5)	69 (21.3)
Severely increased (> 300)	22 (13.5)	26 (16.1)	48 (14.8)
Unclassified	1 (0.6)	5 (3.1)	6 (1.9)
Renal function, eGFR (mL/min/1.73m^2)			
N	163 (100)	161 (100)	324 (100)
Normal (90 <=)	0	0	0
Mild RI (60 <= to < 90)	15 (9.2)	16 (9.9)	31 (9.6)
Moderate RI (30 <= to < 60)	143 (87.7)	142 (88.2)	285 (88.0)
Severe RI (15 <= to < 30)	5 (3.1)	3 (1.9)	8 (2.5)
End-stage renal disease (< 15)	0	0	0
Renal function strata, eGFR (mL/min/1.73m^2)			
N	163 (100)	161 (100)	324 (100)
30 <= to < 45	64 (39.3)	64 (39.8)	128 (39.5)
45 <= to < 60	99 (60.7)	97 (60.2)	196 (60.5)

Not applicable: for ethnicity values recorded as 'missing', 'not done', or 'not-available'; 'Baseline': defined as the latest assessment at or prior to the randomisation visit; 'Smoking': defined as smoking at least one cigarette or equivalent daily; The renal function categories are based on the eGFR as per CKD-EPI; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; RI: renal impairment; N: number of subjects; %: proportion of subjects.

Source: Modified from Table 10-3 CSR PIONEER 5

Reference ID: 4497478

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

Medical history/Concomitant illnesses

The most frequent and clinically relevant concomitant illnesses for oral semaglutide 14 mg and placebo were, respectively; obesity (38.7% and 41.6%), dyslipidemia (25.8% and 31.7%), hepatic steatosis (6.7% and 8.7%) and hypothyroidism (12.3% and 9.9%).

Diabetic retinopathy was reported at baseline in 41.1% and 35.4% for oral semaglutide 14 mg, and placebo, respectively (the majority reported as non-proliferative diabetic retinopathy). Other diabetic complications included diabetic neuropathy (49.1% and 50.3%) for oral semaglutide 14 mg and placebo, respectively.

No clinically relevant differences across treatment groups were observed for histories of renal impairment at screening. The most frequently reported histories and risk factors of renal impairment were hypertension (34.4% and 42.2%) and diabetic nephropathy (81.6% and 81.4%) for oral semaglutide 14 mg and placebo, respectively.

The most frequently reported histories and risk factors of cardiovascular disease were ischemic heart disease (46.0% and 42.9%), myocardial infarction (19.0% and 14.9%) and percutaneous coronary intervention (16.0% and 13.0%) for oral semaglutide 14 mg and placebo, respectively.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant and anti-diabetic medications
The most frequently used concomitant medications were HMG CoA reductase inhibitors, platelet aggregation inhibitors excluding heparin, beta blocking agents and ACE inhibitors. They were evenly distributed between the treatment groups.

In this trial, randomization was stratified based on renal function and pre-trial anti-diabetic background medication (metformin alone, SU ± metformin or basal insulin ± metformin) to ensure an even distribution of the two treatment arms within the three strata. In total, 23.8% of patients were on metformin alone, 40.7% of patients were on SU ± metformin and 35.5% of patients were on basal insulin ± metformin with an equal distribution between treatment groups.

The total daily mean insulin dose was 44 units (range of 8–132 units) in the oral semaglutide 14 mg group (59 patients) and 47 units (range of 4–162 units) in the placebo group (56 patients) The proportions of patients receiving additional anti-diabetic medication, including rescue medication, was lower in the oral semaglutide 14 mg group compared to the placebo group at week 26. The additional and rescue medications are summarized in the table below.

Reference ID: 4494748

Table 35 Additional Anti-Diabetic Medication and Rescue Medication PIONEER 5

	Oral sema 14 mg N (%)		placebo N (%)	
	Additional anti-diabetic medication	Rescue medication	Additional anti-diabetic medication	Rescue medication
Number of subjects in FAS	163		161	
Number of subjects on additional anti-diabetic medication and rescue medication at Week 26	12 (7.4)	7 (4.3)	21 (13.0)	16 (9.9)
Sulfonylureas	1 (0.6)	0	3 (1.9)	2 (1.2)
Metformin	1 (0.6)	1 (0.6)	3 (1.9)	3 (1.9)
DPP-4 inhibitors	2 (1.2)	0	5 (3.1)	2 (1.2)
Insulins				
Long-acting	4 (2.5)	3 (1.8)	7 (4.3)	7 (4.3)
Fast-acting	2 (1.2)	0	2 (1.2)	1 (0.6)
Inter-mediate-acting	1 (0.6)	1 (0.6)	3 (1.9)	3 (1.9)
Inter-mediate- or long-acting combined with fast-acting	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.3)
SGLT-2 inhibitors	1 (0.6)	1 (0.6)	0	0
Other blood glucose lowering drugs	0	-	1 (0.6)	-

Source: Table 10-5 CSR PIONEER 5

Efficacy Results - Primary Endpoint

Superiority of semaglutide vs placebo was shown for both the primary endpoint (change from baseline at week 26 in HbA1c), and the confirmatory secondary endpoint (change from baseline at week 26 in body weight). At baseline, HbA1c levels were similar across treatment groups (7.9–8.0%). For the in-trial observation period (used in the evaluation of the treatment policy estimand), HbA1c levels decreased from 8.0% at baseline to 6.9% at week 26 with oral semaglutide and remained relatively stable with placebo. The observed changes from baseline were −1.1% with oral semaglutide compared to −0.1%.

Table 36 Primary and Confirmatory Secondary Endpoints – PIONEER 5

Reference ID: 4494748

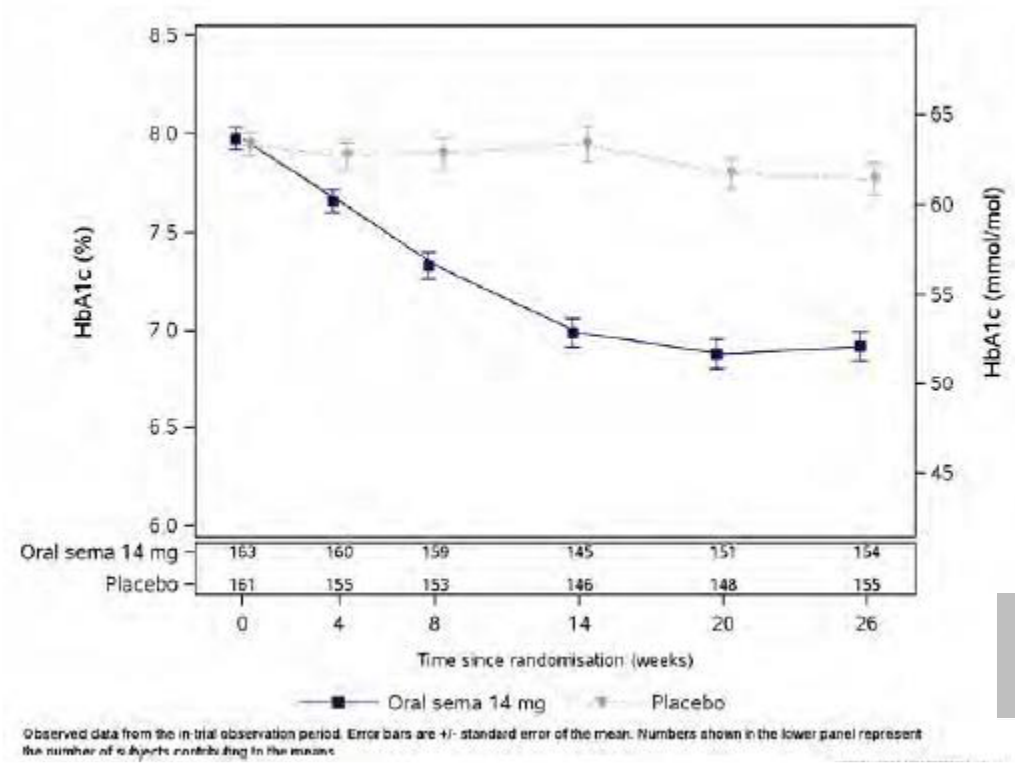
Endpoint	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoint: Change from baseline at week 26 in HbA1c (%-points)					
Oral sema 14 mg - Placebo	-0.8 [-1.0 ; -0.6]	<0.0001		Superiority	Confirmed
Other confirmatory endpoints: Change from baseline at week 26 in body weight (kg)					
Oral sema 14 mg - Placebo	-2.5 [-3.2 ; -1.8]	<0.0001		Superiority	Confirmed

'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval

Source: Table 11-1 CSR PIONEER 5

The decline in HbA1c with semaglutide was seen at week 14 and was sustained throughout the rest of the trial.

Figure 19 Mean HbA1c (%) by Treatment Week - FAS – PIONEER 5



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Source: Figure 11-1 CSR PIONEER 5

Data Quality and Integrity - Reviewers' Assessment

I did not identify any issues with the data integrity.

Efficacy Results - Secondary and other relevant endpoints

<u>Body weight</u>

Reference ID: 4494748

At baseline, body weight was similar across treatment groups (90.4–91.3 kg). At 26 weeks, the observed reduction in body weights were –3.5 kg and –0.9 kg with oral semaglutide 14 mg and placebo, respectively. The body weight decreases with semaglutide did not plateau, but it was rather a gradual decrease to week 26. A small decrease in weight was seen with placebo between baseline and week 20.

HbA1c treatment targets

For the in-trial observation period, at week 26 the observed proportions of patients who had reached the ADA (<7.0%) or AACE (≤6.5%) HbA1c treatment targets were greater with oral semaglutide 14 mg (57.8% and 39.0%, respectively) than with placebo (22.6% and 7.7%, respectively);

Dose/Dose Response

Not applicable as only the 14 mg semaglutide dose was evaluated.

Durability of Response

The HbA1c decrease was progressive to week 20, and it was sustained from week 20-26.

Persistence of Effect

Not applicable, patients were not studied after the end of the trial.

Additional Analyses Conducted on the Individual Trial

The applicant conducted sensitivity analyses for the primary endpoint, and all were supportive of the primary endpoint.

6.6. PIONEER 7 (4257)

6.6.1. Study Design

Overview and Objective

Only the main phase of this study will be reviewed here, as this is proposed for inclusion in the prescribing information, and the applicant is planning to submit the results of the extension phase in a separate report.

Study Title: Efficacy and Safety of Oral Semaglutide Using a Flexible Dose Adjustment Based on Clinical Evaluation versus Sitagliptin in Patients with Type 2 Diabetes Mellitus

Reference ID: 4494748

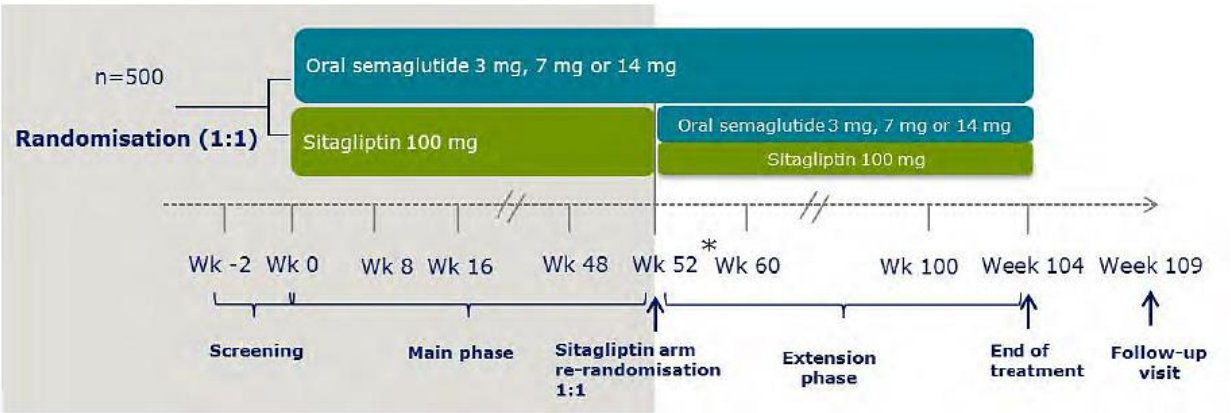
Primary Objective
To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs on glycemic control in patients with T2DM.

Secondary objective
- To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs on body weight in patients with T2DM.
- To compare the safety and tolerability of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs in patients with T2DM.

Trial Design

This trial consisted of two 52-week treatment periods: a 52-week main phase and a 52-week extension phase. The main phase was a 52-week randomized, open-label, active-controlled, 2-arm, parallel-group, multi-center, multi-national treatment period with an initial 2-week screening period and, for patients that did not continue in the extension phase, a 5-week follow-up period.

Figure 20 Trial Design PIONEER 7



Source: Figure 9-1 CSR PIONEER 7

A total of 500 adult patients with T2DM treated with 1-2 OADs (metformin, SU, TZD or SGLT-2 inhibitors) were planned to be randomized in the main phase. Of these, a minimum of 380 patients were planned to continue in the extension phase.

Reference ID: 4494348

Key Inclusion/Exclusion criteria
Same as other PIONEER trials with the following details:
- HbA1c 7.5-9.5% (58-80 mmol/mol) (both inclusive).
- Treatment target of HbA1c < 7.0% (53 mmol/mol), as judged by the investigator.
- Stable daily dose(s) of 1-2 of the following anti-diabetic drugs within 90 days prior to the day of screening:
    a. Metformin (≥1500 mg or maximum tolerated dose documented in the patient medical record).
    b. Sulfonylureas (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in patient medical record).
    c. Sodium glucose co-transporter 2 inhibitors.
    d. Thiazolidinediones (≥ half of the maximum approved dose according to local

Dose selection/study treatments:
In the main phase, patients were randomized 1:1 to receive once-daily treatment for 52 weeks with oral semaglutide flexible dosing (3, 7 or 14 mg) or with sitagliptin 100 mg.

Patients randomized to oral semaglutide in the main phase initiated treatment on the 3 mg dose level and were to maintain this dose for the first 8 weeks. For the remainder of the treatment period, the dose of oral semaglutide was adjusted every 8 weeks according to the dose adjustment criteria:

- HbA1c
    - When HbA1c < 7.0%, the current dose of oral semaglutide was to be continued
    - When HbA1c ≥ 7.0%, the dose of oral semaglutide was to be escalated to the next dose level
- Tolerability
    - In case the patient reports moderate to severe nausea or vomiting for 3 or more days in the week prior to the scheduled visit, the dose of oral semaglutide was to be maintained or reduced, at the investigator's discretion, regardless of HbA1c.

Patients on 3 mg oral semaglutide could not have their dose reduced.

Administration details for oral semaglutide were the same as outlined for the other PIONEER trials.

Procedures and Schedule:
The patients were to attend visits in person at screening, randomization, week 8, 16, 24, 32, 40, 48, 52 (end of treatment), and 57 (follow-up). One telephone visit was set up for week 4.

Eye examinations were performed at screening and end of treatment.

Reference ID: 4494748

Please see study protocol for complete study procedures.

Concurrent medications:
Patients were to continue their anti-diabetic background medication throughout the main phase of the trial at the same dose level as given at trial entrance and with the same frequency during the entire treatment period unless any of the following:

- Rescue medication was needed
- Any safety concerns related to the background medication arose.
- The patient had unacceptable hypoglycemia on a background SU, in which case the dose of SU could be reduced.

Treatment compliance
Treatment compliance was to be assessed by monitoring of drug accountability.

Rescue Medications
Patients with persistent and unacceptable hyperglycemia were to be offered treatment intensification with rescue medication (i.e. intensification of existing anti-diabetic medication and/or initiation of new anti-diabetic medication) if HbA1c > 8.5% from week 32 to end of treatment. Rescue medication was to be prescribed at investigator's discretion as add-on to the randomized treatment and according to ADA/EASD guidelines. As for all PIONEER trials, GLP-1 RAs, DPP-4 inhibitors and amylin analogues were not allowed as rescue medication.

Short-term use (≤ 21 days) of anti-diabetic medication (e.g. in connection with intercurrent illness) was not considered additional anti-diabetic medication (nor rescue medication).

Patient completion, discontinuation, or withdrawal
Same as for other PIONEER trials.

Study Endpoints

The primary endpoint was if a patient after week 52 achieved (yes/no) HbA1c < 7.0% as per the ADA target.

The confirmatory secondary endpoint was the change from baseline to week 52 in body weight (kg).

Statistical Analysis Plan

The sample size was calculated to ensure a statistical power of at least 90% to confirm superiority on HbA1c < 7.0% (yes/no) at week 52 for the treatment policy estimand of semaglutide flexible dosing versus sitagliptin. A total of 500 patients were planned to be randomized.

Reference ID: 4494748

The hierarchal testing strategy was used to preserve the overall type-1 error at a two-sided 5% significance level for the treatment policy estimand only. The statistical testing strategy was based on the principle that glycemic effect was to be established in terms of HbA1c superiority before testing for added benefits in terms of body weight superiority.

Analysis sets and observation periods were as defined for PIONEER 1.

Protocol Amendments

There were 2 substantial amendments to the protocol as outlined in the table below.

Table 37 Amendments to the Protocol PIONEER 7

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes (for changes issued after FSFV)
1	09 November 2016	Approx. 3 weeks after FSFV	Global	Introduction of additional eye examinations and additional data collection on diabetic retinopathy; addition of bicarbonate as part of the biochemistry laboratory assessment; investigator's responsibility in ensuring evaluation and management of certain risk factors and complications; clarification of the criteria for completion, withdrawal and lost to follow-up and other minor adjustments.
2	14 March 2017	Approx. 6 months after FSFV	Global	Created to add a 52-week extension period to the trial in order to assess: (1) sustainability of glycaemic control and long-term safety in subjects exposed to oral semaglutide using flexible dose adjustment for a period of up to 104 weeks and (2) effect of switching from sitagliptin to oral semaglutide on glycaemic control and safety for a period of up to 52 weeks

Source: Table 9-11 CSR PIONEER 7

None of these amendments are likely to impact evaluation of safety and efficacy from PIONEER 7.

Data Quality and Integrity: Sponsor's Assurance

The trial was conducted in accordance with ICH GCP per the sponsor. The investigators were required to have been trained in GCP. The trial was monitored by the sponsor using a risk-based approach by means of on-site monitoring visits, off-site monitoring visits, telephone calls, and regular inspection of the electronic case report forms (eCRFs).

Reference ID: 4494748

6.6.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with ICH GCP.

Financial Disclosure

Of the 411 investigators, 6 had financial disclosures. See Appendix 13.3 for details.

Patient Disposition

In total, 804 patients were screened and 300 patients failed screening; thus, 504 patients were randomized to receive either oral semaglutide flexible dosing (253 patients) or sitagliptin 100 mg (251 patients). Out of the 300 patients who failed screening, the majority (228 patients, 76.0%) failed due to nonfulfillment of HbA1c inclusion criterion.

In total, 439 patients (87.1%) completed the treatment with trial product and 485 patients (96.2%) completed the main phase of the trial. The proportion of patients completing treatment was lower in the semaglutide group (83.4%) compared to the sitagliptin group (90.8%). For patients completing the main phase of the trial, the proportion of patients were similar between the treatment groups (95.3% and 97.2%, respectively). A total of 3.8% of all patients withdrew from the trial; more patients in the semaglutide group (4.7%) than from the sitagliptin group (2.8%).

A total of 65 patients (12.9%) discontinued trial product prematurely for the following reasons: adverse events (6.3%), violation of inclusion and/or exclusion criteria (1.2%), patient withdrawal from trial (0.8%), pregnancy (0.2%) and 'Other' reasons (4.2%).

Reference ID: 4494748

Table 38 Patient Disposition PIONEER 7

	Oral sema flex N (%)	Sita 100 mg N (%)	Total N (%)
Screened			804
Screening failures			300 (37.3)
Randomised	253	251	504
Exposed	253 (100)	250 (99.6)	503 (99.8)
Analysis sets			
Full analysis set	253 (100)	251 (100)	504 (100)
Safety analysis set	253 (100)	250 (99.6)	503 (99.8)
Treatment completers [1]	211 (83.4)	228 (90.8)	439 (87.1)
Without rescue medication	203 (80.2)	190 (75.7)	393 (78.0)
With rescue medication	8 (3.2)	38 (15.1)	46 (9.1)
Premature trial product discontinuation - primary reason	42 (16.6)	23 (9.2)	65 (12.9)
Exposed			
Adverse event(s)	22 (8.7)	10 (4.0)	32 (6.3)
Violation of inclusion and/or exclusion criteria	5 (2.0)	1 (0.4)	6 (1.2)
Intention of becoming pregnant	0	0	0
Participation in another clinical trial [2]	0	0	0
Calcitonin value >=100 ng/L	0	0	0
Subject withdrawal from trial	3 (1.2)	1 (0.4)	4 (0.8)
Pregnancy	0	1 (0.4)	1 (0.2)
Other	12 (4.7)	9 (3.6)	21 (4.2)
Not exposed			
Violation of inclusion and/or exclusion criteria	0	1 (0.4)	1 (0.2)
Trial completers [3]	241 (95.3)	244 (97.2)	485 (96.2)
Completed treatment	211 (83.4)	227 (90.4)	438 (86.9)
Discontinued trial product	30 (11.9)	17 (6.8)	47 (9.3)
Withdrawal from trial - primary reason	12 (4.7)	7 (2.8)	19 (3.8)
Lost to follow-up	7 (2.8)	4 (1.6)	11 (2.2)
Withdrawal by subject	5 (2.0)	1 (0.4)	6 (1.2)
Other	0	2 (0.8)	2 (0.4)
Died	0	2 (0.8)	2 (0.4)

'[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'primary reason': according to the end-of-trial form; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product;
N: number of subjects; %: proportion of randomised subjects except for screening failures where it is proportion of screened subjects.

Source: table 10-1 CSR PIONEER 7

Protocol Violations/Deviations

In total, 223 important PDs were closed before the main phase DBL; the PDs comprised 3 trial-level PDs, 1 country-level PD, 10 site-level PDs and 207 patient-level PDs.

<u>Trial-level PDs</u>

Two PDs belonged to the 'Assessment deviation (incl. lab)' category:

- One PD concerned the reporting of body weight measurements with precisions less than the one specified in the trial protocol (0.1 kg/pound) at some trial sites. This was due to misunderstanding of the trial protocol

Reference ID: 4494748

requirement at these trial sites. The PD was not considered to have had any impact on the data interpretation.

- One PD concerned incorrectly performed bicarbonate testing which resulted in reporting of bicarbonate results below the normal range. The central laboratory inadvertently analyzed bicarbonate after the last biochemistry analyte in a separate step that included reopening of the tube lid. Bicarbonate dissipates from the tube and therefore should have been measured as the first analyte after opening the tube lid. All bicarbonate samples analyzed after the last biochemistry testing were considered invalid.
- One PD belonged to the 'Other' category and concerned a deviation from the predefined process for compilation of adjudication packages, which could have led to potential unblinding of events sent for adjudication. The deviation occurred due to inconsistent redaction of trial treatment assignment, dose or administration route by the CRO. To ensure adjudication was performed on blinded events, all 3 events that had been adjudicated before the deviation was identified were readjudicated by new, uncompromised EAC members after necessary redaction had been ensured.

One important country-level PD was reported in the category 'Other'. This PD concerned the use of an older version of 'log of staff' which led to a few errors in the delegation list. A new version of 'log of staff' was distributed to all sites.

A summary of site and patient level PDs is presented in the table below.

Reference ID: 4494748

Table 39 Site- and Patient-Level PDs – PIONEER 7

Category	Site-level PDs (n)	Subject-level PDs (n)			
		Screening failures	Oral semaglutide flexible dosing	Sitagliptin 100 mg	Total no of subject-level PDs
Informed consent	-	8	17	18	43
Inclusion/exclusion/ randomisation criteria	-	1	22	18	41
Discontinuation criteria	-	-	1	-	1
Trial product handling	-	-	9	3	12
Treatment compliance	-	-	20	15	35
Assessment deviations	-	1	32	22	55
Other	10	-	13	7	20
Total	10	10	114	83	207

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

Source: Table 10-5 CSR PIONEER 7

Table of Demographic Characteristics

The population consisted of more male (56.5%) than female (43.5%) patients, with a mean age of 57 years. The mean body weight was similar between the two treatment groups: 88.9 kg with semaglutide and 88.4 kg with sitagliptin. The mean T2DM duration for the trial population was 8.8 years. The mean baseline HbA1c was 8.3%. Most patients were White (75.6%) and the treatment groups had similar distributions in terms of race and ethnicity. Renal function (based on baseline eGFR) was normal for 71.8% of the patients: 27.8% had mild renal impairment and 0.4% had moderate renal impairment.

Reference ID: 4494748

Table 40 Baseline Characteristics and Demographics – Continuous Variables – FAS

	Oral sema flex	Sita 100 mg	Total
Number of subjects	253	251	504
Age (years)			
N	253	251	504
Mean (SD)	57 (10)	58 (10)	57 (10)
HbA1c (%)			
N	253	251	504
Mean (SD)	8.3 (0.6)	8.3 (0.6)	8.3 (0.6)
Duration of diabetes (years)			
N	253	251	504
Mean (SD)	8.6 (6.3)	9.0 (6.2)	8.8 (6.2)
Body weight (kg)			
N	253	251	504
Mean (SD)	88.9 (19.6)	88.4 (20.1)	88.6 (19.8)
eGFR (mL/min/1.73 m^2)			
N	253	251	504
Mean (SD)	97.0 (14.4)	95.3 (15.6)	96.2 (15.0)
Median	98.0	97.0	98.0
Min; Max	59.0 ; 137.0	51.0 ; 146.0	51.0 ; 146.0

The eGFR was estimated using the CKD-EPI formula.
'Baseline': defined as the latest assessment at or prior to the randomisation visit; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; N: number of subjects; SD: standard deviation.

Source: Modified from Table 10-2 CSR PIONEER 7

Table 41 Baseline Characteristics and Demographics – Categorical Variables –PIONEER 7

Reference ID: 4494748

	Oral sema flex N (%)	Sita 100 mg N (%)	Total N (%)
Number of subjects	253	251	504
Age group (years)			
N	253 (100)	251 (100)	504 (100)
18 <= to < 65	187 (73.9)	180 (71.7)	367 (72.8)
65 <= to < 75	61 (24.1)	58 (23.1)	119 (23.6)
75 <= to < 85	5 (2.0)	12 (4.8)	17 (3.4)
85 <=	0	1 (0.4)	1 (0.2)
Sex			
N	253 (100)	251 (100)	504 (100)
Female	108 (42.7)	111 (44.2)	219 (43.5)
Male	145 (57.3)	140 (55.8)	285 (56.5)
Region			
N	253 (100)	251 (100)	504 (100)
Europe	93 (36.8)	71 (28.3)	164 (32.5)
North America	73 (28.9)	87 (34.7)	160 (31.7)
South America	35 (13.8)	39 (15.5)	74 (14.7)
Africa	24 (9.5)	21 (8.4)	45 (8.9)
Asia	28 (11.1)	33 (13.1)	61 (12.1)
Race			
N	253 (100)	251 (100)	504 (100)
White	195 (77.1)	186 (74.1)	381 (75.6)
Black or African American	22 (8.7)	25 (10.0)	47 (9.3)
Asian	34 (13.4)	38 (15.1)	72 (14.3)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	2 (0.8)	2 (0.8)	4 (0.8)
Ethnicity			
N	253 (100)	251 (100)	504 (100)
Hispanic or Latino	48 (19.0)	57 (22.7)	105 (20.8)
Not Hispanic or Latino	205 (81.0)	194 (77.3)	399 (79.2)
Not applicable	0	0	0
Renal function, eGFR (mL/min/1.73m2)			
N	253 (100)	251 (100)	504 (100)
Normal (90 <=)	192 (75.9)	170 (67.7)	362 (71.8)
Mild RI (60 <= to < 90)	60 (23.7)	80 (31.9)	140 (27.8)
Moderate RI (30 <= to < 60)	1 (0.4)	1 (0.4)	2 (0.4)
Severe RI (15 <= to < 30)	0	0	0
End-stage renal disease (< 15)	0	0	0

NA: for ethnicity values recorded as 'missing', 'not done', or 'not-available'; 'Baseline': defined as the latest assessment at or prior to the randomisation visit; 'Smoking': defined as smoking at least one cigarette or equivalent daily; The renal function categories are based on the eGFR as per CKD-EPI; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; RI: renal impairment; N: number of subjects; %: proportion of subjects.

Source: Modified from table 10-3 CSR PIONEER 7

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

Most patients did not have diabetic retinopathy, only 7.1% on semaglutide and 11.6% of patients on sitagliptin reported a history of non-proliferative diabetic retinopathy. Other diabetic complications included diabetic neuropathy (17.0% and 18.7%) and diabetic nephropathy (6.7% and 5.2%) for semaglutide and sitagliptin, respectively.

Frequent and clinically relevant medical history included: gastrointestinal disorders (5.9% and 7.2%), infections and infestations (7.5% and 8.4%), neoplasms (6.3% and 8.0%), renal and urinary disorders (3.2% and 6.8%), metabolism and nutrition disorders (0.8% and 1.6%), eye

Reference ID: 4494348

disorders (2.0% and 2.8%) and cardiac disorders (0.4% and 1.6%), for patients on semaglutide and sitagliptin, respectively.

The most frequent and clinically relevant concomitant illnesses were: hyperlipidemia (36.8% and 39.0%), dyslipidemia (17.4% and 16.7%), obesity (12.3% and 16.3%), gastrointestinal disorders (13.0% and 14.3%), hepatic steatosis (9.9% and 10.0%), hypothyroidism (7.5% and 7.6%), neoplasms (6.3% and 6.4%), vascular disorders (5.9% and 6.4%) and psychiatric disorders (15.4% and 19.1% [of which depression constituted 7.9% and 10.4%]) for patients on semaglutide and sitagliptin, respectively.

Overall the treatment groups were well matched regarding baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

At baseline, the reported use of concomitant medications was similar between the treatment groups. The most frequently used concomitant medications were lipid lowering agents, especially HMG CoA reductase inhibitors (51.6% of patients). A large proportion of patients used platelet aggregation inhibitors excluding heparin (33.3% of patients) and antihypertensives, especially ACE inhibitors (21.2% of patients), angiotensin II antagonists (20.8%) and selective beta blocking agents (15.3%).

At randomization, a total of 98.0% of patients in the semaglutide group and 94.8% in the sitagliptin group were on metformin, and 49.0% in the semaglutide group and 50.2% in the sitagliptin group were on sulfonylureas.

The proportion of patients receiving additional anti-diabetic medication, including rescue medication, was lower with semaglutide than with sitagliptin.

Reference ID: 4494748

Table 42 Additional Anti-Diabetic Medication and Rescue Medication PIONEER 7

	Oral sema flex N (%)		Sita 100 mg N (%)	
	Additional anti-diabetic medication	Rescue medication	Additional anti-diabetic medication	Rescue medication
Number of subjects in FAS	**253**		**251**	
Total	**22 (8.7)**	**8 (3.2)**	**47 (18.7)**	**40 (15.9)**
Sulfonylureas	6 (2.4)	2 (0.8)	19 (7.6)	18 (7.2)
SGLT-2 inhibitors	5 (2.0)	3 (1.2)	12 (4.8)	12 (4.8)
Insulins, long-acting	4 (1.6)	1 (0.4)	5 (2.0)	5 (2.0)
Insulins, intermediate-acting	1 (0.4)	1 (0.4)	3 (1.2)	3 (1.2)
Insulins, fast-acting	0		1 (0.4)	
Insulins, intermediate- or long-acting combined with fast-acting	1 (0.4)	0	2 (0.8)	1 (0.4)
DPP-4 inhibitors	7 (2.8)	0	4 (1.6)	0
Metformin	0	0	6 (2.4)	4 (1.6)
GLP-1 analogues	1 (0.4)	0	2 (0.8)	0
Thiazolidinediones	0	0	2 (0.8)	1 (0.4)
Other	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)

Source: Table 10-4 CSR PIONEER 7

Efficacy Results - Primary Endpoint

Superiority of flexible dose semaglutide vs sitagliptin was confirmed for both the primary endpoint (HbA1c < 7.0% at week 52) and the confirmatory secondary endpoint (change from baseline at week 52 in body weight). The estimate in the table below represents the estimate of odds ratios for semaglutide vs sitagliptin, for both the primary and confirmatory secondary endpoint.

Table 43 Primary and Confirmatory Secondary Endpoints –PIONEER 7

Endpoint	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoint: HbA1c < 7.0% (ADA) at week 52					
Oral sema flex / Sita 100 mg	4.40 [2.89 ; 6.70]	<.0001		Superiority	Confirmed
Confirmatory secondary endpoint: Change from baseline at week 52 in body weight (kg)					
Oral sema flex - Sita 100 mg	-1.9 [-2.6 ; -1.2]	<.0001		Superiority	Confirmed

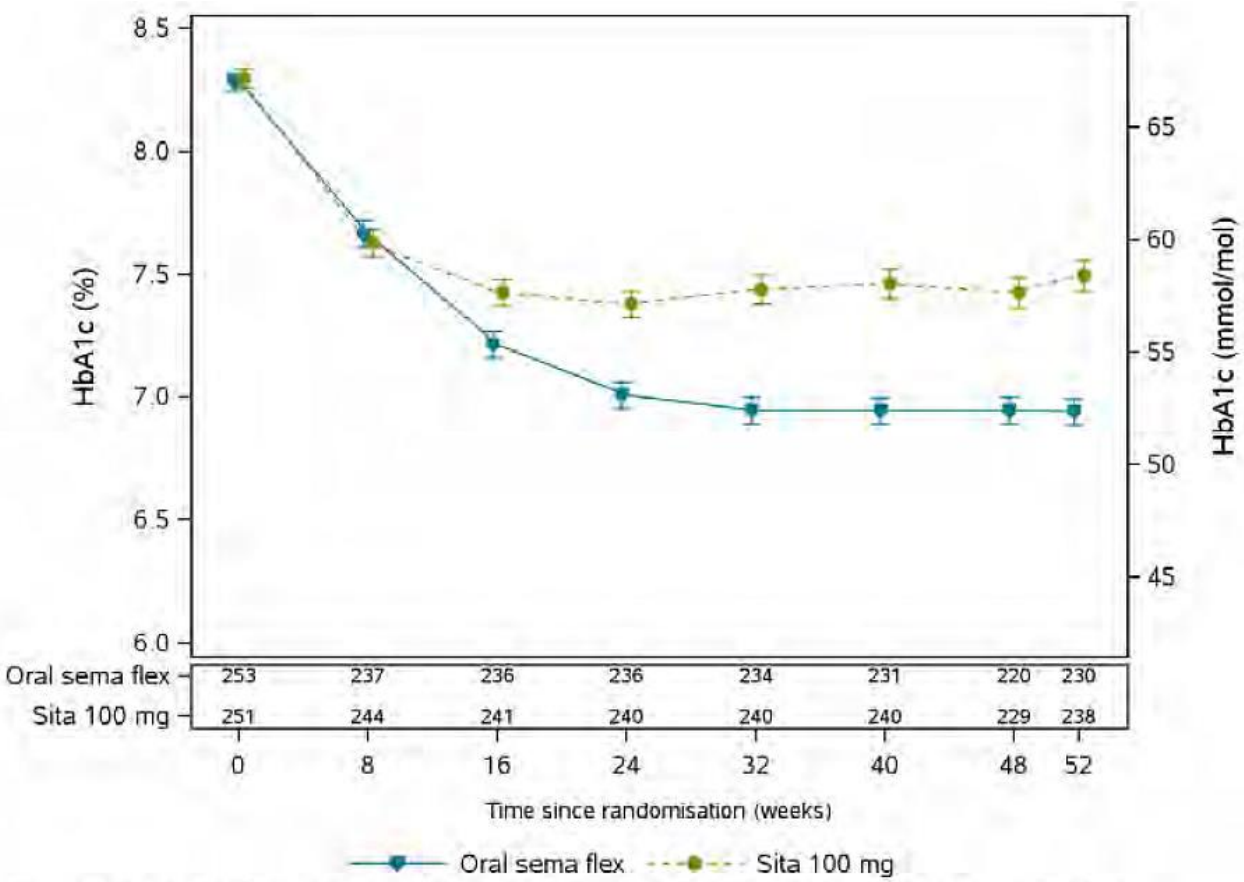
'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval; 'p-value': unadjusted two-sided p-value for test of no difference

Source: Table 11-1 CSR PIONEER 7

Reference ID: 4494748

At baseline, HbA1c levels were similar between the two treatment groups (8.3%). HbA1c levels decreased for both treatment groups from baseline to week 8, after which a separation of the HbA1c levels for semaglutide and sitagliptin was observed. From week 8 through week 32, HbA1c levels further decreased with semaglutide; with sitagliptin, HbA1c levels decreased through week 16. At week 52, the observed changes from baseline were −1.3 % with semaglutide and −0.8 % with sitagliptin.

Figure 21 HbA1c by Week – Mean Plot –PIONEER 7



Observed data from the in-trial observation period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel represent the number of subjects contributing to the means.

Source: Figure 11-1 CSR PIONEER 7

Data Quality and Integrity - Reviewers' Assessment

I did not find any issues with the data quality.

Efficacy Results - Secondary and other relevant endpoints

<u>Body weight</u>

Reference ID: 4494748

At baseline, body weight was similar between the two treatment groups (semaglutide: 88.9 kg, sitagliptin: 88.4 kg). The estimated changes from baseline in body weight were −2.6 kg with semaglutide and −0.7 kg with sitagliptin.

HbA1c targets

More patients on semaglutide achieved either the ADA (HbA1c <7%) or the AACE (HbA1c ≤6.5%) targets compared to sitagliptin. The target of HbA1c <7% was achieved by 58.3% of patients on semaglutide at 52 weeks, vs 25.2% of patients on sitagliptin. The target of HbA1c ≤6.5% was achieved by 33% of patients on semaglutide at 52 weeks, vs 12.2% of patients on sitagliptin.

Durability of Response

The semaglutide effect on glycemic control and weight appeared to be sustained for the duration of the study.

Persistence of Effect

Not applicable as effect persistence was not assessed.

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.7. PIONEER 8 (4280)

6.7.1. Study Design

Overview and Objective

Study Title: Efficacy and Safety of Oral Semaglutide versus Placebo in Patients with Type 2 Diabetes Mellitus treated with insulin.

Primary objective

- To compare the effect of once-daily dosing of three dose levels of oral semaglutide (3 mg, 7 mg and 14 mg) versus placebo on glycemic control in patients with type 2 diabetes mellitus treated with insulin.

Secondary objectives

- To compare the effect of once-daily dosing of three dose levels of oral semaglutide (3 mg, 7 mg and 14 mg) versus placebo on body weight in patients with type 2 diabetes mellitus treated with insulin.

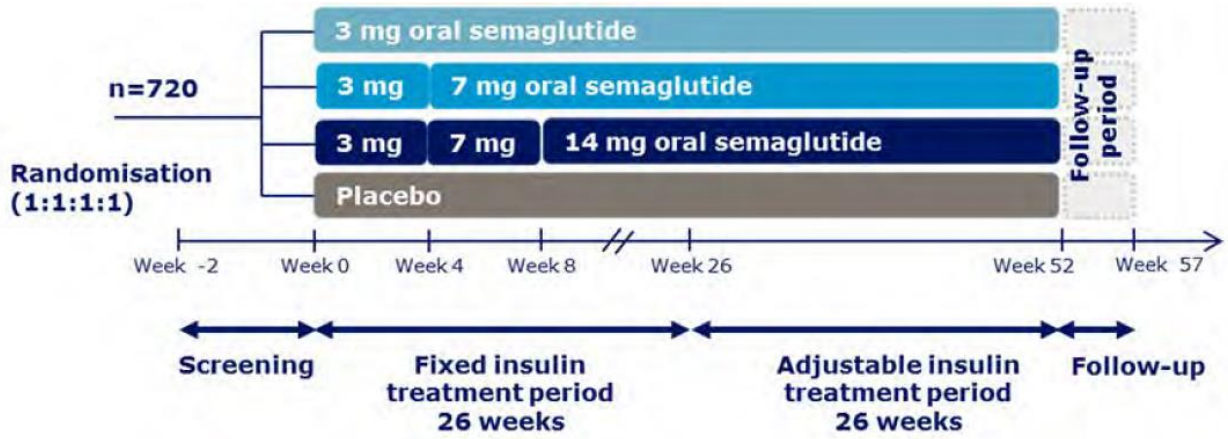
Reference ID: 4494748

- To compare the safety and tolerability of once-daily dosing of three dose levels of oral semaglutide (3 mg, 7 mg and 14 mg) versus placebo in patients with type 2 diabetes mellitus treated with insulin.

Trial Design

This was a 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational trial. The total trial duration for the individual patient was approximately 59 weeks. The trial included a 2-week screening period followed by a 52-week randomized treatment period and a 5-week follow-up period. The 52-week randomized treatment period was split into two treatment periods; an initial 26-week fixed insulin treatment period where the insulin treatment was restricted, followed by a 26-week period where the insulin treatment was adjustable without any restrictions. The efficacy endpoints were assessed at 26 weeks.

Figure 22 Trial Design PIONEER 8



Source: Figure 9-1 CSR PIONEER 8

Randomization was 1:1:1:1.

<u>Key Inclusion/Exclusion criteria</u>
Similar to PIONEER 2.

For complete inclusion/exclusion criteria please see study report.

<u>Dose selection/study treatments:</u>
All three semaglutide dose were studies. Dose titration, and semaglutide administration was similar to that used in all other PIONEER trials.

<u>Procedures and Schedule:</u>

Reference ID: 4494748

The patients were to attend in person visits at screening, randomization, weeks 4, 8, 14, 20, 26, 32, 38 45, 52 (end of treatment), and 57 (follow-up). Telephone visits were scheduled for weeks 2, 10, 12, 16, 29, 35, and 41.

Eye examinations were performed at screening and end of treatment.

Concurrent medications:
At baseline, the reported use of concomitant medications was similar across the treatment groups with no clinically relevant differences and reflecting what would be expected in the enrolled population. The most frequently used concomitant medications were HMG CoA reductase inhibitors, platelet aggregation inhibitors excluding heparin, angiotensin II antagonists, ACE inhibitors, dihydropyridine derivatives, beta blocking agents and proton pump inhibitors.

The concomitant non-insulin antidiabetic medications reported at screening and at randomization are presented below. No imbalances are noted between treatment arms. Most patients were on metformin in all treatment groups, in addition to insulin.

Table 44 Concomitant Non-Insulin Anti-Diabetic Medication Ongoing at Screening and Randomization PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N(%)
Number of subjects	184	182	181	184	731
On-going at screening					
Biguanides,	123 (66.8)	122 (67.0)	121 (66.9)	125 (67.9)	491 (67.2)
DPP-4 inhibitor	0	1 (0.5)	0	0	1 (0.1)
On-going at randomisation					
Biguanides	123 (66.8)	122 (67.0)	121 (66.9)	125 (67.9)	491 (67.2)
DPP-4 inhibitor	0	1 (0.5)	0	0	1 (0.1)

N: number of subjects; %: proportion of subjects. nn9924/nn9924-4280/20181130 ctr er

Source: Table 10-4 CSR PIONEER 8

Treatment compliance
Compliance was assessed by monitoring of drug accountability.

Rescue medications
Patients with persistent and unacceptable hyperglycemia (as judged by the investigator) were to be offered treatment intensification. To allow time for dose escalation to maximum dose and to observe the expected effect of treatment on glycemic parameters as well as the effect of insulin up-titration from week 8 to week 16, a rescue medication was to be offered if a confirmatory FPG was 200 mg/dL from week 16 to end of treatment. In addition, patients were to be offered rescue medication if their HbA1c was >8.5% from week 26 to end of treatment.

Reference ID: 4494748

Rescue medication was to be prescribed at the investigator's discretion as add-on to trial product and according to ADA/EASD guidelines; GLP-1 RAs, DPP-4 inhibitors and amylin analogues were not allowed as rescue medication.

Total daily insulin dose adjustments during the trial

At randomization, a 20% reduction in total daily insulin dose was recommended to minimize the risk of hypoglycemia when trial product was initiated.

During the fixed insulin treatment period, an increase in the total daily insulin dose before week 18 was to be avoided, unless required to prevent acute diabetic complications.

Between weeks 18-26, insulin could be adjusted by titration of either basal or premixed insulin. However, the protocol specified that the total insulin dose should not have been adjusted to above the dose recorded at randomization. After week 26, until the end of the trial, there were no restrictions to insulin adjustments.

Insulin was titrated based on the lowest of three SMPG values measured on three consecutive days prior to each phone contact/site visit.

Table 45 Increase in Insulin Dose Guidelines

Lowest of 3 pre-breakfast/pre-dinner SMPG values		Titration of dose of basal or premixed insulin including combinations of soluble insulins IU (*)
mmol/L	mg/dL	
4.0 – 5.5	71 – 99	No titration
5.6 – 7.0	100 – 126	+2
7.1 – 8.0	127 – 144	+4
8.1 – 9.0	145 – 162	+6
>9.0	>162	+8

(*)
- V5 to P9 (both included): The total daily insulin dose should not be adjusted above the dose taken prior to randomisation, recorded at V2 as pre-randomisation dose.
- V11 to V18: No restrictions on maximum total daily insulin doses

Source: Table 9-2 CSR PIONEER 8

Reference ID: 4494348

Table 46 Decrease in Insulin Dose Guidelines

Lowest of 3 pre-breakfast/pre-dinner SMPG values		Titration of dose of basal or premixed insulin including combinations of soluble insulins IU (*)
mmol/L	mg/dL	
< 3.1	< 56	-4 (for doses >45 IU, suggest dose reduction of 10%)
3.1 – 3.9	56 – 70	-2 (for doses >45 IU, suggest dose reduction of 5%)
(*) Entire trial: No restrictions on minimum total daily insulin doses		

Source: Table 9-3 CSR PIONEER 8

Patient completion, discontinuation, or withdrawal
Similar to PIONEER 1.

Study Endpoints

The primary endpoint was change from baseline to week 26 in HbA1c (%-points).

The confirmatory secondary endpoint was change from baseline to week 26 in body weight (kg).

Statistical Analysis Plan

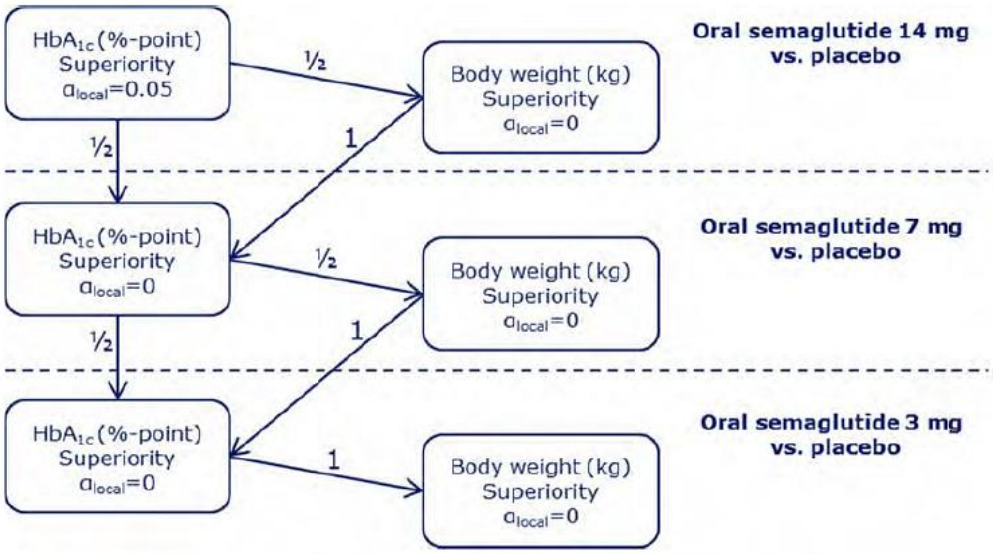
The analysis sets and observation periods were defined as for all other PIONEER trials.

The sample size was calculated to ensure a statistical power of at least 90% to confirm superiority on change from baseline at week 26 in HbA1c for the treatment policy estimand of all doses of oral semaglutide versus placebo. A total of 720 patients were planned to be randomized.

The hypothesis testing is outlined in the figure below.

Reference ID: 4494748

Figure 23 Statistical Testing Strategy PIONEER 8



The total significance level of α = 0.05 (two-sided) was initially allocated to the hypothesis of superiority of oral semaglutide 14 mg versus placebo on change from baseline at week 26 in HbA_{1c}; if that hypothesis was confirmed, the local significance level (α-local) was reallocated to the other hypotheses in the testing strategy according to the indicated weight (½ or 1) of the arrows. Each hypothesis was tested at its updated local significance level (α-local) until all hypotheses had been confirmed or until no hypothesis could be confirmed.

Source: Figure 9-7 CSR PIONEER 8

Protocol Amendments

There were 3 substantial amendments to the protocol.

Reference ID: 4494748

Table 47 Protocol Amendments PIONEER 8

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
1	06-Oct-2016	Before FPFV	Canada	New text addressing exclusion criteria and the recommended contraceptive methods concerning women of childbearing potential was added to accommodate the request of the Canadian Regulatory Authority
2	22-Nov-2016	Before FPFV	Global	New text addressing : • Additional eye examinations and additional data collection on diabetic retinopathy • Investigator's responsibility in ensuring evaluation and management of certain risk factors and complications • Clarification of the criteria for completion, withdrawal and lost to follow-up • Week 26 reporting of trial results • Other minor corrections and clarifications
3	15-May-2017	Approximately 3 months after FPFV	Global	New text addressing the inclusion in the flow chart of the 7-point SMPG profile at visit 18A, and inclusion of an "Eye Examination Category" in section 17.2 "Definition of analysis sets", and correction of a minor typographical error in section 8.1.5.

Source: Table 9-13 CSR PIONEER 8

It is not likely that either these amendments had any effect on evaluation of efficacy and/or safety.

Data Quality and Integrity: Sponsor's Assurance

The trial was monitored by Novo Nordisk by on-site visits, telephone calls and regular inspection of the eCRFs.

6.7.2. Study Results

Compliance with Good Clinical Practices

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

Financial Disclosure

Of the total of 615 investigators, 7 had financial disclosures. See Appendix 13.3 for details.

Reference ID: 4494748

Patient Disposition

In total, 1038 patients were screened and 307 patients were screening failures; thus, 731 patients were randomized to receive either oral semaglutide 3 mg (184 patients), 7 mg (182 patients) or 14 mg (181 patients), or placebo (184 patients). One patient in the oral semaglutide 7 mg group was not exposed to trial product; thus, the FAS contains 1 patient more than the SAS.

Out of the 307 patients who failed screening, the majority failed due to non-fulfilment of HbA1c inclusion (175 patients, 57.0% of all screening failures), due to renal exclusion criteria (64 patients, 20.8% of all screening failures), and due to the proliferative retinopathy or maculopathy exclusion criteria 15 (24 patients, 7.8% of all screening failures).

In total, 614 patients (84.0%) completed the treatment with trial product and 697 patients (95.3%) completed the trial.

A total of 117 patients (16.0%) discontinued trial product prematurely for the following reasons: adverse events (8.2%), violation of inclusion or exclusion criteria (1.4%), intention to become pregnant (0.1%), patient withdrawal from trial (1.0%), pregnancy (0.1%) and 'Other' reasons (5.1%).

The proportion of patients who prematurely discontinued trial product due to AEs was greater with oral semaglutide 14 mg (14.4%) than with oral semaglutide 7 mg (8.8%), 3 mg (7.1%) and placebo (2.7%). Gastrointestinal AEs were the event type that most frequently led to premature trial product discontinuation (4.9%, 6.6% and 10.5% for oral semaglutide 3 mg, 7 mg and 14 mg, respectively, and 0.5% with placebo).

Reference ID: 4494748

Table 48 Patient Disposition – PIONEER 8

	Oral sema 3 mg		Oral sema 7 mg		Oral sema 14 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Screened									1038	
Screening failures									307	(29.6)
Randomised	184		182		181		184		731	
Exposed	184	(100)	181	(99.5)	181	(100)	184	(100)	730	(99.9)
Treatment completers [1]	160	(87.0)	148	(81.3)	144	(79.6)	162	(88.0)	614	(84.0)
Without rescue medication	110	(59.8)	115	(63.2)	115	(63.5)	100	(54.3)	440	(60.2)
With rescue medication	50	(27.2)	33	(18.1)	29	(16.0)	62	(33.7)	174	(23.8)
Premature trial product discontinuation	24	(13.0)	34	(18.7)	37	(20.4)	22	(12.0)	117	(16.0)
Exposed										
Adverse event(s)	13	(7.1)	16	(8.8)	26	(14.4)	5	(2.7)	60	(8.2)
Violation of in-/excl. crit.	2	(1.1)	4	(2.2)	2	(1.1)	2	(1.1)	10	(1.4)
Intention of becoming pregnant	0		0		0		1	(0.5)	1	(0.1)
Participate another clin. trial [2]	0		0		0		0		0	
Calcitonin value >= 100 ng/L	0		0		0		0		0	
Subject withdrawal from trial	0		2	(1.1)	2	(1.1)	3	(1.6)	7	(1.0)
Pregnancy	0		1	(0.5)	0		0		1	(0.1)
Other	9	(4.9)	10	(5.5)	7	(3.9)	11	(6.0)	37	(5.1)
Not exposed										
Violation of in-/excl. crit.	0		1	(0.5)	0		0		1	(0.1)
Trial completers [3]	174	(94.6)	173	(95.1)	175	(96.7)	175	(95.1)	697	(95.3)
Completed treatment	157	(85.3)	148	(81.3)	144	(79.6)	160	(87.0)	609	(83.3)
Discontinued trial product	17	(9.2)	25	(13.7)	31	(17.1)	15	(8.2)	88	(12.0)
Withdrawal from trial- primary reason	10	(5.4)	9	(4.9)	6	(3.3)	9	(4.9)	34	(4.7)
Lost to follow-up	10	(5.4)	3	(1.6)	1	(0.6)	4	(2.2)	18	(2.5)
Withdrawal by subject	0		6	(3.3)	2	(1.1)	5	(2.7)	13	(1.8)
Other	0		0		3	(1.7)	0		3	(0.4)
Died	0		0		3	(1.7)	0		3	(0.4)

'[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'primary reason': according to the end-of-trial form; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication other than insulin (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product, and/or intensification of insulin (a more than 20% increase in dose relative to baseline) across 2 consecutive visits or more, with the intensification at or after randomisation and before last day on trial product; N: number of subjects; %: proportion of randomised subjects except for screening failures where it is proportion of screened subjects.

Source: Table 10-1 CSR PIONEER 8

Protocol Violations/Deviations

Protocol deviations

PDs were categorized as important/non-important and reported into different categories according to a set of pre-specified categories and subcategories. 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, 285 important PDs were closed; the PDs comprised 28 site-level PDs and 253 patient-level PDs, 1 trial-level PD, and 3 country-level PDs.

Reference ID: 4494348

Important PDs at trial level

One important trial level PD was reported: during review of EDC data, it was noted that some sites appear to use scales with a precision of 0.5 kg (and not 0.1 as expected) or to round the weight value to the nearest half or whole kilogram. Sites were instructed to use the same scale if more than half of the planned patients at the site have been randomized, or to switch to a scale with a precision of one decimal if less than half of the planned patients have been randomized at the site.

The applicant did not consider these PDs to have impacted the trial results, and I agree with the assessment.

Important PDs at country level

A total of 3 important PDs were reported: all involved patient diaries. In Canada, the patient diary for premature discontinuation was not submitted for approval to the central Institutional Review Board (IRB) and was therefore not used at the sites. In India, the patient diary that had to be provided to patients who had prematurely discontinued treatment was not provided to patients. In Mexico, a section for the date and time of the last trial medication prior to a low blood glucose episode section was not included in the Spanish version of the diary. Per the applicant, these protocol deviations did not impact patient safety or data interpretation.

Site and patient level PDs
The site and patient level deviations are summarized in the table below.

Reference ID: 4494748

Table 49 Site and Patient-Level Protocol Deviations PIONEER 8

Category	Site-level PDs (n)	Subject-level PDs (n)					
		Screening failures	Oral sema 3 mg	Oral sema 7 mg	Oral sema 14 mg	Oral placebo	Total no of subject-level PDs
Informed consent	1	20	5	12	12	10	59
Inclusion/exclusion/ randomisation criteria	-	-	5	14	7	9	35
Discontinuation criteria	-	-	1	-	-	-	1
Trial product handling	3	-	3	5	5	10	23
Treatment compliance	1	-	3	5	14	5	27
Assessment deviations	2	-	19	12	11	13	55
Other	21	-	17	15	8	13	53
Total	28	20	53	63	57	60	253

Abbreviations: PD: protocol deviation; n: number of PDs

'-': indicate no PDs reported under this category

Source: Table 10-9 CSR PIONEER 8

In total, 20 patients were excluded from the FAS because the patients were screening failures that were randomized in error and were never exposed to the trial product.

Table of Demographic Characteristics

Overall, demographics and baseline characteristics were well matched between patients in all treatment groups. More male (395 patients, 54%) than female patients (336 patients, 46%) were randomized in the trial. The mean age of the population was 61 years. The mean T2DM duration was around 14–16 years. The mean HbA1c was 8.2%. The proportions of patients per region were similar across the treatment groups. Most patients were either White (51.4%) or Asian (36.0) and there was no noteworthy difference between the treatment groups in terms of race and ethnicity. Renal function (based on baseline eGFR) was normal for 59.1% of the patients; 39.0% had mild renal impairment and 1.9% had moderate renal impairment. The overall mean GFR was 92 mL/min/1.73 m2, with no relevant differences observed across treatment groups.

Reference ID: 4494748

Table 50 Selected Demographics and Baseline Characteristics for Continuous Variables – FAS – PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N(%)
Age (years)					
N	184	182	181	184	731
Mean (SD)	61 (9)	60 (10)	61 (10)	60 (10)	61 (10)
HbA_{1c} (%)					
N	184	182	181	184	731
Mean (SD)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)
Duration of diabetes (years)					
N	184	182	181	184	731
Mean (SD)	15.1 (7.9)	16.2 (8.6)	14.1 (8.0)	14.8 (7.9)	15.0 (8.1)
Body weight (kg)					
N	184	182	181	184	731
Mean (SD)	85.9 (21.5)	87.1 (23.6)	84.6 (21.0)	86.0 (21.4)	85.9 (21.8)
eGFR (mL/min/1.73 m^2)					
N	184	182	181	184	731
Mean (SD)	92 (16)	92 (16)	91 (14)	91 (15)	92 (15)

The eGFR was estimated using the CKD-EPI formula. 'Baseline': defined as the latest assessment at or prior to the randomisation visit; eGFR: estimated glomerular filtration rate; CKD_EPI; N: number of subjects; SD: standard deviation. nn9924/nn9924-4280/20181130_ctr_er

Source: Modified from Table 10-2 CSR PIONEER 8

Reference ID: 4494748

Table 51 Selected Demographics and Baseline Characteristics for Categorical Variables – FAS – PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N(%)
Number of subjects	184	182	181	184	731
Age group (years)					
N	184 (100)	182 (100)	181 (100)	184 (100)	731 (100)
18 <= to < 65	110 (59.8)	121 (66.5)	108 (59.7)	114 (62.0)	453 (62.0)
65 <= to < 75	67 (36.4)	49 (26.9)	60 (33.1)	63 (34.2)	239 (32.7)
75 <= to < 85	7 (3.8)	12 (6.6)	11 (6.1)	7 (3.8)	37 (5.1)
85 <=	0	0	2 (1.1)	0	2 (0.3)
Sex					
N	184 (100)	182 (100)	181 (100)	184 (100)	731 (100)
Female	82 (44.6)	79 (43.4)	96 (53.0)	79 (42.9)	336 (46.0)
Male	102 (55.4)	103 (56.6)	85 (47.0)	105 (57.1)	395 (54.0)
Region					
N	184 (100)	182 (100)	181 (100)	184 (100)	731 (100)
Europe	50 (27.2)	48 (26.4)	46 (25.4)	51 (27.7)	195 (26.7)
North America	67 (36.4)	64 (35.2)	60 (33.1)	60 (32.6)	251 (34.3)
South America	6 (3.3)	10 (5.5)	14 (7.7)	10 (5.4)	40 (5.5)
Asia	61 (33.2)	60 (33.0)	61 (33.7)	63 (34.2)	245 (33.5)
Race					
N	184 (100)	182 (100)	181 (100)	184 (100)	731 (100)
White	89 (48.4)	95 (52.2)	94 (51.9)	98 (53.3)	376 (51.4)
Black or African American	15 (8.2)	10 (5.5)	11 (6.1)	13 (7.1)	49 (6.7)
Asian	66 (35.9)	66 (36.3)	66 (36.5)	65 (35.3)	263 (36.0)
American Indian or Alaska Native	1 (0.5)	0	1 (0.6)	0	2 (0.3)
Native Hawaiian or other Pacific	0	0	0	0	0
Other	1 (0.5)	1 (0.5)	1 (0.6)	0	3 (0.4)
NA*	12 (6.5)	10 (5.5)	8 (4.4)	8 (4.3)	38 (5.2)
Ethnicity					
N	184 (100)	182 (100)	181 (100)	184 (100)	731 (100)
Hispanic or Latino	18 (9.8)	24 (13.2)	30 (16.6)	25 (13.6)	97 (13.3)
Not Hispanic or Latino	154 (83.7)	148 (81.3)	143 (79.0)	150 (81.5)	595 (81.4)
NA**	12 (6.5)	10 (5.5)	8 (4.4)	9 (4.9)	39 (5.3)
Renal function, eGFR (mL/min/1.73 m^2)					
N	184 (100)	182 (100)	181 (100)	184 (100)	731 (100)
Normal (90 <=)	112 (60.9)	109 (59.9)	104 (57.5)	107 (58.2)	432 (59.1)
Mild RI (60 <= to < 90)	66 (35.9)	71 (39.0)	75 (41.4)	73 (39.7)	285 (39.0)
Moderate RI (30 <= to < 60)	6 (3.3)	2 (1.1)	2 (1.1)	4 (2.2)	14 (1.9)
Severe RI (15 <= to < 30)	0	0	0	0	0
End-stage renal disease (< 15)	0	0	0	0	0

NA*: race is recorded as 'NA' for France as per local regulation; NA**: ethnicity is recorded as 'NA' for France as per local regulation; NA: for ethnicity values recorded as 'missing', 'not done', or 'not-available'; 'Baseline': defined as the latest assessment at or prior to the randomisation visit; 'Smoking': defined as smoking at least one cigarette or equivalent daily; The renal function categories are based on the eGFR as per CKD-EPI; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; RI: renal impairment; N: number of subjects; %: proportion of subjects. nn9924/nn9924-4280/20181130_ctr_er

Source: Modified from Table 10-3 CSR PIONEER 8

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

<u>Medical history and concomitant illnesses</u>

Reference ID: 4494748

There were no clinically relevant differences in medical history and concomitant illnesses between the treatment groups. Frequent and clinically relevant concomitant illnesses for all treatment groups were: metabolism and nutrition disorders (74.5–81.3%), musculoskeletal and connective tissue disorders (37.5–45.1%), eye disorders (25.4–29.1%), gastrointestinal disorders (17.1–29.3%), respiratory thoracic and mediastinal disorders (16.8–25.8%), hepatobiliary disorders (15.9–22.8%), psychiatric disorders (17.9–20.4%), renal and urinary disorders (13.0–19.8%), infections and infestations (11.4–19.0%), cardiac disorders (8.2–13.6%) and neoplasms (6.0–7.2%).

The most frequent and clinically relevant concomitant illnesses for all treatment groups were: dyslipidemia (36.4–46.2%), obesity (14.4–21.7%), osteoarthritis (13.2–16.0%), hepatic steatosis (13.7–15.8%), cataract (12.0–19.2%), hypothyroidism (6.6–14.4%) and depression (7.1–12.5%).

At baseline, diabetic retinopathy was present in 28.6–37.0% of patients, with no relevant differences across treatment groups. Most of the diabetic retinopathies were reported as nonproliferative. Other diabetic complications included diabetic neuropathy (33.7–36.4%), with no relevant differences across treatment groups. The proportion of patients with a reported history of diabetic nephropathy was 14.3–20.7%.

No clinically relevant differences across treatment groups were observed for histories of cardiovascular disease at screening. The most frequently reported histories of cardiovascular disease were hypertension (76.2–79.9%) and ischemic heart disease (16.8–20.9%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Background antidiabetic medications

Patients were to be on a stable insulin regimen (basal insulin alone, basal and bolus insulin in any combination, premixed insulin including combinations of soluble insulin) for ≥ 90 days prior to screening. Patients were also allowed to be taking a stable daily dose of metformin (≥ 1500 mg or maximum tolerated dose) for ≥ 90 days prior to the day of screening.

The concomitant non-insulin antidiabetic medications reported at screening and at randomization are presented below. Notably, one patient was on DPP-4 inhibitor. This was discovered at day 100. Although the patient continued in the trial, data points after the premature trial product discontinuation visit were excluded from the analysis of effect for this patient which is in violation of eligibility criteria.

Reference ID: 4494748

Table 52 Concomitant Non-Insulin Anti-Diabetic Medication Ongoing at Screening and Randomization – PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N(%)
Number of subjects	184	182	181	184	731
On-going at screening					
Biguanides,	123 (66.8)	122 (67.0)	121 (66.9)	125 (67.9)	491 (67.2)
DPP-4 inhibitor	0	1 (0.5)	0	0	1 (0.1)
On-going at randomisation					
Biguanides	123 (66.8)	122 (67.0)	121 (66.9)	125 (67.9)	491 (67.2)
DPP-4 inhibitor	0	1 (0.5)	0	0	1 (0.1)

N: number of subjects; %: proportion of subjects. nn9924/nn9924-4280/20181130_ctr_er

Source: Table 10-4 CSR PIONEER 8

At screening, long-acting (basal) insulin was the most commonly used insulin regimen, used by 41.9% of the trial patients, followed by a basal and bolus insulin regimen (38.9%) and a premix insulin regimen (17.6%). The concomitant insulin types reported at screening and at randomization are presented in the table below.

Table 53 Concomitant Insulin at Screening and Randomization – PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N(%)
Number of subjects	184	182	181	184	731
On-going at screening					
Basal insulin:	76 (41.3)	76 (41.8)	75 (41.4)	79 (42.9)	306 (41.9)
Basal and bolus insulin:	71 (38.6)	72 (39.6)	70 (38.7)	71 (38.6)	284 (38.9)
Premix insulin:	35 (19.0)	28 (15.4)	34 (18.8)	32 (17.4)	129 (17.6)
Bolus insulin:	1 (0.5)	2 (1.1)	1 (0.6)	1 (0.5)	5 (0.7)
Basal and premix insulin:	0	2 (1.1)	0	1 (0.5)	3 (0.4)
Bolus and premix insulin:	1 (0.5)	2 (1.1)	1 (0.6)	0	4 (0.5)
On-going at randomisation					
Basal insulin	77 (41.8)	73 (40.1)	74 (40.9)	81 (44.0)	305 (41.7)
Basal and bolus insulin	70 (38.0)	71 (39.0)	68 (37.6)	66 (35.9)	275 (37.6)
Premix insulin	34 (18.5)	28 (15.4)	32 (17.7)	30 (16.3)	124 (17.0)
Bolus insulin	0	1 (0.5)	0	0	1 (0.1)
Basal and premix insulin	0	1 (0.5)	0	0	1 (0.1)
Bolus and premix insulin	0	1 (0.5)	0	0	1 (0.1)

N: number of subjects; %: proportion of subjects. nn9924/nn9924-4280/20181130 ctr er

Source: Table 10-5 CSR PIONEER 8

The insulin doses are presented below by treatment arms. No major differences were seen for the insulin regimens that were used by a significant proportion of patients, however, wide variations were seen for insulin regimens used by only a few patients (for example only a few

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patients were using premixed insulin and insulin bolus, and the minimum and maximum total daily dose varied from tens to hundreds of units).

Table 54 Insulin Dose at Screening by Insulin Treatment – PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N (%)
Total daily dose (U)					
N	184	182	181	184	731
Mean (SD)	60 (50)	62 (64)	54 (42)	56 (46)	58 (51)
Median	48	44	44	42	44
Min; Max	10 ; 360	10 ; 500	10 ; 330	10 ; 300	10 ; 500
Basal insulin:					
Total daily dose (U)					
N	76	76	75	79	306
Mean (SD)	35 (24)	35 (29)	33 (25)	34 (27)	34 (26)
Median	26	25	25	28	26
Min; Max	10 ; 100	10 ; 160	10 ; 174	10 ; 162	10 ; 174
Basal and Bolus insulin:					
Total daily dose (U)					
N	71	72	70	71	284
Mean (SD)	83 (48)	89 (64)	75 (49)	84 (52)	83 (54)
Median	70	75	65	75	72
Min; Max	14 ; 220	11 ; 445	14 ; 330	16 ; 300	11 ; 445
Premix insulin:					
Total daily dose (U)					
N	35	28	34	32	129
Mean (SD)	60 (60)	47 (50)	53 (36)	42 (22)	51 (45)
Median	48	28	46	38	42
Min; Max	14 ; 360	10 ; 244	12 ; 180	10 ; 100	10 ; 360
Bolus insulin:					
Total daily dose (U)					
N	1	2	1	1	5
Mean (SD)	220 (0)	293 (293)	32 (0)	200 (0)	208 (181)
Median	220	293	32	200	200
Min; Max	220 ; 220	86 ; 500	32 ; 32	200 ; 200	32 ; 500
Basal and Premix insulin:					
Total daily dose (U)					
N	0	2	0	1	3
Mean (SD)		84 (6)		69 (0)	79 (10)
Median		84		69	80
Min; Max		80 ; 88		69 ; 69	69 ; 88
Bolus and Premix insulin:					
Total daily dose (U)					
N	1	2	1	0	4
Mean (SD)	150 (0)	36 (14)	120 (0)		86 (59)
Median	150	36	120		83
Min; Max	150 ; 150	26 ; 46	120 ; 120		26 ; 150

N: number of subjects contributing to the summary statistic; SD: standard deviation; U: unit.
Source: Table 10-6 CSR PIONEER 8

Additional antidiabetic medications and rescue medications

A total of 36 patients (4.9%) initiated additional anti-diabetic medication prior to week 26. The proportions of patients initiating additional anti-diabetic medication prior to week 26 were comparable across treatment groups (4.4–6.0%).

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A total of 20 patients (2.7%) initiated rescue medication (as add-on to trial product) prior to week 26. The proportions of patients initiating rescue medication prior to week 26 were lowest in the oral semaglutide 7 mg and 14 mg groups (1.1% and 2.2%, respectively) compared to the oral semaglutide 3 mg and placebo groups (2.7% and 4.9%, respectively).

Table 55 Additional Anti-Diabetic Medication and Rescue Medication Initiated Prior to Week 26 – PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	184	182	181	184	731
ADDITIONAL ANTI-DIABETIC MEDICATION					
Number of subjects	9 (4.9)	8 (4.4)	8 (4.4)	11 (6.0)	36 (4.9)
INTENSIFICATION OF INSULIN	8 (4.3)	4 (2.2)	6 (3.3)	10 (5.4)	28 (3.8)
DPP-4 INHIBITORS	0	3 (1.6)	1 (0.6)	0	4 (0.5)
SULFONYLUREAS, A10BB	1 (0.5)	1 (0.5)	0	1 (0.5)	3 (0.4)
BIGUANIDES, A10BA	0	0	2 (1.1)	0	2 (0.3)
SGLT2 INHIBITORS	1 (0.5)	0	0	1 (0.5)	2 (0.3)
GLP-1 ANALOGUES	0	1 (0.5)	0	0	1 (0.1)
OTHER GLUCOSE LOWERING DRUGS	0	0	0	1 (0.5)	1 (0.1)
RESCUE MEDICATION (subset of additional anti-diabetic medication)					
Number of subjects	5 (2.7)	2 (1.1)	4 (2.2)	9 (4.9)	20 (2.7)
INTENSIFICATION OF INSULIN	5 (2.7)	2 (1.1)	3 (1.7)	8 (4.3)	18 (2.5)
SULFONYLUREAS	1 (0.5)	0	0	1 (0.5)	2 (0.3)
BIGUANIDES	0	0	1 (0.6)	0	1 (0.1)
SGLT2 INHIBITORS	0	0	0	1 (0.5)	1 (0.1)
OTHER GLUCOSE LOWERING DRUGS	0	0	0	1 (0.5)	1 (0.1)

Source: Table 10-7 CSR PIONEER 8

A total of 225 patients (30.8%) initiated additional anti-diabetic medication prior to week 52. Intensification of insulin was the additional anti-diabetic medication initiated most by patients by week 52 (by 199 of the 225 patients initiating additional anti-diabetic medication). The proportions of patients intensifying insulin as an additional anti-diabetic medication prior to week 52 decreased with increasing oral semaglutide dose and was highest in the placebo group (31.0%, 21.4%, 18.8% and 37.5% for the oral semaglutide 3 mg, 7 mg, 14 mg and placebo groups, respectively).

A total of 185 patients (25.3%) initiated rescue medication (as add-on to trial product) prior to week 52. As seen with additional anti-diabetic medication, the proportions of patients initiating rescue medication prior to week 52 decreased with increasing oral semaglutide dose and was highest in the placebo group (29.3%, 18.1%, 17.1% and 36.4% for the 3 mg, 7 mg, 14 mg and placebo groups, respectively). Intensification of insulin was the rescue medication initiated most by patients at week 52 (by 167 of the 185 patients initiating rescue medication). The proportions of patients intensifying insulin as a rescue medication prior to week 52 decreased

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with increasing oral semaglutide dose and was highest in the placebo group (27.2%, 17.6%, 13.8% and 32.6% for the 3 mg, 7 mg, 14 mg and placebo groups, respectively).

Table 56 Additional Anti-Diabetic Medication and Rescue Medication Initiated Prior to Week 52 – PIONEER 8

	Oral sema 3 mg N (%)	Oral sema 7 mg N (%)	Oral sema 14 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	184	182	181	184	731
ADDITIONAL ANTI-DIABETIC MEDICATION					
Number of subjects	61 (33.2)	45 (24.7)	44 (24.3)	75 (40.8)	225 (30.8)
INTENSIFICATION OF INSULIN	57 (31.0)	39 (21.4)	34 (18.8)	69 (37.5)	199 (27.2)
SGLT2 INHIBITORS,	3 (1.6)	1 (0.5)	3 (1.7)	7 (3.8)	14 (1.9)
SULFONYLUREAS	3 (1.6)	4 (2.2)	2 (1.1)	4 (2.2)	13 (1.8)
BIGUANIDES	2 (1.1)	0	7 (3.9)	3 (1.6)	12 (1.6)
DPP-4 INHIBITORS	0	4 (2.2)	2 (1.1)	0	6 (0.8)
GLP-1 ANALOGUES	0	2 (1.1)	1 (0.6)	0	3 (0.4)
COMB ORAL GLUCOSE LOWERING DRUGS	1 (0.5)	0	0	0	1 (0.1)
ALPHA GLUCOSIDASE INHIBITORS	0	0	1 (0.6)	0	1 (0.1)
OTHER LOWERING DRUGS	0	0	0	1 (0.5)	1 (0.1)
RESCUE MEDICATION (subset of additional anti-diabetic medication)					
Number of subjects	54 (29.3)	33 (18.1)	31 (17.1)	67 (36.4)	185 (25.3)
INTENSIFICATION OF INSULIN	50 (27.2)	32 (17.6)	25 (13.8)	60 (32.6)	167 (22.8)
SGLT2 INHIBITORS	2 (1.1)	1 (0.5)	2 (1.1)	7 (3.8)	12 (1.6)
SULFONYLUREAS	3 (1.6)	3 (1.6)	2 (1.1)	3 (1.6)	11 (1.5)
BIGUANIDES	2 (1.1)	0	4 (2.2)	3 (1.6)	9 (1.2)
DPP-4 INHIBITORS	0	0	1 (0.6)	0	1 (0.1)
OTHER GLUCOSE LOWERING DRUGS	0	0	0	1 (0.5)	1 (0.1)

Source: Table 10-8 CSR PIONEER 8

Efficacy Results - Primary Endpoint

For the primary endpoint (change from baseline in HbA1c at week 26) superiority of all doses of semaglutide vs placebo was confirmed.

Table 57 Primary and Confirmatory Secondary Endpoints – PIONEER 8

Reference ID: 4497478

Endpoint	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoint: HbA_{1c} (%-points) change from baseline at week 26					
Oral sema 14 mg - Placebo	-1.2 [-1.4 ; -1.0]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-0.9 [-1.1 ; -0.7]	<0.0001		Superiority	Confirmed
Oral sema 3 mg - Placebo	-0.5 [-0.7 ; -0.3]	<0.0001		Superiority	Confirmed
Other confirmatory endpoints: Body weight (kg) change from baseline at week 26					
Oral sema 14 mg - Placebo	-3.3 [-4.2 ; -2.3]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-2.0 [-3.0 ; -1.0]	0.0001		Superiority	Confirmed
Oral sema 3 mg - Placebo	-0.9 [-1.8 ; -0.0]	0.0392		Superiority	Confirmed

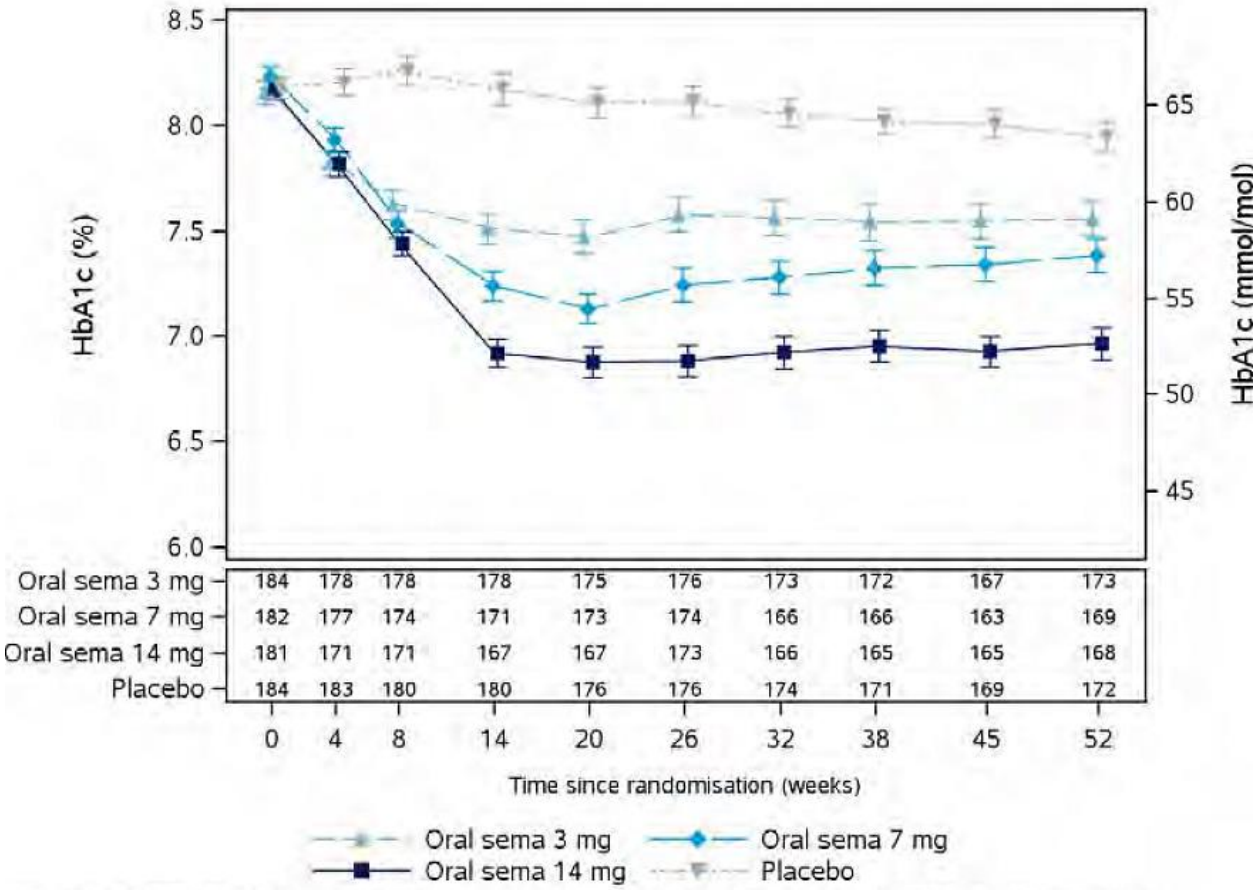
'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval; 'p-value': unadjusted two-sided p-value for test of no difference from 0

Source: Table 11-1 CSR PIONEER 8

At baseline, HbA1c levels were identical for all treatment groups (8.2%). For the in-trial observation period (used in the evaluation of the treatment policy estimand), HbA1c levels decreased from baseline through weeks 14-20 in all three oral semaglutide treatment groups. The decreases were sustained through to week 52. HbA1c levels increased through week 8 with placebo and decreased slightly thereafter through week 52.

Figure 24 HbA1c by Week – Mean Plot –PIONEER 8

Reference ID: 4494748



Source: Figure 11-1 CSR PIONEER 8

For week 26, the observed HbA1c changes from baseline were −0.5% with semaglutide 3 mg, −1.0% with semaglutide 7 mg, −1.3% with semaglutide 14 mg and −0.1%- with placebo.

Data Quality and Integrity - Reviewers' Assessment

I did not find any issues with the data quality.

Efficacy Results - Secondary and other relevant endpoints

<u>Body weight</u>

For the secondary confirmatory endpoint of change from baseline at week 26 in body weight, superiority of all doses of semaglutide vs placebo was also confirmed.

At baseline, the mean body weight was similar for all treatment groups; the mean body weight for the trial population was 85.9 kg. The observed decrease in body weight at week 26 was

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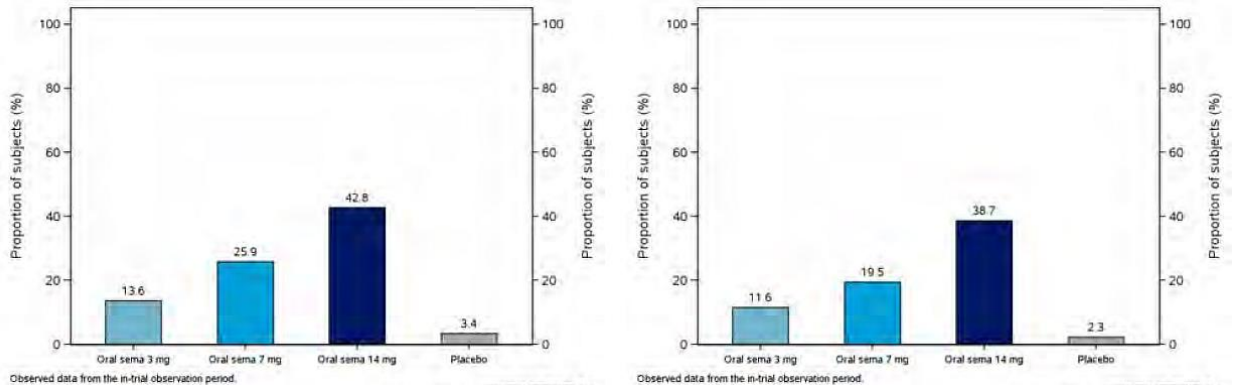
greater with semaglutide 3 mg (−1.4 kg), semaglutide 7 mg (−2.6 kg) and semaglutide 14 mg (−3.7 kg) than with placebo (−0.5 kg). From weeks 26 through 52, body weight was sustained in the semaglutide 14 mg group, while body weight in the semaglutide 3 and 7 mg, and placebo groups increased through week 52.

HbA1c targets

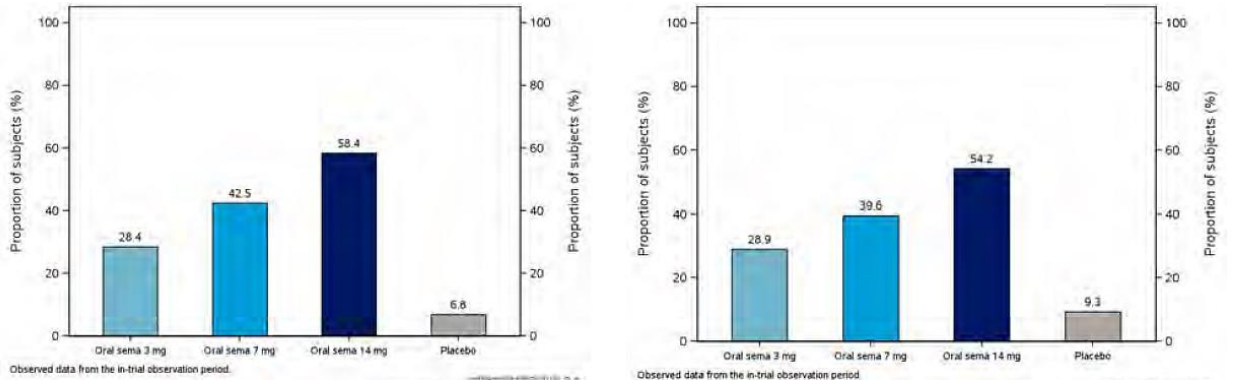
More patients on semaglutide (dose-dependent) achieved either the AACE goal (HbA1c ≤6,5%) or the ADA goal (HbA1c <7%) when compared to placebo. The differences at week 26, and 52, are summarized in the figures below.

Figure 25 Proportion of Patients with HbA1c ≤6.5% at Week 26 (Left) and at Week 52 (Right) – PIONEER 8



Source: Figure 11-8 CSR PIONEER 8

Figure 26 Proportion of Patients with HbA1c <7.0% at Week 26 (Left) and at Week 52 (Right) – PIONEER 8



Source: Figure 11-9 CSR PIONEER 8

Durability of Response

Reference ID: 4494348

The semaglutide effect on glycemic control and weight appeared to be sustained for the duration of the study.

Persistence of Effect

Not applicable as effect persistence was not assessed.

Additional Analyses Conducted on the Individual Trial

See Biometrics review by Dr Robert Abugov for FDA analyses pertaining to PIONEER 8.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary endpoint for most phase 3 studies pertained to glycemic control as evidenced by the change in HbA1c from baseline to week 26 (or week 52 in PIONEER 7). The endpoints were met for the 7 and 14 mg doses of oral semaglutide in all trials, therefore supporting the indication.

Change in HbA1c from baseline

Baseline levels of HbA1c ranged from 8% to 8.3% in the efficacy trials. HbA1c was reduced by up to 0.9 % with oral semaglutide 3 mg, 1.2 % with 7 mg, 1.4 % with 14 mg, and 1.3 % with oral semaglutide flexible dose. The HbA1c reduction with semaglutide 7 and 14 mg was statistically superior to placebo, and sitagliptin 100 mg. Semaglutide 14 mg was statistically superior empagliflozin 25 mg, but not statistically superior to liraglutide 1.8 mg (it was non-inferior) regarding glycemic control. The HbA1c reduction with semaglutide 3 mg was superior to placebo only. The results for the primary analyses based on the intention-to-treat principle are summarized below.

Table 58 Confirmatory Analyses of Change from Baseline in HbA1c (%) – PIONEER 1-5 and 8

Reference ID: 4494748

HbA_{1c} (%-point)	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
PIONEER 1 - week 26					
Oral sema 14 mg - Placebo	-1.1 [-1.3 ; -0.9]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-0.9 [-1.1 ; -0.6]	<0.0001		Superiority	Confirmed
Oral sema 3 mg - Placebo	-0.6 [-0.8 ; -0.4]	<0.0001		Superiority	Confirmed
PIONEER 2 - week 26					
Oral sema 14 mg - Empa 25 mg	-0.4 [-0.6 ; -0.3]	<0.0001		Non-inferiority	Confirmed
Oral sema 14 mg - Empa 25 mg	-0.4 [-0.6 ; -0.3]	<0.0001		Superiority	Confirmed
PIONEER 3 - week 26					
Oral sema 14 mg - Sita 100 mg	-0.5 [-0.6 ; -0.4]	<0.0001		Non-inferiority	Confirmed
Oral sema 14 mg - Sita 100 mg	-0.5 [-0.6 ; -0.4]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Sita 100 mg	-0.2 [-0.4 ; -0.1]	<0.0001		Non-inferiority	Confirmed
Oral sema 7 mg - Sita 100 mg	-0.3 [-0.4 ; -0.1]	<0.0001		Superiority	Confirmed
Oral sema 3 mg - Sita 100 mg	0.2 [0.1 ; 0.3]	0.0856	0.05	Non-inferiority	Not confirmed
Oral sema 3 mg - Sita 100 mg	0.2 [0.0 ; 0.3]	0.0080		Superiority	Not tested
PIONEER 4 - week 26					
Oral sema 14 mg - Placebo	-1.1 [-1.2 ; -0.9]	<0.0001		Superiority	Confirmed
Oral sema 14 mg - Lira 1.8 mg	-0.1 [-0.3 ; 0.0]	<0.0001		Non-inferiority	Confirmed
Oral sema 14 mg - Lira 1.8 mg	-0.1 [-0.3 ; 0.0]	0.0645	0.05	Superiority	Not confirmed
PIONEER 5 - week 26					
Oral sema 14 mg - Placebo	-0.8 [-1.0 ; -0.6]	<0.0001		Superiority	Confirmed
PIONEER 8 - week 26					
Oral sema 14 mg - Placebo	-1.2 [-1.4 ; -1.0]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-0.9 [-1.1 ; -0.7]	<0.0001		Superiority	Confirmed
Oral sema 3 mg - Placebo	-0.5 [-0.7 ; -0.3]	<0.0001		Superiority	Confirmed

'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval; 'p-value': unadjusted two-sided p-value for test of no difference from 0 (superiority) or for test of no difference from the non-inferiority margin (non-inferiority);

Source: Table 3-6 Summary of Clinical Efficacy

The reduction in HbA1c with oral semaglutide occurred in the first 14 weeks of treatment and was sustained for the duration of the trials, from 26 weeks, up to 78 weeks as observed in PIONEER 3. The reduction in HbA1c by trial is presented in the Figure 27 below. Most of the results presented below are at week 26 which was the set point for the primary endpoint, except for PIONEER 7 where the 52 weeks timepoint was used for the primary analysis.

A numerical dose-response was seen in the trial that evaluated more than one dose of semaglutide.

Figure 27 Estimated Change from Baseline in HbA1c (%–Point) – Phase 3 Trials

Reference ID: 4494348

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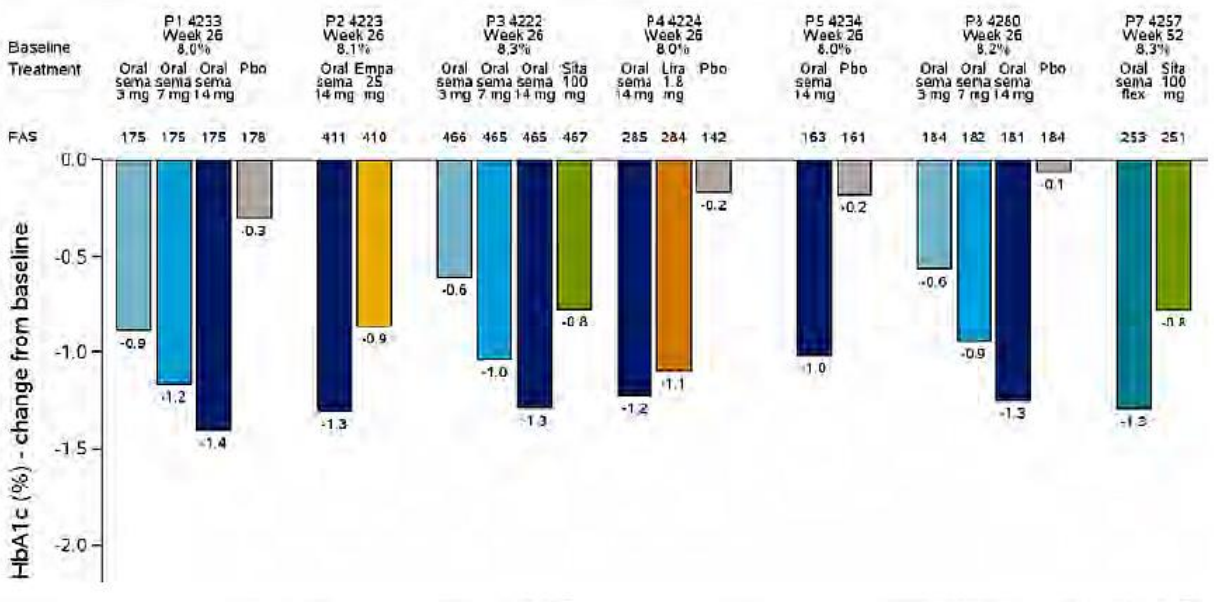

Source: Excerpted from Figure 4-1 clinical overview

Reviewer Comment: Overall, the clinical development program is supportive of the glycemic lowering indication of semaglutide 7 and 14 mg doses, in a variety of patients, both as monotherapy and on a background of oral antidiabetics and insulin. Semaglutide was also found to be efficacious and superior to placebo in patients with moderate renal impairment (PIONEER 5).

7.1.2. **Secondary and Other Endpoints**

A summary of selected secondary endpoints is presented below.

<u>Body Weight</u>

The change in body weight was the confirmatory secondary endpoint in all trials, included in the testing hierarchy and controlled for type 1 error.

Semaglutide was found to be superior in body weight reduction when compared to placebo, sitagliptin, and liraglutide, but not when compared to empagliflozin. The analyses for the confirmatory secondary endpoint are summarized in the table below.

Reference ID: 4494348

Table 59 Confirmatory Analyses of Change from Baseline in Body Weight (kg) – PIONEER 1-5, 7, and 8

Endpoint	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
PIONEER 1 – week 26					
Oral sema 14 mg - Placebo	-2.3 [-3.1 ; -1.5]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-0.9 [-1.9 ; 0.1]	0.0866	0.025	Superiority	Not confirmed
Oral sema 3 mg - Placebo	-0.1 [-0.9 ; 0.8]	0.8692	0.025	Superiority	Not confirmed
PIONEER 2 – week 26					
Oral sema 14 mg - Empa 25 mg	-0.1 [-0.7 ; 0.5]	0.7593	0.05	Superiority	Not confirmed
PIONEER 3 – week 26					
Oral sema 14 mg - Sita 100 mg	-2.5 [-3.0 ; -2.0]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Sita 100 mg	-1.6 [-2.0 ; -1.1]	<0.0001		Superiority	Confirmed
Oral sema 3 mg - Sita 100 mg	-0.6 [-1.1 ; -0.1]	0.0185		Superiority	Not tested
PIONEER 4 – week 26					
Oral sema 14 mg - Placebo	-3.8 [-4.7 ; -3.0]	<0.0001		Superiority	Confirmed
Oral sema 14 mg - Lira 1.8 mg	-1.2 [-1.9 ; -0.6]	0.0003		Superiority	Confirmed
PIONEER 5 – week 26					
Oral sema 14 mg - Placebo	-2.5 [-3.2 ; -1.8]	<0.0001		Superiority	Confirmed
PIONEER 8 – week 26					
Oral sema 14 mg - Placebo	-3.3 [-4.2 ; -2.3]	<0.0001		Superiority	Confirmed
Oral sema 7 mg - Placebo	-2.0 [-3.0 ; -1.0]	0.0001		Superiority	Confirmed
Oral sema 3 mg - Placebo	-0.9 [-1.8 ; -0.0]	0.0392		Superiority	Confirmed
PIONEER 7 – week 52					
Oral sema flex - Sita 100 mg	-1.9 [-2.6 ; -1.2]	<0.0001		Superiority	Confirmed

'alpha': local significance level according to the testing strategy for hypotheses that are not confirmed; CI: confidence interval; 'p-value': unadjusted two-sided p-value for test of no difference from 0 (superiority).

Source: Table 3-7 Summary of Clinical Efficacy

Body weight was reduced by up to 1.5 kg with oral semaglutide 3 mg, 2.4 kg with 7 mg and 4.4 kg with 14 mg at week 26. The maximum body weight reduction was achieved around week 26 and was sustained for the remainder of the trials (52 to 78 weeks).

The reduction in body weight was numerically dose-dependent when more than one dose of semaglutide was evaluated.

Reference ID: 4494348

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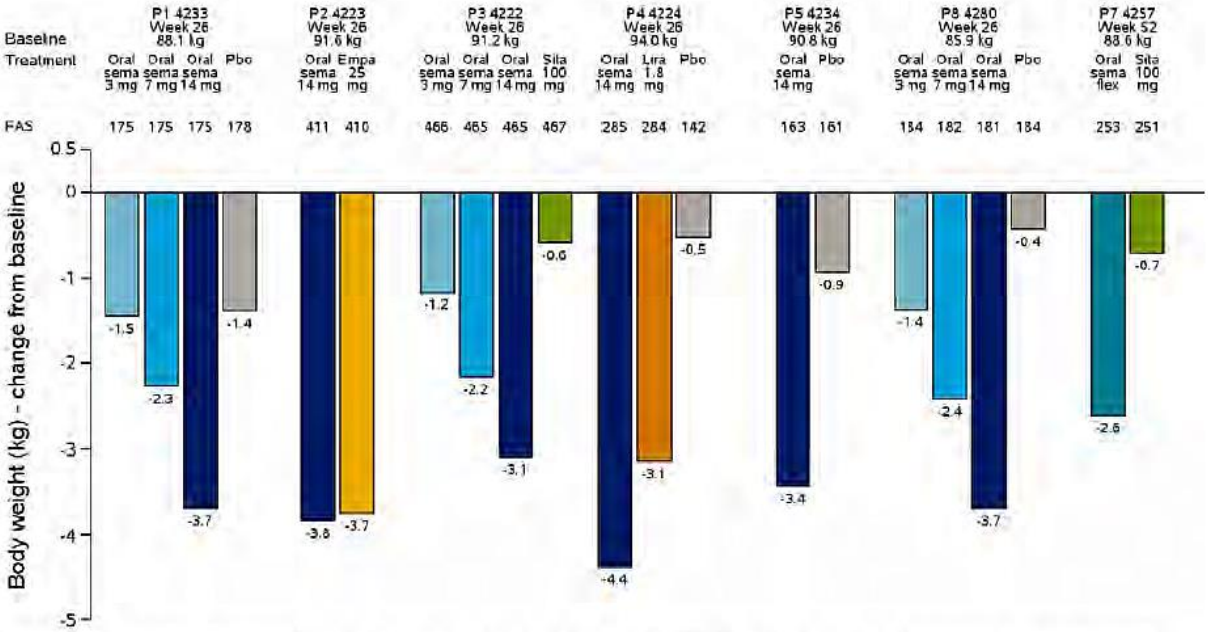
Figure 28 Estimated Change in Body Weight (Kg) – Phase 3 Trials



Source: Excerpted from Figure 4-4 Clinical overview

<u>HbA1c targets</u>

The proportion of patients achieving the treatment targets defined by ADA and AACE of HbA1c <7% and HbA1c ≤6.5%, respectively, were evaluated as exploratory outcomes in all trials. In line with the reduction observed in mean HbA1c with semaglutide, greater proportions of patients with semaglutide than with comparators achieved pre-defined treatment targets of HbA1c <7% (ADA target), HbA1c ≤6.5% (AACE) which were nominally significant, with the exception of the comparison between semaglutide 14 mg and liraglutide, and semaglutide 3 mg and sitagliptin 100 mg. The proportion of patients achieving HbA1c <7% by trial is represented in the figure below.

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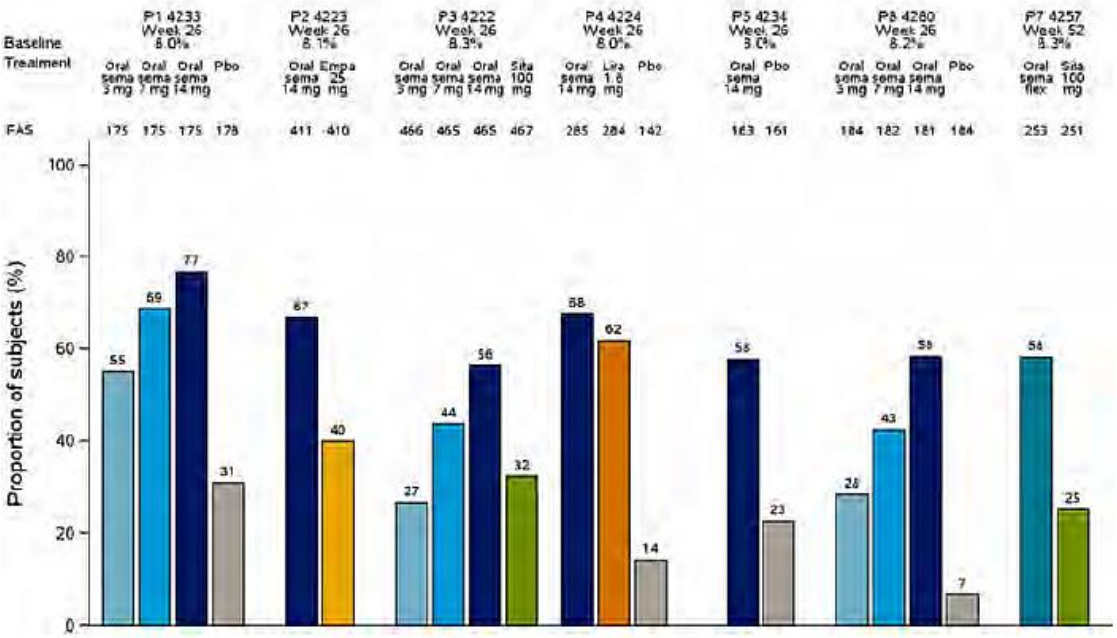
Figure 29 Proportion of Patients Reaching HbA1c <7.0% PIONEER Trials



Source: Figure 4-3 Clinical overview

7.1.3. 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.

7.1.4. Dose and Dose-Response

Five of the ten phase 3a trials (PIONEER 1, 3 and 8–10) evaluated all three doses of oral semaglutide. Of these, I will focus on the three multinational studies as the Japanese studies were not evaluated for efficacy as part of this NDA review.

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The dose-response of oral semaglutide 3, 7 and 14 mg is evaluated for the estimated treatment differences in HbA1c and body weight at week 26, and the odds ratios of the proportion of patients achieving HbA1c <7.0% at week 26 (week 52 for PIONEER 7).

A larger reduction in HbA1c from baseline to end-of-treatment was obtained with semaglutide 14 mg vs 7 mg vs 3 mg in all trials. No differences were seen across subgroups suggesting that the treatment response to various doses of semaglutide is similar across subgroups.

Similar results were observed for HbA1c targets and body weight, with the higher semaglutide dose having a stronger effect.

Because the lower dose of semaglutide, 3 mg, was shown to have limited efficacy, the applicant is only proposing the 7 and 14 mg for the diabetes indication, and the 3 mg dose as a start/titration dose.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The change in HbA1c overtime for semaglutide for the phase 3 multi-national trials is discussed in the individual trial sections. Overall, reduction in HbA1c occurred in the first 14 weeks for most trials, and remained relatively stable or increased slightly over time for treatment periods going up to 52 and 78 weeks

The decrease in weight with semaglutide also appeared relatively early and appeared to persist for the duration of the trials.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In general, semaglutide has been studied in a variety of diabetic patients, and on a variety of therapeutic backgrounds. The clinical program appears adequate for the NDA submission. The premarket assessment of cardiovascular risk was also performed in a short-term cardiovascular outcomes trial. However, oral semaglutide has only been studied for less than 2 years. In this context, events such as pancreatitis, gallbladder disease, malignancies, acute renal events, etc. could potentially be more common postmarketing, and with longer use of the drug. This would be in line with what was observed with other drugs in this class, and with injectable semaglutide. So far, for the currently marketed GLP-1 RAs, the benefit-risk profile has not changed significantly in the post-marketing setting.

7.2.2. Other Relevant Benefits

Semaglutide is to be administered orally, once daily. Of the currently marketed GLP-1 RAs, all

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are injectable and administered from twice daily to once weekly. Semaglutide would offer an additional option for the patients who prefer oral administration to injectable products. With the available data, it is not clear how semaglutide compared to the other members of the GLP-1 RA class of drugs, as such comparison is not the purpose of an anti-diabetic development program. Semaglutide appears to offer robust glycemic control based on the data in the clinical development program, which is the mainstay of diabetes treatment. Additionally, reductions in body weight, which is a class effect, could also be regarded as advantageous in patients with T2DM and obesity, which constitute the great majority of patients with T2DM.

7.3. Integrated Assessment of Effectiveness

Semaglutide is the first oral GLP-1 RA, evaluated for the treatment of T2DM. As presented in Section 2.2, GLP1 RAs are a class of medications commonly used in the treatment of T2DM. Semaglutide is already approved for treatment of T2DM in subcutaneous injection form (Ozempic).

Semaglutide is administered orally once daily, as opposed to all other members of the class which are injectable. While this could potentially constitute an advantage for semaglutide, the administration is very specific due to low bioavailability. The efficacy and safety of oral semaglutide was studied fasting, at least 30 minutes before a meal or other oral medications, with up to 120 ml water. Any deviations from the above could result in more, or less semaglutide being absorbed, and therefore affect both efficacy and safety of the product.

The semaglutide phase 3 development program is comprised of 7 efficacy trials, one CVOT which was conducted to rule out excess CV risk pre-marketing, and two Japanese trials. Of the efficacy trials, two were open label as blinding would have been difficult due to the nature of the comparator (PIONEER 2 vs empagliflozin, and PIONEER 7 – flexible dose semaglutide vs sitagliptin). The remaining 5 efficacy trials were double-blind as follows: three vs placebo – one as monotherapy in treatment-naïve patients (PIONEER 1), one in renally impaired patients (PIONEER 7), and one on a background of insulin (PIONEER 8), one trial vs sitagliptin on a background of metformin +/- SU (PIONEER 3), and one vs liraglutide and vs placebo, all in combination with metformin with or without a SGLT-2 inhibitor (PIONEER 4).

In all the efficacy trials, semaglutide showed a dose-dependent reduction on HbA1c, sustained over the duration of the trials. This reduction was generally shown to be superior to placebo as monotherapy, on a background of insulin, and in patients with renal impairment. Semaglutide was also found to be statistically superior to empagliflozin and sitagliptin, but not to liraglutide, regarding HbA1c lowering.

In conclusion, regarding glycemic outcomes, the clinical program provides evidence that oral semaglutide, at 7 and 14 mg daily dose, is efficacious in improving glycemic control in patients with T2DM both as monotherapy, and as add-on to various OADs/insulin.

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8. Review of Safety

8.1. Safety Review Approach

The primary focus of the safety evaluation is on the data from the 8 completed multinational phase 3 trials, including the CVOT, as these trials represent the intended target population as well as the majority of the overall exposure to the studied semaglutide doses. The two studies conducted in Japan are also included in the evaluation of safety. Details regarding the 10 PIONEER trials are presented below.

Table 60 Key Trial Designs for the Phase 3 Trials

Trial ID (Subjects)[a]	Duration (weeks)	Oral semaglutide			Comparator		Randomisation ratio	Blinding	Stratification		Background anti-diabetic medication during the trials
									By background medication	By other parameters	
PIONEER 1 (N=703)	26	3 mg	7 mg	14 mg		Placebo	1:1:1:1	Double-blind		Japanese/ non-Japanese	None
PIONEER 2 (N=819)	52			14 mg	Empa 25 mg		1:1	Open-label	no stratification		Met
PIONEER 3 (N=1861)	78	3 mg	7 mg	14 mg	Sita 100 mg		1:1:1:1	Double-blind, double-dummy	met/ met + SU		Met ± SU
PIONEER 4 (N=711)	52			14 mg	Lira 1.8 mg	Placebo	2:2:1	Double-blind, double-dummy	met/ met + SGLT-2i	Japanese/ non-Japanese	Met ± SGLT-2i
PIONEER 5 (N=324)	26			14 mg		Placebo	1:1	Double-blind	met/ SU ± met/ basal insulin ± met	eGFR 30–44 / 45–59 mL/min/1.73m^2	Met ± SU *or* Met ± basal insulin
PIONEER 6 (N=3183)	Event driven	14 mg[b]				Placebo	1:1	Double-blind		Presence of cardiovascular disease or risk factors only	Add-on to standard of care[c] at the investigator's discretion
PIONEER 7 (N=503)	52	Flexible dose adjustment			Sita 100 mg		1:1	Open-label	SU/ no SU		1-2 OADs (Met, SU, SGLT-2i, TZD)
PIONEER 8 (N=730)	52	3 mg	7 mg	14 mg		Placebo	1:1:1:1	Double-blind	Basal insulin/ basal-bolus/ premix insulin	Japanese/ non-Japanese	basal insulin ± met *or* basal-bolus insulin ± met *or* premix insulin ± met
PIONEER 9 (N=243)	52	3 mg	7 mg	14 mg	Lira 0.9 mg	Placebo	1:1:1:1:1	Double-blind, Open-label[e]	OAD at screening/ no OAD at screening		None
PIONEER 10 (N=458)	52	3 mg	7 mg	14 mg	Dula 0.75 mg		2:2:2:1	Open-label	SU/ glinide/ TZD/ α-GI/ SGLT-2i		1 OAD (SU, glinide, TZD, α-GI or SGLT-2i)

[a] Number of subjects based on SAS for PIONEER 1-5 and 7-10 and FAS for PIONEER 6. [b] Subjects were to remain on the 14 mg, but were allowed to reduce the dose or delay dose escalation due to tolerability issues. [c]Antidiabetic medication (excluding GLP-1 RAs, DPP-4 inhibitors and pramlintide from visit 1 to 17) could be adjusted or added at the investigator's discretion and in accordance with standard of care and the current local label; [d] Combination of basal-bolus or premix insulin with metformin was not allowed for Japanese subjects; [e] Double-blind versus placebo, open-label versus lira.
α-GI: alpha-glucosidase inhibitor; DPP-4i: dipeptidyl peptidase-4 inhibitor; dula: dulaglutide; empa: empagliflozin; GLP-1 RA: glucagon-like peptide-1 receptor agonist; lira: liraglutide; met: metformin; OAD: oral anti-diabetic drug; SGLT-2i: sodium-glucose cotransporter-2 inhibitor; sita: sitagliptin; SU: sulfonylurea; TZD: thiazolidinediones.

Source: Table 1-1 ISS

Analysis sets

For PIONEER 1−5 and 7−10 and the trial pools, the safety analysis set (SAS) was used for the safety evaluation, whereas the full analysis set (FAS) was used for PIONEER 6.

- The full analysis set (FAS) comprises all randomized patients. Patients contribute to a treatment group based on the trial product they were randomized to receive.
- The safety analysis set (SAS) comprises all randomized patients who received at least one dose of trial product. Patients contribute to a treatment group

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based on the trial product they actually received for the majority of the on-treatment observation period.

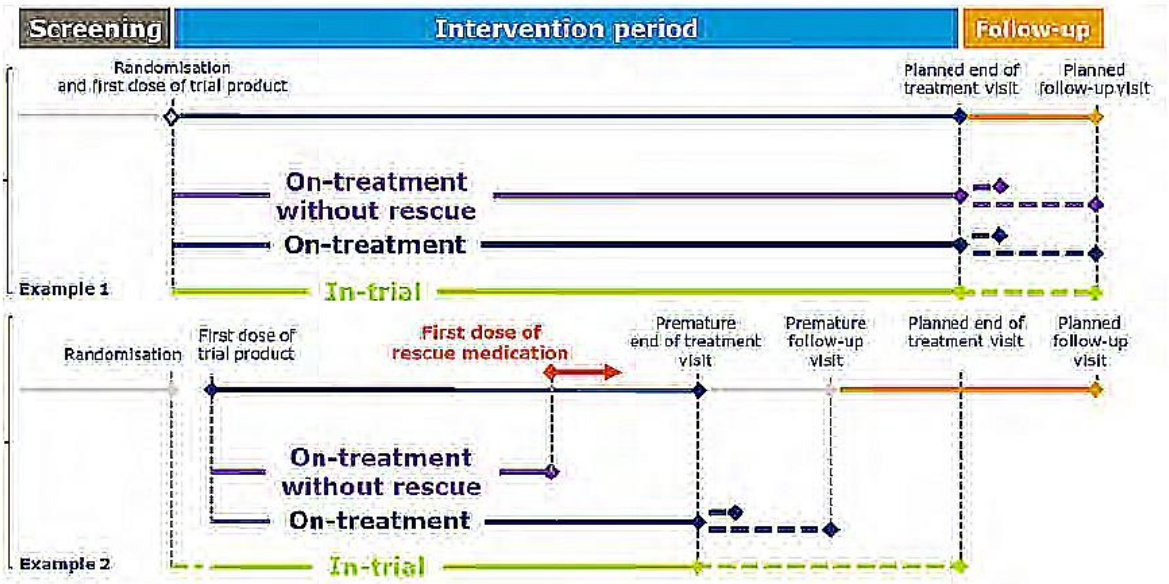
The phase 3a trials were designed to follow-up and collect data on all randomized patients for the planned duration of the trials, including the period after premature discontinuation of trial product or initiation of rescue medication and until the planned end-of-treatment visit.

Observation periods

Three different observation periods were defined for the safety evaluations:

- The in-trial observation period – entire time period from when a patient was randomized until the final scheduled visit, including any period before initiation of treatment or after initiation of rescue medication or premature discontinuation of trial product.
- The on-treatment observation period – time period when a patient was on treatment with trial product, including any period after initiation of rescue medication and until stop of trial product
- The on-treatment without rescue medication observation period – time period when a patient was on treatment with trial product, excluding any period after initiation of rescue medication.

Figure 30 Observation Periods PIONEER Trials



The on-treatment period includes an ascertainment window after last dose of trial product of either +3 days (laboratory assessments, physical examination and vital signs) or +38 days (AEs, adjudicated events, hypoglycaemic episodes, ECGs and eye examination results). The same ascertainment windows apply to the on-treatment without rescue medication period, unless rescue medication was initiated, in which case the period stops at the date of initiating rescue medication. The in-trial period stops at the final scheduled visit and does not include any ascertainment windows. The dashed lines illustrate the part of an observation period outside the period when a subject is taking trial product.

Source: Figure 1-5 ISS

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The observation period determined which post-baseline data points a patient contributed with for an evaluation. Baseline values were by definition included in all observation periods. In PIONEER 6, treatment pauses were allowed. Although trial product was stopped during a treatment pause, data from the treatment pause was still included in the on-treatment period. Treatment pauses were not allowed in any of the other trials.

The on-treatment period was used for most safety evaluations, except for deaths and event types with potentially long latency between onset and diagnosis for which the in-trial period was used. AEs with onset during the on-treatment period correspond to treatment-emergent adverse events.

Applicant defined pools used for safety evaluation:

Three different pools were defined by the applicant.

Three different trial pools were defined:
- The phase 3a pool comprising all phase 3a trials, except PIONEER 6 – to compare oral semaglutide (all doses combined) to all comparators (active and placebo) combined.
- The placebo pool comprising the multinational placebo-controlled phase 3a trials (PIONEER 1, 4, 5 and 8) – to compare oral semaglutide (all doses combined) to placebo.
- The placebo dose pool comprising the two multinational placebo-controlled phase 3a trials investigating all three doses of oral semaglutide (PIONEER 1 and 8) – to evaluate dose response of oral semaglutide versus placebo.

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Table 61 Phase 3 trials Contributing to Different Pools

		Treatments					Trial pools		
Trial ID (Subjects)	Duration (weeks)	Oral semaglutide			Comparator		Phase 3a pool (N=6352)	Placebo pool (N=2184)	Placebo dose pool (N=1433)
P1 4233 (N=703)	26	3 mg	7 mg	14 mg		Placebo	X	X	X
P2 4223 (N=819)	52			14 mg	Empagliflozin		X		
P3 4222 (N=1861)	78	3 mg	7 mg	14 mg	Sitagliptin		X		
P4 4224 (N=711)	52			14 mg	Liraglutide	Placebo	X	X	
P5 4234 (N=324)	26			14 mg		Placebo	X	X	
P7 4257 [a] (N=503)	52	Flexible dose adjustment			Sitagliptin		X		
P8 4280 (N=730)	52	3 mg	7 mg	14 mg		Placebo	X	X	X
P9 4281 (JP) (N=243)	52	3 mg	7 mg	14 mg	Liraglutide	Placebo	X		
P10 4282 (JP) (N=458)	52	3 mg	7 mg	14 mg	Dulaglutide		X		

[a] PIONEER 7 has a 52-week extension phase that is included as ongoing.
N: number of subjects in the safety analysis set; JP: Japanese trial.

Source: Table 1-2 ISS

Data from PIONEER 6 is presented separately, since the CVOT differs on important parameters making it unsuitable for pooling with the other phase 3 trials. Key differences include a longer trial duration, a trial population at high risk of CV events, limited reporting for AEs that were not SAEs or events of special interest, and randomized treatment provided in addition to standard-of-care.

In addition to the trial pools, data from PIONEER 3, and 5 are used to address specific topics:

- PIONEER 3 – to assess dose-response and long-term safety as the trial had extension to 78 weeks.
- PIONEER 5 – to assess the safety and tolerability of oral semaglutide in patients with moderate renal impairment.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The cut-off date for data in this application was November 2, 2018, corresponding to the database lock (DBL) date for PIONEER 6. This cut-off date allowed inclusion of data from 28 completed clinical trials with oral semaglutide (10 phase 3a trials, 1 phase 2 trial and 17 clinical pharmacology trials) and 2 clinical pharmacology trials with SNAC. For the 3 ongoing trials

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(trials 4248 and 4427, and PIONEER 7ext) only blinded information about deaths, SAEs and pregnancies reported in these trials is included.

Exposure was defined as the length of the on-treatment observation period including the 38 day ascertainment window.

The total exposure to oral semaglutide in the on-treatment observation period was 4379 patient-year of exposure (PYE) in the phase 3a pool (PIONEER 1–5 and 7-10), 1197 PYE in the placebo pool (PIONEER 1, 4, 5 and 8) and 1932 in PIONEER 6.

Table 62 Total Exposure – Phase 3a Trials and Pools

SAS	Oral sema 3 mg		Oral sema 7 mg		Oral sema 14 mg		Oral sema[a]		Comparator[b]		Placebo	
	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE
Phase 3a pool							4116	4379	2236	2335		
Placebo pool							1519	1197			665	523
Placebo dose pool	359	288	356	274	356	267					362	290
P1 4233	175	101	175	98	175	96	525	296			178	101
P2 4223					410	400	410	400	409	420		
P3 4222	466	662	464	669	465	650	1395	1981	466	687		
P4 4224					285	281	285	281	284	285	142	143
P5 4234					163	89	163	89			161	90
P7 4257							253	238	250	247		
P8 4280	184	186	181	176	181	170	546	532			184	190
P9 4281	49	50	49	53	48	50	146	153	48	51	49	54
P10 4282	131	139	132	138	130	133	393	410	65	68		

FAS	Oral sema[a]		Placebo	
	N	PYE	N	PYE
P6 4221	1591	1932	1592	1987

Phase 3a pool: PIONEER 1-5 and 7-10. Placebo pool: PIONEER 1, 4, 5 and 8.
Placebo dose pool: PIONEER 1 and 8. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). [a] In PIONEER 1-5 and 8-10 this column is the pooled oral semaglutide data across the doses used in the individual trials. In PIONEER 7 and 6, subjects were allowed to delay dose escalation of oral semaglutide to 14 mg and to decrease the dose if experiencing unacceptable AEs. 1 subject in the placebo group of PIONEER 6 was not exposed to trial product. [b]'Comparator' for the phase 3a pool: sitagliptin, empagliflozin, liraglutide and placebo; 'Comparator' for the individual trials only includes the active comparator. N: number of subjects; PYE: patient-years of exposure
Source: Table 11-1 ISS

CVOT exposure

The on-treatment period relates to the exposure time for each patient. The mean time on-treatment was 14.8 months, ranging from 0 to 19.9 months.

The treatment time (i.e. duration of exposure including any treatment pauses) for the individual patients ranged from 0 to 82 weeks with most patients being treated for 53 to 79 weeks.

In PIONEER 6 the target maintenance dose was 14 mg, however, if treatment with the trial product was associated with unacceptable AEs (as judged by the investigator), treatment

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pauses, dose reductions and extensions of dose escalation periods were allowed. At end-of-treatment, most patients were treated with 14 mg (oral semaglutide: 69.5%; placebo: 85.9%).

Table 63 Duration of Exposure – PIONEER 6 – FAS

	Oral semaglutide N (%)	Placebo N (%)	Total N (%)
Number of subjects	1591	1592	3183
Duration of exposure (weeks)			
0 <= to <4	25 (1.6)	10 (0.6)	35 (1.1)
4 <= to <8	31 (1.9)	26 (1.6)	57 (1.8)
8 <= to <12	32 (2.0)	12 (0.8)	44 (1.4)
12 <= to <16	16 (1.0)	9 (0.6)	25 (0.8)
16 <= to <26	35 (2.2)	30 (1.9)	65 (2.0)
26 <= to <53	296 (18.6)	285 (17.9)	581 (18.3)
53 <= to <79	1152 (72.4)	1219 (76.6)	2371 (74.5)
79 <=	4 (0.3)	0	4 (0.1)

'Duration of exposure': time from first date to last date of dose of trial product (both dates inclusive); N: number of subjects; %: proportion of subjects.

Source: Table 1-14 ISS

8.2.2. Relevant characteristics of the safety population:

Per the applicant, the inclusion and exclusion criteria in the phase 3a trials were chosen to allow enrolment of patients from the intended target population in terms of demographics, comorbidities, concomitant medication, duration of T2DM and diabetes complications including CV disease and renal impairment.

In the phase 3a pool, treatment completers were defined as patients that did not discontinue treatment prematurely. Trial completers were defined as patients who were not lost to follow-up, or withdrawn from the trial, or did not die.

In PIONEER 6, trial completers were defined as patients that either attended the last follow-up visit or who died while considered active trial participants. A patient was considered lost to follow-up if the patient did not complete the trial and did not withdraw consent.

In the phase 3a pool, 4116 patients were exposed to oral semaglutide. In the nine trials of the phase 3a pool and in PIONEER 6, the proportions of patients on oral semaglutide completing the trials was 93.6–99.7% and completing the treatment with trial product was 81.6–94.5%.

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Table 64 Patient Disposition – Phase 3a Trials and Pools

Trial	Oral semaglutide (all doses)		Comparators	
	Number of subjects exposed	Number of completers of treatment/trial	Number of subjects exposed	Number of completers of treatment/trial
Phase 3a pool	4116	3507 (85.2%)/3923 (95.3%)	2236	1988 (88.9%)/2147 (96.0%)
Placebo pool	1519	1297 (85.4%)/1449 (95.4%)	665	587 (88.3%)/635 (95.5%)
Placebo dose pool	1071	923 (86.2%)/ 1014 (94.7%)	1433	1244 (86.8%)/1359 (94.8%)
PIONEER 1	525	471 (89.7%)/493 (93.9%)	178	159 (89.3%)/170 (95.5%)
PIONEER 2	411	339 (82.3%)/400 (97.3%)	409	365 (89%)/387 (94.4%)
PIONEER 3	1395	1160 (83.1%)/1307 (93.6%)	466	406 (86.9%)/451 (96.6%)
PIONEER 4	285	241 (84.6%)/277 (97.2%)	426	373 (87.6%)/408 (95.8%)
PIONEER 5	163	133 (81.6%)/158 (96.9%)	161	141 (87.6%)/156 (96.9%)
PIONEER 6	1591[a]	1347 (84.7)/1586 (99.7%)	1592[a]	1435 (90.1)/1586 (99.6)
PIONEER 7	253	211 (83.4%)/241 (95.3%)	250	228 (90.8%)/244 (97.2%)
PIONEER 8	546	452 (82.8%)/522 (95.6%)	184	162 (88.0%)/175 (95.1%)
PIONEER 9	146	138 (94.5%)/142 (97.3%)	97	93 (95.9%)/95 (97.9%)
PIONEER 10	393	362 (92.1%)/385 (98.0%)	65	61 (93.8%)/63 (96.9%)

Subjects exposed are subjects exposed to at least one dose of oral semaglutide or comparator. Treatment completers are subjects who completed the planned treatment period according to the investigator; trial completers are subjects who were not lost to follow-up or withdrawn from the trial, or did not die. Proportions are number of completers relative to the number of subjects in the safety analysis set. [a] PIONEER 6 is based on FAS data, comprising all randomised subjects instead of exposed subjects.

Source: Table 1-17 ISS

In both phase 3 pool and PIONEER 6, the primary reasons for not completing treatment were adverse events. The proportion of patients who discontinued the trial product prematurely was higher with semaglutide vs comparator in both pools, and this was driven, as expected, by GI events.

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Table 65 Patient Disposition Overview Phase 3 Pool SAS

	Oral sema N	(%)	Comparator N	(%)	Total N	(%)
Number of subjects	4116	(100)	2236	(100)	6352	(100)
Treatment completers [1]	3507	(85.2)	1988	(88.9)	5495	(86.5)
Without rescue medication	2990	(72.6)	1602	(71.6)	4592	(72.3)
With rescue medication	517	(12.6)	386	(17.3)	903	(14.2)
Premature trial product discontinuation - primary reason	609	(14.8)	248	(11.1)	857	(13.5)
Adverse event(s)	336	(8.2)	109	(4.9)	445	(7.0)
Violation of inclusion and/or exclusion criteria	31	(0.8)	11	(0.5)	42	(0.7)
Intention of becoming pregnant	1	(<0.1)	1	(<0.1)	2	(<0.1)
Participation in another clinical trial [2]	6	(0.1)	2	(0.1)	8	(0.1)
Calcitonin value >= 100 ng/L	1	(<0.1)	0		1	(<0.1)
Subject withdrawal from trial	57	(1.4)	27	(1.2)	84	(1.3)
Pregnancy	2	(<0.1)	1	(<0.1)	3	(<0.1)
Other	175	(4.3)	97	(4.3)	272	(4.3)
Trial completers [3]	3923	(95.3)	2147	(96.0)	6070	(95.6)
Withdrawal from trial - primary reason	193	(4.7)	89	(4.0)	282	(4.4)
Lost to follow-up	69	(1.7)	30	(1.3)	99	(1.6)
Withdrawal by subject	100	(2.4)	44	(2.0)	144	(2.3)
Other	24	(0.6)	15	(0.7)	39	(0.6)
Died	17	(0.4)	13	(0.6)	30	(0.5)

Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
N: number of subjects; %: proportion of subjects; '[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product.

Source: Table 7.1.2 ISS

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Table 66 Patient Disposition Placebo Pool SAS

	Oral sema N	(%)	Placebo N	(%)	Total N	(%)
Number of subjects	1519	(100)	665	(100)	2184	(100)
Treatment completers [1]	1297	(85.4)	587	(88.3)	1884	(86.3)
Without rescue medication	1144	(75.3)	444	(66.8)	1588	(72.7)
With rescue medication	153	(10.1)	143	(21.5)	296	(13.6)
Premature trial product discontinuation - primary reason	222	(14.6)	78	(11.7)	300	(13.7)
Adverse event(s)	136	(9.0)	25	(3.8)	161	(7.4)
Violation of inclusion and/or exclusion criteria	13	(0.9)	5	(0.8)	18	(0.8)
Intention of becoming pregnant	0		1	(0.2)	1	(<0.1)
Participation in another clinical trial [2]	2	(0.1)	0		2	(0.1)
Calcitonin value >= 100 ng/L	0		0		0	
Subject withdrawal from trial	17	(1.1)	11	(1.7)	28	(1.3)
Pregnancy	1	(0.1)	0		1	(<0.1)
Other	53	(3.5)	36	(5.4)	89	(4.1)
Trial completers [3]	1449	(95.4)	635	(95.5)	2084	(95.4)
Withdrawal from trial - primary reason	70	(4.6)	30	(4.5)	100	(4.6)
Lost to follow-up	34	(2.2)	11	(1.7)	45	(2.1)
Withdrawal by subject	24	(1.6)	14	(2.1)	38	(1.7)
Other	12	(0.8)	5	(0.8)	17	(0.8)
Died	8	(0.5)	3	(0.5)	11	(0.5)

Placebo pool: PIONEER 1, 4, 5 and 8.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).
N: number of subjects; %: proportion of subjects; '[1]': subjects who completed treatment with trial product according to the end-of-trial form; '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product; '[3]': subjects who attended the final scheduled visit; 'Rescue medication': use of new anti-diabetic medication as add-on to trial product and used for more than 21 days with the initiation at or after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product.

Source: Table 7.1.7 ISS

Table 67 Patient Disposition PIONEER 6

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	Oral sema N (%)	Placebo N (%)	Total N (%)
Screened			3418
Screening failures			235 (6.9)
Randomised	1591	1592	3183
Exposed	1591 (100)	1591 (99.9)	3182 (100)
Not exposed	0	1 (0.1)	1 (0.0)
Full analysis set	1591 (100)	1592 (100)	3183 (100)
Treatment completers [1]	1347 (84.7)	1435 (90.1)	2782 (87.4)
Permanent trial product discontinuation - primary reason	244 (15.3)	156 (9.8)	400 (12.6)
Adverse event(s)	185 (11.6)	104 (6.5)	289 (9.1)
Lack of effect	4 (0.3)	5 (0.3)	9 (0.3)
Participation in another clinical trial [2]	0	0	0
Pregnancy	0	0	0
Intention of becoming pregnant	0	0	0
Calcitonin value >= 100 ng/L	0	0	0
Withdrawal of consent	0	0	0
Lost to follow-up	2 (0.1)	2 (0.1)	4 (0.1)
Other	53 (3.3)	45 (2.8)	98 (3.1)
Trial completers [3]	1586 (99.7)	1586 (99.6)	3172 (99.7)
Attended follow-up visit (P18)	1563 (98.2)	1541 (96.8)	3104 (97.5)
Died during trial	23 (1.4)	45 (2.8)	68 (2.1)
Non-completers - primary reason and last known vital status	5 (0.3)	6 (0.4)	11 (0.3)
Withdrawal by subject	3 (0.2)	1 (0.1)	4 (0.1)
Alive	3 (0.2)	1 (0.1)	4 (0.1)
Deceased	0	0	0
Unknown	0	0	0
Lost to follow-up	2 (0.1)	5 (0.3)	7 (0.2)
Alive	1 (0.1)	4 (0.3)	5 (0.2)
Deceased	1 (0.1)	1 (0.1)	2 (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 except for screening failures where it is proportion of screened subjects.

Source: Table 14.1.1 CSR

Baseline characteristics for each phase 3 study are detailed in Section 6 of this review.

8.2.3. Adequacy of the safety database

The phase 3 clinical program for oral semaglutide include 7 trials comparing semaglutide to placebo or active comparator drugs with treatment duration from 26 to 78 weeks. The phase 3 program also included an event-driven, pre-market CVOT (PIONEER 6). Two additional studies were conducted in Japan, required by the Japanese authorities, and they are somewhat redundant for the purpose of this NDA. Regardless, all these studies are included in the safety database. The clinical program also included a study in patients with moderate renal impairment (PIONEER 5).

A total of 4116 patients with T2DM were exposed to oral semaglutide in the completed phase 3 trials, and an additional 1591 patients were exposed to oral semaglutide in the pre-market CVOT. The size of the safety database appears adequate for pre-marketing safety assessment.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

OSI audits did not identify any issues regarding data integrity, and the submission is well organized.

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8.3.2. Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a product, whether it had a causal relationship with the treatment, and it included clinically significant worsening of a concomitant illness. All AEs were collected via investigator reporting and were to be reported on the AE for in the CRF.

For SAEs, a safety information form (SIF) was to be completed in addition to the AE form, to collect additional safety information to be included in the narrative. SAEs were to be followed until the outcome of the event was recovered, recovered with sequelae or fatal, and until all queries had been resolved except for cases of chronic conditions, cancer or AEs ongoing at the time of death (where death is due to another AE). Non-serious AEs were to be followed until the outcome of the event was recovering, recovered, or recovered with sequelae or until the end of the follow-up period, whichever came first, and until all queries related to the AEs had been resolved.

In PIONEER 6, systematic collection of data on AEs was limited to SAEs, AEs leading to treatment discontinuation and a few other AE categories of special interest (medication errors, severe hypoglycemic episodes, hepatic events, diabetic retinopathy and related complications, and pregnancies).

Additionally, certain events of special interest were defined for the oral semaglutide program as requiring additional data collection or an event to be sent for adjudication. Such events are presented in the table below.

Table 68 AEs with Additional Data Collection and/or in Scope for Event Adjudication

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Event categories with additional data collection	Events in scope for adjudication
Acute coronary syndrome	Acute myocardial infarct Silent myocardial infarct UAP requiring hospitalisation
Cerebrovascular event	Stroke TIA
Heart failure	Heart failure requiring hospitalisation
Renal event	Acute kidney injury
Pancreatitis	Acute pancreatitis
Acute gallstone disease	None
Neoplasm	Malignant neoplasm
Thyroid disease	Malignant thyroid neoplasm C-cell hyperplasia
Lactic acidosis	Lactic acidosis
Hypersensitivity reaction	None
Medication error	None
Increased creatine kinase (CK >10xULN)	None
Hepatic events, defined as: • ALT or AST >5xULN • ALT or AST >3xULN and TBL >2xULN • Hepatic events leading to premature discontinuation of trial product	None
Diabetic retinopathy or related complications	None
Death	All events with fatal outcome

Source: Table 1-4 ISS

The investigator was to evaluate whether an AE matched one of the AE categories of special interest and if yes, in addition to the standard AE form, the investigator was to fill in the relevant event-specific forms. The information collected on the additional data collection forms was used for the evaluation of individual AEs and is included in the case narratives and/or data listings in the CTRs.

Event adjudication

Adjudication of events was done by an external event adjudication committee (EAC). The adjudication was based on blinded review of pre-defined clinical data related to the specific event types according to criteria and guidelines outlined in the EAC charter. For randomized patients, all events in scope were adjudicated, including events with onset during the screening period. Events sent for adjudication were identified by the investigator, central ECG review, EAC (review of the source document), and preferred term search. An overview of the

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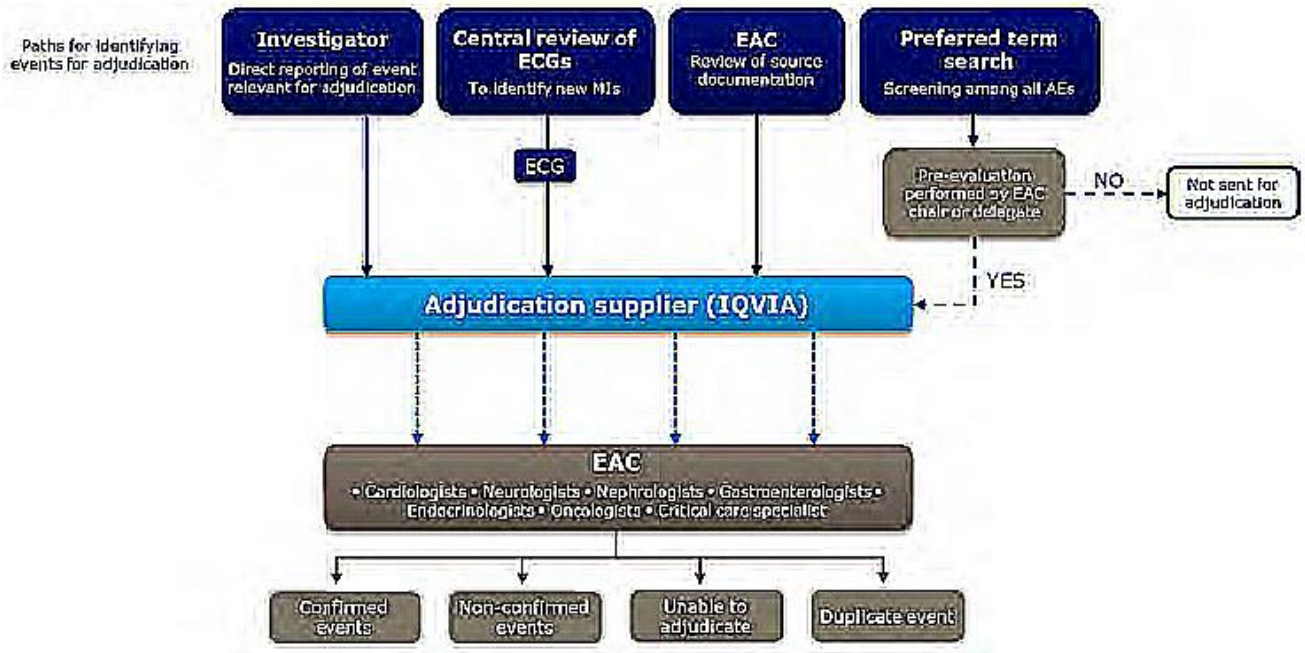
adjudication process is presented below.



Source: Figure 1-4 ISS

PIONEER 6 followed the same adjudication process as described above, and included the same event categories for adjudication as in the other phase 3a trials. The applicant submitted all adjudication packages for PIONEER 6.

Narratives were submitted for fatal events, other SAEs, non-serious AEs within a safety focus area leading to trial product discontinuation, pregnancies, rare events, laboratory outliers. The applicant did not prepare narratives for GI AEs leading to discontinuation that were non-serious because these were expected, and case narratives were unlikely to contribute any new information to the safety profile of oral semaglutide.

Episodes of hypoglycemia were to be reported on the hypoglycemic episode form rather than the AE form. Initially hypoglycemia episodes were categorized using the ADA 2013 definition, but they were re-classified using the ADA 2018 and IHSG 2017 classification of hypoglycemia.

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Table 69 Hypoglycemia Definition

Level		Glycaemic criteria	Description
Level 1	Hypoglycaemia alert value	≤3.9 mmol/L (70 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Level 2	Clinically significant hypoglycaemia	<3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Level 3	Severe hypoglycaemia	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

Source: Table 1-8 ISS

The following clinical laboratory tests were collected during the oral semaglutide trials.

Table 70 Clinical Laboratories

Biochemistry (measured in serum)	**Hormones (measured in serum)**
Amylase	Calcitonin
Lipase	
ALT, AST, ALP, TBL	**Renal function tests (measured in serum or urine)**
CK	Creatinine
Albumin	eGFR (CKD-EPI)
Urea	UACR[a]
Calcium (total)	
Potassium	**Haematology (measured whole blood)**
Sodium	Haemoglobin
CRP[b]	Haematocrit
Bicarbonate[c]	Leucocytes
Lactate[d]	Thrombocytes
Lipids (triglycerides, FFA, and HDL-, LDL-, VLDL- and total cholesterol)	Differential cell count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)
Glucose parameters (HbA_{1c}, FPG, and fasting values of insulin, C-peptide, pro-insulin and glucagon)	

[a] only collected in the renal impairment trial PIONEER 5; [b] only collected in PIONEER 1, 2 and 5; [c] only collected in PIONEER 4, 6, 7 and 10; [d] only collected in PIONEER 1 and 2. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; CK: creatine kinase; CRP: C-reactive protein; eGFR (CKD-EPI): estimated glomerular filtration rate (eGFR) as per the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI); TBL: total bilirubin; UACR: urinary albumin to creatinine ratio

Source: Table 1-5 ISS

For all laboratory parameters, except for ALT, AST, TBL and CK, there was no threshold for what outliers should elicit an AE report. For abnormal clinically significant findings discovered through screening or baseline assessments, the investigator was to include a comment in the patient's medical record and record this in the concomitant illness and medical history form.

Semaglutide plasma concentrations were measured in all patients in PIONEER 1, 2, 5, 8 and 9,

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and in half of the patients in PIONEER 3.

Anti-semaglutide antibodies were measured in PIONEER 1–5 and 9.

Safety assessments related to SNAC:
SNAC is the absorption enhancer used to facilitate oral administration for the semaglutide formulation under review. Nonclinical findings have shown that SNAC may impair cellular respiration at exposure levels much higher than the intended clinical exposure. The expected clinical manifestation of impaired cellular respiration includes lactic acidosis, and the occurrence of lactic acidosis was therefore considered a safety focus area. SNAC plasma levels and concurrent venous lactate levels were measured in PIONEER 1 and 2, per regulatory request. SNAC and lactate were measured at week 4 and 26 in both trials. Lactate was measured pre-dosing, and 25 and 40 minutes post-dosing.

Arterial lactate and other blood gas parameters were assessed in the clinical pharmacology trial NN9924-4247 that explored the effect of SNAC on the QTc interval where SNAC was dosed at supra-therapeutic doses of up to 3.6 g, which is 12 times higher than what is administered in an oral semaglutide tablet.

Systolic and diastolic blood pressure and pulse rate were measured in all phase 3a trials at designated site visits, in a sitting position after the patient had been resting for at least 5 minutes and by using the standard clinical practice at the site.

Eye examination
In all phase 3a trials, a fundus photography or a dilated fundoscopy was performed at:
- Screening visit (results available before randomization)
- End-of-treatment visit (or within 5 weeks thereafter)
- In PIONEER 3 and 6, the examination was also performed after 1 year in the trials

The fundus photography or fundoscopy was performed by the investigator or other qualified health care professional according to local practice. The fundoscopy required pharmacological dilation of both pupils.

Coding of AEs

All serious and non-serious AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) using the current MedDRA version at the time of reporting. MedDRA version 20.1 was used for reporting of all phase 3 trials.

8.3.3. Routine Clinical Tests

Routine clinical tests performed during the semaglutide phase 3 trial are discussed in section 6

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under the individual trials.

8.4. Safety Results

8.4.1. Deaths

The evaluation of death was based on the entire development program for oral semaglutide. A total of 106 deaths were reported in the 28 trials as follows:

- One death in the hepatic impairment clinical pharmacology trial (bacterial peritonitis in a patient with severe hepatic impairment, the patient received oral semaglutide in the trial, however the baseline disease is likely what caused the death)
- 31 deaths in phase 3a pool
- 74 deaths in PIONEER 6

Phase 3a pool

One of the 31 deaths was in a patient in PIONEER 3 who was randomized but never treated, the other 30 deaths were in patients exposed to either semaglutide or comparator, all had onset and occurred during the in-trial period. The breakdown of deaths by study is presented below.

Table 71 Deaths by Trial – Phase 3a Pool

Trial	Treatment group	Number of deaths per treatment group
PIONEER 1	Semaglutide 14 mg	1
PIONEER 2	Empa 25 mg	1
PIONEER 3	Not treated	1
	Semaglutide 3 mg	5
	Semaglutide 7 mg	3
	Semaglutide 14 mg	1
	Sitagliptin 100 mg	3
PIONEER 4	Semaglutide 14 mg	3
	Liraglutide 1.8 mg	4
	Placebo	1
PIONEER 5	Semaglutide 14 mg	1
	Placebo	2
PIONEER 7	Sitagliptin 100 mg	2
PIONEER 8	Semaglutide 14 mg	3

Source: Abbreviated from Table 2-4 Summary of Clinical Safety

In the placebo pool, 11 patients experienced a fatal event, 0.6% with semaglutide, and 0.4% with placebo. In the phase 3a pool, the proportion of patients who died was similar between pooled semaglutide (0.4%) and all comparators (0.5%).

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Table 72 Total Deaths and EAC-Confirmed Deaths in the Phase 3a Pool and Placebo Pool

	Oral sema				Comparator/Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Observation time (years)	4719				2452			
Fatal AEs	17	(0.4)	21	0.4	13	(0.5)	16	0.6
EAC confirmed death								
Cardiovascular death	5	(0.1)	5	0.1	5	(0.2)	5	0.2
Undetermined cause of death	6	(0.1)	6	0.1	3	(0.1)	3	0.1
Non-cardiovascular death	6	(0.1)	6	0.1	5	(0.2)	5	0.2
Placebo pool								
Number of subjects	1519				665			
Observation time (years)	1292				548			
Fatal AEs	8	(0.6)	8	0.7	3	(0.4)	3	0.5
EAC confirmed death								
Cardiovascular death	2	(0.2)	2	0.3	1	(0.1)	1	0.2
Undetermined cause of death	4	(0.2)	4	0.3	1	(0.1)	1	0.2
Non-cardiovascular death	2	(0.1)	2	0.1	1	(0.1)	1	0.1

Source: Excerpted from Table 2-5 Summary of Clinical Safety

The breakdown of deaths by SOC and PT is presented below for the phase 3a pool. Overall no trends can be observed due to the small number of deaths under each SOC.

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Table 73 Deaths in the Phase 3a Pool by SOC and PT – In-Trial

	Oral sema N	(Adj.%)	E	Adj.R	Comparator N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Observation time (years)	4719				2452			
All events	17	(0.4)	21	0.4	13	(0.5)	16	0.6
Cardiac disorders	9	(0.2)	9	0.2	4	(0.1)	4	0.1
Myocardial infarction	3	(<0.1)	3	<0.1	1	(<0.1)	1	<0.1
Cardio-respiratory arrest	2	(<0.1)	2	<0.1	0			
Acute myocardial infarction	1	(<0.1)	1	<0.1	2	(<0.1)	2	<0.1
Cardiogenic shock	1	(<0.1)	1	<0.1	0			
Atrial fibrillation	1	(<0.1)	1	<0.1	0			
Cardiac arrest	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Infections and infestations	3	(<0.1)	4	<0.1	1	(<0.1)	1	<0.1
Postoperative wound infection	1	(<0.1)	1	<0.1	0			
Encephalitis	1	(<0.1)	1	<0.1	0			
Peritonitis bacterial	1	(<0.1)	1	<0.1	0			
Septic shock	1	(<0.1)	1	<0.1	0			
Pneumonia	0				1	(<0.1)	1	<0.1
Nervous system disorders	3	(<0.1)	3	<0.1	0			
Ischaemic cerebral infarction	1	(<0.1)	1	<0.1	0			
Encephalopathy	1	(<0.1)	1	<0.1	0			
Haemorrhagic stroke	1	(<0.1)	1	<0.1	0			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(<0.1)	1	<0.1	4	(0.2)	4	0.1
Lung adenocarcinoma	1	(<0.1)	1	<0.1	0			
Adenocarcinoma gastric	0				1	(<0.1)	1	<0.1
Ovarian cancer metastatic	0				1	(<0.1)	1	<0.1
Pancreatic carcinoma	0				1	(<0.1)	1	<0.1
Pancreatic carcinoma metastatic	0				1	(<0.1)	1	<0.1
Respiratory, thoracic and mediastina disorders	2	(<0.1)	2	<0.1	1	(<0.1)	1	<0.1
Acute respiratory distress syndrome	1	(<0.1)	1	<0.1	0			
Respiratory failure	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
General disorders and administration site conditions	1	(<0.1)	1	<0.1	2	(<0.1)	2	<0.1
Death	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Sudden death	0				1	(<0.1)	1	<0.1
Renal and urinary disorders	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Acute kidney injury	1	(<0.1)	1	<0.1	0			
End stage renal disease	0				1	(<0.1)	1	<0.1
Hepatobiliary disorders	0				1	(<0.1)	2	<0.1
Chronic hepatic failure	0				1	(<0.1)	1	<0.1
Cirrhosis alcoholic	0				1	(<0.1)	1	<0.1
Injury, poisoning and procedural complications	0				1	(<0.1)	1	<0.1
Accidental overdose	0				1	(<0.1)	1	<0.1

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

Source: Table 2-6 Summary of Clinical Safety

My analysis using JReview and ISS datasets confirmed the sponsor provided table.

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All 30 deaths were evaluated and classified by the EAC. The classification is presented in the table below.

Table 74 EAC-Confirmed Deaths – Phase 3a Pool – In-Trial

	Oral sema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Observation time (years)	4719				2452			
Cardiovascular and undetermined cause of death	11	(0.3)	11	0.3	8	(0.3)	8	0.3
Cardiovascular death	5	(0.1)	5	0.1	5	(0.2)	5	0.2
Acute myocardial infarction	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Sudden cardiac death	1	(<0.1)	1	<0.1	4	(0.1)	4	0.2
Stroke	2	(<0.1)	2	<0.1	0			
Cardiovascular procedure	1	(<0.1)	1	<0.1	0			
Undetermined cause of death	6	(0.1)	6	0.1	3	(0.1)	3	0.1
Non-cardiovascular death	6	(0.1)	6	0.1	5	(0.2)	5	0.2
Renal causes	1	(<0.1)	1	<0.1	0			
Malignancy	1	(<0.1)	1	<0.1	3	(0.1)	3	<0.1
Pancreatic causes	1	(<0.1)	1	<0.1	0			
Neurological	1	(<0.1)	1	<0.1	0			
Non-prescription drug reaction or overdose	0				1	(<0.1)	1	<0.1
Infection	2	(<0.1)	2	<0.1	0			
Hepatobiliary causes	0				1	(<0.1)	1	<0.1

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

Source: Table 2-7 Summary of Clinical Safety

My analysis using JReview and the death reason category in the adjudication dataset confirmed the results reported by the applicant.

<u>CVOT</u>

PIONEER 6 is presented separately from the other phase 3 studies. Of the total of 74 deaths, 71 had onset during the in-trial period. The proportion of patients with fatal AEs was lower with oral semaglutide (25 patients (1.6%)) than with placebo (46 patients (2.9%)).

The distribution of fatal AEs occurring in the in-trial period by SOC and PT is presented below by treatment arm.

Table 75 Deaths by SOC and PT – PIONEER 6

Body System or Organ Class	Dictionary Derived Term	Oral sema N=1591	Placebo N=1592
Cardiac disorders	Acute myocardial infarction	1 (0.1%)	3 (0.2%)
	Cardiac arrest	3 (0.2%)	0 (0.0%)

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	Cardiac failure	0 (0.0%)	1 (0.1%)
	Cardiac failure chronic	0 (0.0%)	3 (0.2%)
	Cardiac failure congestive	1 (0.1%)	0 (0.0%)
	Cardiogenic shock	0 (0.0%)	1 (0.1%)
	Cardiopulmonary failure	0 (0.0%)	1 (0.1%)
	Cardiorenal syndrome	0 (0.0%)	1 (0.1%)
	Cardio-respiratory arrest	1 (0.1%)	5 (0.3%)
	Coronary artery disease	1 (0.1%)	1 (0.1%)
	Coronary artery thrombosis	0 (0.0%)	1 (0.1%)
	Hypertensive heart disease	0 (0.0%)	1 (0.1%)
	Myocardial infarction	4 (0.3%)	5 (0.3%)
	Myocardial ischemia	0 (0.0%)	2 (0.1%)
	Pulseless electrical activity	0 (0.0%)	1 (0.1%)
	Sinus node dysfunction	0 (0.0%)	1 (0.1%)
General disorders and administration site conditions	Death	2 (0.1%)	5 (0.3%)
	Drowning	0 (0.0%)	1 (0.1%)
	Sudden cardiac death	0 (0.0%)	2 (0.1%)
Infections and infestations	Abdominal sepsis	0 (0.0%)	1 (0.1%)
	Bacterial sepsis	1 (0.1%)	0 (0.0%)
	Bronchitis	1 (0.1%)	0 (0.0%)
	Lower respiratory tract infection	1 (0.1%)	0 (0.0%)
	Pneumonia	0 (0.0%)	5 (0.3%)
	Septic shock	1 (0.1%)	3 (0.2%)
Injury, poisoning and procedural complications	Chemical peritonitis	0 (0.0%)	1 (0.1%)
	Subdural hematoma	1 (0.1%)	0 (0.0%)
Metabolism and nutrition disorders	Hyperkaliemia	0 (0.0%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma gastric	1 (0.1%)	1 (0.1%)
	Cholangiocarcinoma	0 (0.0%)	1 (0.1%)
	Diffuse large B-cell lymphoma	1 (0.1%)	1 (0.1%)
	Hepatic cancer	0 (0.0%)	1 (0.1%)
	Hepatocellular carcinoma	2 (0.1%)	1 (0.1%)
	Lung neoplasm malignant	1 (0.1%)	0 (0.0%)
	Mesothelioma malignant	0 (0.0%)	1 (0.1%)
	Metastases to liver	0 (0.0%)	1 (0.1%)
	Metastatic malignant melanoma	1 (0.1%)	0 (0.0%)
	Pancreatic carcinoma metastatic	1 (0.1%)	1 (0.1%)
	Squamous cell carcinoma of the tongue	0 (0.0%)	1 (0.1%)
Nervous system disorders	Ischemic stroke	1 (0.1%)	0 (0.0%)
Renal and urinary disorders	Acute kidney injury	0 (0.0%)	1 (0.1%)
	Renal impairment	1 (0.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	1 (0.1%)	0 (0.0%)

Reference ID: 4494748

	Lung disorder	1 (0.1%)	0 (0.0%)
	Respiratory failure	0 (0.0%)	1 (0.1%)
Vascular disorders	Aortic dissection	1 (0.1%)	0 (0.0%)
	Total	25 (1.6%)	46 (2.9%)

Source: Reviewer generated using JReview

The cause of death as assigned by the EAC is documented below.

Table 76 EAC-Confirmed Deaths – PIONEER 6

	Oral sema				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1591				1592			
Observation time (years)	2101				2081			
All-cause death	23	(1.4)	23	1.1	45	(2.8)	45	2.2
Cardiovascular and undetermined cause of death	15	(0.9)	15	0.7	30	(1.9)	30	1.4
Cardiovascular death	10	(0.6)	10	0.5	23	(1.4)	23	1.1
Acute myocardial infarction	0				4	(0.3)	4	0.2
Sudden cardiac death	8	(0.5)	8	0.4	14	(0.9)	14	0.7
Heart failure	0				2	(0.1)	2	0.1
Stroke	1	(0.1)	1	0.0	1	(0.1)	1	0.0
Cardiovascular procedure	0				1	(0.1)	1	0.0
Other	1	(0.1)	1	0.0	1	(0.1)	1	0.0
Undetermined cause of death	5	(0.3)	5	0.2	7	(0.4)	7	0.3
Non-cardiovascular death	8	(0.5)	8	0.4	15	(0.9)	15	0.7
Renal causes	0				1	(0.1)	1	0.0
Malignancy	5	(0.3)	5	0.2	8	(0.5)	8	0.4
Infection	3	(0.2)	3	0.1	2	(0.1)	2	0.1
Non-CV procedure or surgery	0				1	(0.1)	1	0.0
Pulmonary causes	0				2	(0.1)	2	0.1
Other	0				1	(0.1)	1	0.0

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.

Source: Table 2-9 Summary of Clinical Safety

Additionally, one death was reported from a clinical pharmacology trial (hepatic impairment trial), a case of bacterial peritonitis in a 54 year old female patient with severe hepatic impairment who received semaglutide. The patient experienced abdominal pain, vomiting, and fever on day 5 of treatment with oral semaglutide 5 mg, was admitted to the hospital where she decompensated rapidly and died. Notably this patient had a history of spontaneous bacterial peritonitis prior to enrollment in the trial, as well as cirrhosis and esophageal varices. It is likely that her death was caused by the underlying disease rather than semaglutide treatment.

Reviewer comment: No imbalance in death not favoring semaglutide was observed in the oral semaglutide clinical program.

8.4.2. Serious Adverse Events

Reference ID: 4494348

The proportions of patients with SAEs and rates of SAEs were similar for oral semaglutide and comparator in the phase 3a pool and for oral semaglutide and placebo in the placebo pool.

In PIONEER 6 the proportion of patients reporting SAEs during the trial was lower with oral semaglutide (18.9% of patients) than with placebo (22.5% of patients).

Table 77 Total SAEs – Phase 3a Pool, Placebo Pool and PIONEER 6 – On-Treatment

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

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

Source: Table 2-11 ISS

The most frequently reported SAEs in the phase 3a pool were within the SOCs: cardiac disorders, neoplasms and infections and infestations. No differences were observed in the SOC cardiac disorders between semaglutide and comparator.

Reference ID: 4494748

Table 78 SAEs Reported by ≥0.2% of Patients by SOC and PT – Phase 3a Pool – On-Treatment

	Oral sema N (Adj.%)	E	Adj.R	Comparator N (Adj.%)	E	Adj.R
Number of subjects	4116			2236		
Exposure time (years)	4379			2335		
All events	345 (8.6)	518	12.8	202 (9.0)	282	12.2
Cardiac disorders	70 (1.7)	85	2.1	36 (1.7)	43	1.7
Acute myocardial infarction	11 (0.3)	11	0.4	6 (0.3)	6	0.2
Angina unstable	12 (0.3)	12	0.3	3 (0.2)	3	0.1
Myocardial infarction	9 (0.2)	9	0.2	3 (0.1)	3	0.1
Atrial fibrillation	8 (0.2)	8	0.2	9 (0.4)	9	0.4
Coronary artery disease	7 (0.2)	7	0.2	4 (0.2)	4	0.2
Cardiac failure chronic	6 (0.2)	6	0.1	5 (0.2)	6	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	47 (1.3)	48	1.4	22 (1.0)	22	1.0
Invasive ductal breast carcinoma	4 (0.1)	4	0.1	4 (0.2)	4	0.2
Infections and infestations	54 (1.3)	67	1.6	34 (1.6)	38	1.8
Pneumonia	10 (0.2)	10	0.2	5 (0.3)	5	0.2
Cellulitis	8 (0.2)	8	0.1	2 (0.1)	3	0.1
Pyelonephritis	2 (<0.1)	2	<0.1	3 (0.2)	3	0.1
Nervous system disorders	38 (1.0)	42	1.1	25 (1.1)	33	1.4
Syncope	5 (0.2)	7	0.2	1 (<0.1)	1	<0.1
Ischaemic stroke	7 (0.1)	7	0.1	9 (0.4)	9	0.5
Musculoskeletal and connective tissue disorders	33 (0.8)	38	0.9	19 (0.8)	19	0.8
Osteoarthritis	10 (0.2)	10	0.2	5 (0.2)	5	0.2
Renal and urinary disorders	19 (0.5)	19	0.6	10 (0.4)	10	0.5
Acute kidney injury	8 (0.2)	8	0.2	2 (<0.1)	2	0.1
Hepatobiliary disorders	15 (0.4)	18	0.4	11 (0.5)	18	0.7
Cholelithiasis	5 (0.1)	5	0.1	4 (0.2)	4	0.1
Cholecystitis acute	2 (<0.1)	2	<0.1	5 (0.2)	5	0.2

Phase 3a pool: PIONEER 1-5 and 7-10.'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
This table includes SOCs and PTs, where PTs were reported by ≥ 0.2% of subjects in either treatment group. The numbers in the SOC row represent the total number for the SOC. Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 2-12 ISS

A higher proportion of patients in the semaglutide group experienced SAEs that were reported as not recovered compared to placebo (1.3% of patients compared to 1% of patients), but this difference is small and of unclear significance. A similar proportion of patients in both treatment groups experienced SAEs that lead to premature trial product discontinuation (1.2% with semaglutide, and 1.3% with placebo).

A similar pattern was seen in the placebo pool.

In PIONEER 6, the most frequently reported SAEs in either treatment arm were in the SOC Cardiac disorders. The proportion of patients with SAEs was lower with semaglutide (18.9% of patients) compared to placebo (22.5% of patients). In the SOC cardiac disorders, fewer patients on semaglutide experienced an SAE (6.2%) compared to placebo (7%). No other pattern is identified due to the small number of SAEs in each SOC and/or PT category. A similar

Reference ID: 4494348

proportion of patients experienced SAEs leading to treatment discontinuation with semaglutide (2.6% of patients) vs placebo (3% of patients).

Table 79 SAEs Reported by ≥0.5% of Patients by SOC and PT - PIONEER 6 – On-Treatment

	Oral semaglutide				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
Events	301	(18.9)	545	28	358	(22.5)	618	31
Cardiac disorders	97	(6.1)	134	7	111	(7.0)	148	7
Acute myocardial infarction	21	(1.3)	25	1	22	(1.4)	25	1
Angina unstable	19	(1.2)	20	1	15	(0.9)	18	1
Myocardial infarction	11	(0.7)	11	1	9	(0.6)	9	0
Cardiac failure congestive	9	(0.6)	12	1	9	(0.6)	11	1
Coronary artery disease	9	(0.6)	9	0	13	(0.8)	13	1
Angina pectoris	8	(0.5)	9	0	7	(0.4)	7	0
Atrial fibrillation	6	(0.4)	8	0	14	(0.9)	14	1
Cardiac failure chronic	5	(0.3)	5	0	8	(0.5)	9	0
Infections and infestations	67	(4.2)	75	4	73	(4.6)	93	5
Pneumonia	12	(0.8)	13	1	21	(1.3)	21	1
Cellulitis	9	(0.6)	9	0	7	(0.4)	7	0
Nervous system disorders	38	(2.4)	52	3	45	(2.8)	57	3
Hypoglycaemic unconsciousness	9	(0.6)	11	1	6	(0.4)	8	0
Ischaemic stroke	9	(0.6)	9	0	11	(0.7)	12	1
Renal and urinary disorders	25	(1.6)	27	1	32	(2.0)	37	2
Acute kidney injury	13	(0.8)	14	1	14	(0.9)	18	1
Respiratory, thoracic and mediastinal dis.	22	(1.4)	29	2	18	(1.1)	21	1
Chronic obstructive pulmonary disease	8	(0.5)	11	1	4	(0.3)	4	0
Injury, poisoning and procedural compl.	21	(1.3)	31	2	34	(2.1)	43	2
Fall	5	(0.3)	5	0	11	(0.7)	11	1
General disorders and adm. site cond.	17	(1.1)	19	1	19	(1.2)	21	1
Non-cardiac chest pain	9	(0.6)	11	1	7	(0.4)	9	0
Musculoskeletal and connective tissue dis.	17	(1.1)	17	1	25	(1.6)	26	1
Osteoarthritis	6	(0.4)	6	0	10	(0.6)	10	1
Eye disorders	9	(0.6)	9	0	6	(0.4)	7	0
Cataract	8	(0.5)	8	0	5	(0.3)	6	0

Table is sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide arm. This table includes SOCs and PTs, where PTs were reported by ≥ 0.5% of subjects in either treatment group. The numbers in the SOC row represent the total number for the SOC.
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 exposure.

Source: Table 2-13 ISS

Additionally, 12 SAEs were reported from the 17 clinical pharmacology trials, 10 (0.7%) with semaglutide, and 2 (0.6%) on comparator. One event with oral semaglutide was fatal – discusses in the Death section above. Six SAEs were in the GI SOC (5 with semaglutide, and 1 with comparator), the rest of the SAES were dispersed across multiple SOCs.

Reviewer's comment: Generally, the proportion of patients with SAEs was similar between semaglutide and placebo/comparator, with no indication of an increase rate of SAEs overall

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with semaglutide. GI SAEs were not very commonly reported with either semaglutide or comparator. Cardiac disorders was the most common SOC where SAEs were reported with either semaglutide or comparator. While fewer cardiac disorders were seen with semaglutide vs placebo in PIONEER 6, the rate of events was similar in the phase 3 pool.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the phase 3a pool, the placebo pool and PIONEER 6, the proportions of patients with AEs leading to premature treatment discontinuation and the rates of AEs leading to premature discontinuation were higher with oral semaglutide than with pooled comparators. This difference was driven by non-serious GI AEs.

In PIONEER 6, patients who prematurely discontinued trial product were allowed to restart trial product later. If they did not restart trial product they were classified as permanently discontinued. For PIONEER 6, focus in this section is therefore on the AEs leading to permanent treatment discontinuation.

An overview of AEs leading to treatment discontinuation is presented below. In all pools, there were more discontinuations due to AE with semaglutide vs placebo/comparator, mostly due to non-serious AEs.

Reference ID: 4494748

Table 80 Overview of AEs Leading to Permanent Premature Trial Product Discontinuation – Phase 3a Pool, Placebo Pool and PIONEER 6 – On-Treatment

	Oral sema N (Adj.%)	E	Adj.R	Comparator or Placebo N (Adj.%)	E	Adj.R
Phase 3a pool						
Number of subjects	4116			2236		
Exposure time (years)	4379			2335		
AEs	329 (8.7)	554	15.8	100 (4.2)	141	5.8
Non-serious AEs	288 (7.7)	485	14.1	74 (3.1)	107	4.2
SAEs	47 (1.2)	69	1.7	30 (1.3)	34	1.7
Fatal	3 (<0.1)	3	<0.1	4 (0.1)	5	0.2
Placebo pool						
Number of subjects	1519			665		
Exposure time (years)	1197			523		
AEs	132 (9.3)	242	22.0	22 (3.2)	28	5.6
Non-serious adverse events	121 (8.6)	224	20.5	12 (1.7)	16	3.0
SAEs	12 (0.8)	18	1.5	11 (1.6)	12	2.6
Fatal	2 (0.1)	2	0.1	0		
	Oral semaglutide N (%)	**E**	**R**	**Placebo N (%)**	**E**	**R**
PIONEER 6						
Number of subjects	1591			1592		
Exposure time (years)	1932			1987		
AEs	184 (11.6)	253	13	104 (6.5)	132	7
Non-serious AEs	144 (9.1)	199	10	57 (3.6)	75	4
SAEs	41 (2.6)	54	3	48 (3.0)	57	3
Fatal	9 (0.6)	10	1	11 (0.7)	11	1

Phase 3a pool: PIONEER 1-5 and 7-10. Placebo pool: PIONEER 1, 4, 5 and 8. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator' for phase 3a pool: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. 'Comparator' for placebo pool: placebo. Premature treatment discontinuation in PIONEER 1-5 and 7-10 corresponded to permanent treatment discontinuation in PIONEER 6.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events; 'Relationship to trial product': as judged by the investigator; seq.: sequelae.

Source: Table 2-15 ISS

The increased rate of AEs leading to discontinuation with semaglutide was mostly due to GI AEs as expected with this class of drugs. AEs leading to discontinuation by SOC and PT are presented below for the phase 3 a pool, and PIONEER 6.

Reference ID: 4494748

Table 81 AEs (≥0.2 %) Leading to Permanent Trial Product Discontinuation by SOC and PT – Phase 3a Pool – On-Treatment

	Oral sema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
Events	329	(8.7)	554	15.8	100	(4.2)	141	5.8
Gastrointestinal disorders	217	(5.9)	335	10.1	43	(1.8)	55	2.1
Nausea	98	(2.9)	98	3.1	16	(0.6)	16	0.6
Vomiting	56	(1.7)	59	1.9	5	(0.2)	5	0.2
Diarrhoea	37	(0.9)	37	0.9	10	(0.4)	10	0.4
Abdominal pain	19	(0.6)	20	0.7	5	(0.2)	5	0.2
Abdominal pain upper	20	(0.5)	20	0.6	2	(<0.1)	2	0.1
Abdominal discomfort	16	(0.4)	16	0.5	3	(0.1)	3	0.2
Dyspepsia	12	(0.3)	12	0.4	1	(<0.1)	1	<0.1
Constipation	11	(0.3)	11	0.4	1	(<0.1)	1	<0.1
Abdominal distension	12	(0.3)	12	0.3	2	(<0.1)	2	<0.1
Gastritis	7	(0.2)	7	0.2	1	(<0.1)	1	<0.1
Gastrooesophageal reflux disease	8	(0.2)	8	0.2	1	(<0.1)	1	<0.1
Pancreatitis acute	7	(0.2)	7	0.1	3	(0.1)	3	<0.1
Metabolism and nutrition disorders	34	(0.8)	36	0.9	6	(0.3)	6	0.2
Decreased appetite	31	(0.7)	31	0.8	3	(0.1)	3	0.1
Investigations	28	(0.7)	32	0.9	9	(0.4)	9	0.3
Weight decreased	13	(0.3)	13	0.3	1	(<0.1)	1	<0.1
Lipase increased	6	(0.2)	6	0.2	4	(0.2)	4	0.1
General disorders and administration site conditions	20	(0.5)	22	0.6	5	(0.2)	5	0.2
Asthenia	7	(0.2)	7	0.2	1	(<0.1)	1	<0.1
Musculoskeletal and connective tissue disorders	4	(0.1)	4	<0.1	6	(0.3)	6	0.3
Arthralgia	0				4	(0.2)	4	0.2

Phase 3a pool: PIONEER 1-5 and 7-10. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. This table includes SOCs and PTs, where PTs were reported by ≥ 0.2% of subjects in either treatment group. The numbers in the SOC row represent the total number for the SOC. All PTs can be found in the referenced table. Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 2-17 ISS

Reference ID: 4494348

Table 82 AEs (≥0.2 %) Leading to Permanent Trial Product Discontinuation by SOC and PT – PIONEER 6 – On-Treatment

	Oral sema N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
Events	184	(11.6)	253	13	104	(6.5)	132	7
Gastrointestinal disorders	108	(6.8)	133	7	26	(1.6)	33	2
Nausea	46	(2.9)	46	2	8	(0.5)	8	0
Vomiting	24	(1.5)	25	1	4	(0.3)	4	0
Diarrhoea	22	(1.4)	22	1	6	(0.4)	6	0
Abdominal discomfort	10	(0.6)	10	1	2	(0.1)	2	0
Dyspepsia	7	(0.4)	7	0	4	(0.3)	4	0
Constipation	6	(0.4)	6	0	0			
Gastrooesophageal reflux disease	4	(0.3)	4	0	0			
Metabolism and nutrition disorders	19	(1.2)	19	1	7	(0.4)	7	0
Decreased appetite	16	(1.0)	16	1	2	(0.1)	2	0
Investigations	15	(0.9)	18	1	3	(0.2)	3	0
Lipase increased	6	(0.4)	6	0	0			
Amylase increased	4	(0.3)	4	0	0			
Pancreatic enzymes increased	3	(0.2)	3	0	1	(0.1)	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15	(0.9)	16	1	15	(0.9)	15	1
Adenocarcinoma of colon	3	(0.2)	3	0	1	(0.1)	1	0
General disorders and administration site cond.	8	(0.5)	8	0	5	(0.3)	6	0
Asthenia	3	(0.2)	3	0	2	(0.1)	2	0
Cardiac disorders	6	(0.4)	8	0	10	(0.6)	10	1
Acute myocardial infarction	1	(0.1)	1	0	3	(0.2)	3	0
Infections and infestations	6	(0.4)	6	0	7	(0.4)	8	0
Pneumonia	0				3	(0.2)	3	0
Renal and urinary disorders	3	(0.2)	3	0	9	(0.6)	9	0
Acute kidney injury	1	(0.1)	1	0	4	(0.3)	4	0
Hepatobiliary disorders	1	(0.1)	1	0	5	(0.3)	5	0
Cholelithiasis	0				3	(0.2)	3	0

Table is sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide arm. This table includes SOCs and PTs, where PTs were reported by ≥ 0.2% of subjects in either treatment group. The numbers in the SOC row represent the total number for the SOC. 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 exposure.

Source: Table 2-18 ISS

SAEs led to premature treatment discontinuation in a similar rate and proportion of patients across the pools and PIONEER 6, as follows:
- Phase 3a pool: oral semaglutide (1.7 SAEs/100 PYE, 1.2%); comparator (1.7 SAEs/100 PYE, 1.3%)
- Placebo pool: oral semaglutide (1.5 SAEs/100 PYE, 0.8%); placebo (2.6 SAEs/100 PYE, 1.6%)
- PIONEER 6: oral semaglutide (3 AEs/100 PYE, 2.6%); placebo (3 AEs/100 PYE, 3.0%)

It does appear that the discontinuations due to AEs were dose-dependent for the oral semaglutide. In PIONEER 3, the proportion of patients with AEs leading to premature treatment discontinuation was similar between the oral semaglutide 3 mg, 7 mg and sitagliptin,

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but higher with oral semaglutide 14 mg. In the placebo dose pool, the proportion of patients with AEs leading to premature treatment discontinuation increased with dose and all three oral semaglutide doses had a higher proportion of patients with AEs leading to treatment discontinuation than placebo.

Table 83 Overview of AEs Leading to Premature Treatment Discontinuation by Dose – PIONEER 3 and Placebo Dose Pool – On-Treatment

	Oral sema 3 mg			Oral sema 7 mg			Oral sema 14 mg			Sitagliptin/Placebo		
	N	(%)	R	N	(%)	R	N	(%)	R	N	(%)	R
Number of subjects												
PIONEER 3	466			464			465			466		
Placebo dose pool	359			356			356			362		
Exposure time (years)												
PIONEER 3	662			669			650			687		
Placebo dose pool	288			274			267			290		
AEs leading to premature trial product discontinuation												
PIONEER 3	26	(5.6)	5.7	27	(5.8)	6.1	54	(11.6)	13.1	24	(5.2)	4.1
Placebo dose pool[a]	17	(4.7)	11.6	23	(6.5)	15.2	37	(10.4)	27.2	9	(2.5)	4.3

PIONEER 3 comparator: sitagliptin. Placebo dose pool: PIONEER 1 and 8. comparator: placebo.
N: number of subjects with at least one event; [a]In the placebo dose pool, the % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 2-19 ISS

The dose-dependent increase in AEs leading to premature treatment discontinuation was driven by the dose-dependent increases in GI AEs (nausea, vomiting, diarrhea, and terms related to abdominal pain) in both PIONEER 3 and the placebo dose pool.

Reviewer's comment: Oral semaglutide lead to more AEs leading to treatment discontinuation compared to placebo/other comparators, and this was mostly due to a difference in non-serious GI AEs. The AEs leading to discontinuation appeared to be dose-dependent with oral semaglutide, as expected based on our experience with subcutaneous semaglutide, and other drug products in the class.

8.4.4. Significant Adverse Events

The following definitions were used by the applicant when assessing the severity of an AE:

- Mild - no or transient symptoms, no interference with the patient's daily activities.
- Moderate - marked symptoms, moderate interference with the patient's daily activities.
- Severe - considerable interference with the patient's daily activities; unacceptable.

Additionally, the applicant also analyzed the outcome of the AEs. Outcome categories and definitions are presented below:

- Recovered/resolved - The patient had fully recovered, or by medical or surgical treatment the condition had returned to the level observed at the first trial-related

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activity after the patient signed the informed consent.

- Recovering/resolving - The condition was improving and the patient was expected to recover from the event. This term was only applicable if the patient had completed the trial or had died from another AE.
- Recovered/resolved with sequelae - The patient had recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela met an SAE criterion, the AE was to be reported as an SAE.
- Not recovered/not resolved - The condition of the patient had not improved and the symptoms were unchanged, or the outcome was not known.
- Fatal - This term was only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died were to be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome was to be reported as an SAE.

Phase 3a pool

No significant differences were seen between the treatment arms regarding the severity, or the outcome of the adverse events. More than 60% of AEs were listed as recovered in all treatment groups.

Table 84 Adverse Events by Severity and Outcome – Phase 3a Pool

	Oral sema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
All events	3087	(74.9)	12459	302.2	1616	(73.0)	6004	259.0
Severity								
Severe	264	(6.6)	399	9.9	152	(6.8)	223	9.4
Moderate	1321	(33.9)	3060	76.9	683	(30.8)	1470	62.5
Mild	2721	(65.2)	9000	215.3	1401	(63.4)	4311	187.1
Outcome								
Fatal	13	(0.3)	14	0.4	12	(0.5)	15	0.6
Not recovered	1391	(32.7)	2731	62.2	746	(34.5)	1480	64.3
Recovered with seq.	25	(0.6)	28	0.7	13	(0.6)	16	0.6
Recovering	281	(6.6)	357	8.6	135	(6.3)	176	8.5
Recovered	2777	(67.5)	9307	229.7	1409	(63.5)	4313	184.8
Unknown	11	(0.3)	22	0.6	3	(0.1)	4	0.2

Source: Table 7.2.4 ISS

Placebo pool

A similar trend was observed in the placebo pool, although a small increase in the rate of events was seen in each category of severity with semaglutide vs placebo. A similar proportion of events were listed as not recovered in both treatment groups.

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Table 85 Adverse Events by Severity and Outcome – Placebo Pool

	Oral sema N	(Adj.%)	E	Adj.R	Placebo N	(Adj.%)	E	Adj.R
Number of subjects	1519				665			
Exposure time (years)	1197				523			
All events	1072	(71.3)	4055	356.7	438	(65.9)	1358	264.5
Severity								
Severe	92	(6.2)	148	12.4	36	(5.1)	48	9.3
Moderate	473	(32.2)	1082	95.1	180	(27.3)	326	65.2
Mild	935	(62.1)	2825	249.2	376	(56.5)	984	189.9
Outcome								
Fatal	7	(0.5)	7	0.6	3	(0.4)	3	0.6
Not recovered	423	(27.8)	750	65.1	185	(28.3)	322	63.7
Recovered with seq.	14	(0.9)	15	1.3	4	(0.6)	5	0.8
Recovering	88	(6.0)	111	10.6	44	(6.4)	51	11.0
Recovered	976	(65.0)	3160	277.7	361	(54.3)	975	188.1
Unknown	6	(0.4)	12	1.3	1	(0.1)	2	0.4

Source: Table 7.2.18 ISS

PIONEER 6

Only SAEs were reported for PIONEER 6, and therefore the information available is somewhat limited. No imbalance in AEs of any severity was reported with semaglutide vs placebo.

Table 86 SAEs by Severity and Outcome – PIONEER 6

	Oral semaglutide N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
Total number of events	301	(18.9)	545	28	358	(22.5)	618	31
Severity								
Severe	171	(10.7)	267	14	192	(12.1)	285	14
Moderate	145	(9.1)	228	12	175	(11.0)	263	13
Mild	40	(2.5)	50	3	61	(3.8)	70	4
Outcome								
Fatal	20	(1.3)	24	1	38	(2.4)	46	2
Not recovered	38	(2.4)	43	2	49	(3.1)	62	3
Recovered with seq.	10	(0.6)	12	1	21	(1.3)	22	1
Recovering	13	(0.8)	16	1	15	(0.9)	17	1
Recovered	256	(16.1)	450	23	281	(17.7)	470	24
Unknown	0				1	(0.1)	1	0

Source: Table 12-3 CSR PIONEER 6

Reviewer comment: While no overall differences were observed between the treatment groups, I believe that this severity categorization is subjective, and does not add any important information to the analysis of adverse events.

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8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Common Adverse Events

Because PIONEER 6 employed a targeted data collection for safety, this section will evaluate common AEs in the phase 3a and placebo pools.

Overall, 74.9% of patients on oral semaglutide in the phase 3 pool experienced an AE, compared to 73% of patients on comparator. In the placebo pool, the difference was more pronounced, with 71.3% of patients on oral semaglutide experiencing an AE, compared to 65.9% of patients on placebo.

The applicant conducted a time to first event analysis for AEs and concluded that the time to first event was shorter with oral semaglutide vs comparator in the phase 3a pool, with approximately 50% of patients reporting their first AE with semaglutide in the first 12 weeks of treatment. An analysis of the placebo pool yielded similar results.

With regards to the type of AEs reported, in the phase 3a and placebo pools, only GI events appeared to be reported more with semaglutide vs comparator, while other events were reported by a similar proportion of patients in either arm. This is as expected for this drug class, and similar to the subcutaneous semaglutide product.

Reference ID: 4494748

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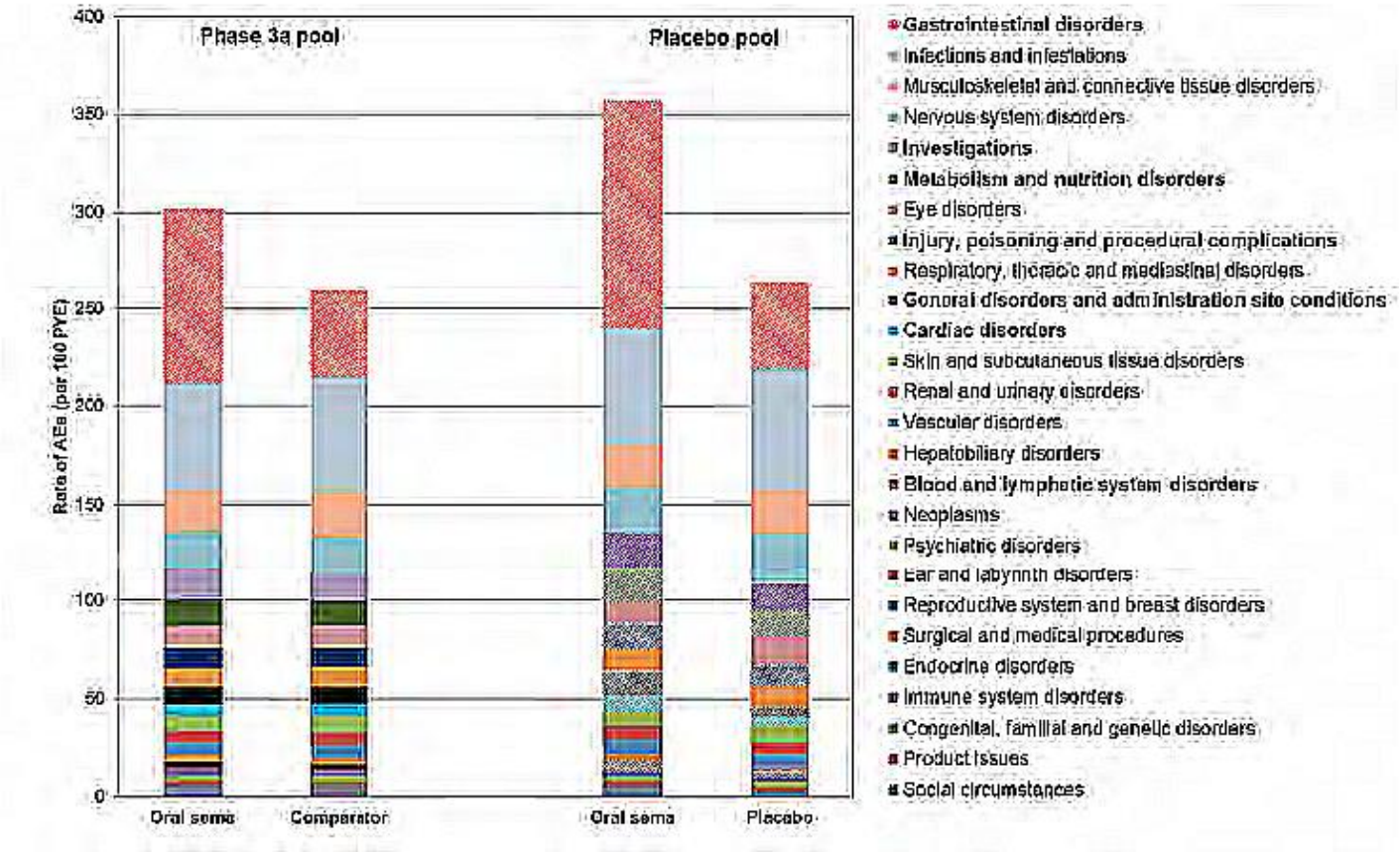
Figure 31 Rate of AEs by SOC – Phase 3a Pool and Placebo Pool – On-Treatment



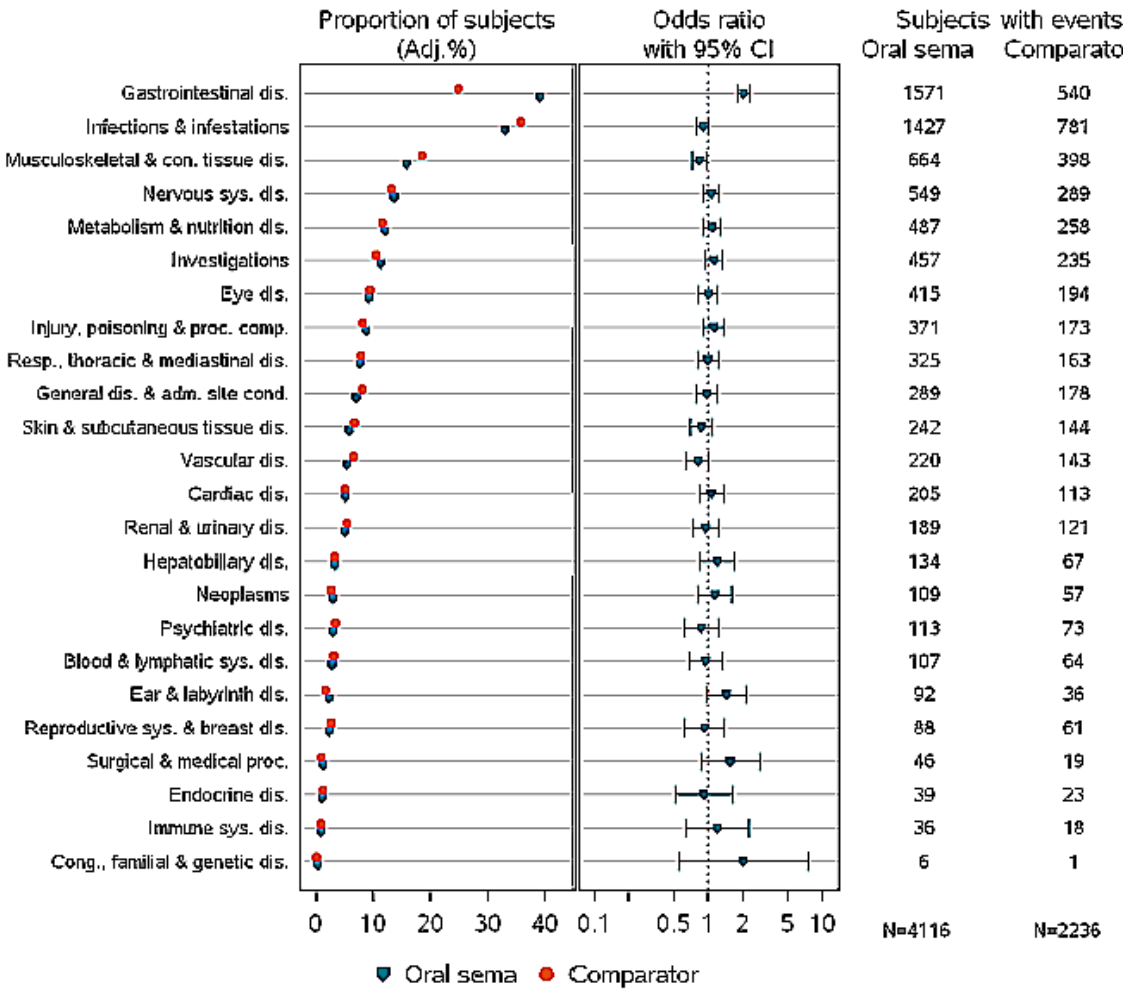
SOCs are ordered by frequency from highest to lowest with oral semaglutide in the phase 3a pool. Bars were shaded and legend bolded for SOCs where the differences between oral semaglutide and comparator or placebo were greater than 2 AEs/100 PYE.

Source: Figure 2-8 ISS

Further analyses looking at imbalances by SOC are presented in the two figures below, for the phase 3a and placebo pool.

Reference ID: 4494348

Figure 32 AEs – Statistical Analysis by SOC – Phase 3a Pool – On-Treatment

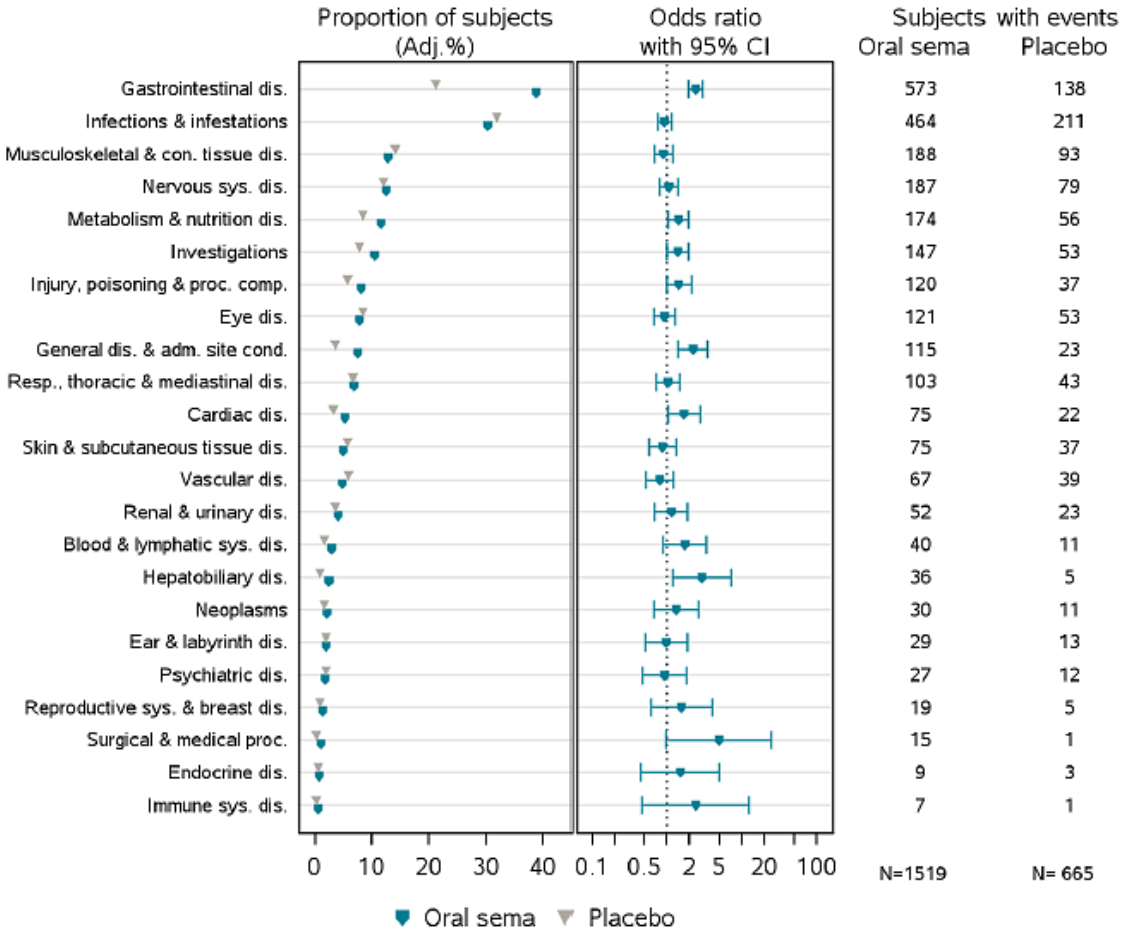


Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
System organ classes with more than 5 events in total are presented.
Sorted in descending order by system organ class based on the proportion of subjects with at least one event in the oral semaglutide group.
Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%); CI: confidence interval; dis.: disorders; con.: connective; sys.: system; proc.: procedural/procedures; resp.: respiratory; adm.: administration; cond.: conditions; cong.: congenital; N: number of subjects.

Source: Figure 2-9 ISS

Reference ID: 4494348

Figure 33 AEs– Statistical Analysis by SOC – Placebo Pool – On-Treatment



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

Source: Figure 2-10 ISS

Apart from the GI AEs, which were more commonly seen with semaglutide as expected, AEs in other SOCs were more commonly with oral semaglutide vs comparator as follows:

- Metabolism and nutritional disorders
- Investigations
- Injury, poisoning and procedural complications
- General disorders and administration site conditions
- Cardiac disorders
- Blood and lymphatic system disorders.
- Hepatobiliary disorders
- Surgical and medical procedures

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Metabolism and nutritional disorders

The difference between oral semaglutide and comparator was driven by the decreased appetite PT which was reported by 5% of patients on semaglutide in each pool vs 2% with comparator in phase 3a pool, and 0.5% with placebo (placebo pool). This is expected with GLP-1RA agonists.

Investigations

The protocols specifically mandated AE reporting for AST or ALT >5xULN and CK >10xULN. For all other laboratory parameters there were no pre-specified limits and considerable variation was seen as to when a laboratory value was considered clinically significant by investigators.

- Lipase, amylase and pancreatic enzyme increase: An increase in the PTs lipase increased, amylase increased and pancreatic enzymes increased was reported more frequently in patients on oral semaglutide than comparators (phase 3a pool: 3.1%, 0.9% and 0.7% vs 2.6%, 0.6% and 0.3%) and placebo (placebo pool: 2.5%, 0.8% and 0.7% vs 0.6%, 0 patients and 0 patients) respectively. These changes are expected with the GLP-1 RA class and they do not seem to be associated with an increase in clinical events of pancreatitis.
- Blood creatine phosphokinase increased: In the phase 3 pool, 1.8% of patients on oral semaglutide vs 1.4% with comparator. The same was true of the placebo pool with 1.3% of patients in oral semaglutide arm reporting an increase in CK, vs 0.6% in the placebo pool. The clinical significance of an increase in CK reported with semaglutide vs comparator is unclear as the numbers were small, and no concerning CK outliers were identified in the trial, and there were no imbalances in musculoskeletal and connective tissue disorders SOC.
- Weight decreased: As expected based on the mechanism of action, the proportion of patients with weight decrease was higher in the semaglutide arm vs comparator (0.9% vs 0.2% in the phase 3a pool, and 1% vs 0.2% in the placebo pool.
- Blood potassium and creatinine increased, GFR decreased: These events were balanced in the phase 3 pool, but an imbalance not favoring semaglutide was seen in the placebo pool (0.4% of patients on oral semaglutide vs 0.1% of patients on placebo). However, the number of events was small (14 events with semaglutide), and the clinical significance is unclear. Renal events will be reviewed under events of special interest.

Injury, poisoning and procedural complications

Oral semaglutide appears to be associated with an increased incidence in the rate of events in this SOC in the placebo pool. While some events occurring more frequently with semaglutide vs placebo are random such as insect or arthropod bites, thermal burns, etc., other events may raise concerns as follows. The most prominent preferred terms in this SOC are falls and contusions, where more patients in the semaglutide group experienced an event (0.4% vs 0.2% for each event), and these could be suggestive of hypoglycemia which is a concern with any

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antidiabetic drug. The difference in falls was less prominent in the phase 3a pool (1.1% with semaglutide vs 0.9% with comparator), but contusions were more common with semaglutide 1.3% vs comparator 0.7%. None of the falls or contusions were SAEs in the placebo pool, and only 5 falls in the phase 3 pool were SAEs (one with comparator and 4 with semaglutide). The applicant also evaluated the falls due to concerns of hypoglycemia, and concluded that they were not hypoglycemia related, and also not related to dehydration, hypotension, or other similar events. I reviewed the fall SAEs and hypoglycemia or hypotension did not appear to play a role, however glucose or blood pressure at the time of the event were not reported, and the reason for the falls was not always clear. The applicant concluded that it must be due to chance, however, in my opinion, the clinical significance of this imbalance is not clear.

General disorders and administration site conditions

Asthenia and fatigue were seen more commonly with oral semaglutide in the placebo pool (1.7% and 1.4% of patients on semaglutide vs 0 and 0.5% of patients on placebo). The applicant noted that these events were frequently co-reported with GI AEs particularly during the dose escalation period.

Pyrexia was also more commonly reported with semaglutide (1.2% vs 0.7% with placebo in the placebo pool), but no imbalance was seen in the phase 3 pool. There did not appear to be a dose-response for pyrexia, and the mechanism by which oral semaglutide would lead to pyrexia is not obvious.

Pain was reported by a higher proportion of patients on semaglutide vs comparator in both pools (0.7% vs 0.2% in the placebo pool, and 0.5% vs 0.3% in the phase 3a pool)

Cardiac disorders

No difference was seen in the phase 3a pool, but in the placebo pool there were more patients on semaglutide reporting such events compared to placebo (5.2% vs 3.1%). The difference in the placebo pool was driven by tachycardia and palpitations PTs. An increase in heart rate (HR) is seen with this class of drugs.

Blood and lymphatic system disorders

The difference between semaglutide and placebo in the placebo pool (2.9% vs 1.7%) was not driven by any particular PT. The imbalance was not seen in the phase 3a pool.

Hepatobiliary disorders

There was a difference in the proportion of patients with AEs between oral semaglutide (2.4%) and placebo (0.8%) in the placebo pool, which was not seen in the phase 3a pool (3.2% vs 3.1%). In the placebo pool, this difference was driven by hepatic steatosis (1.5% vs 1.2%) and cholelithiasis PTs (0.6% vs 0.1%).

Common AEs reported by >5% of patients

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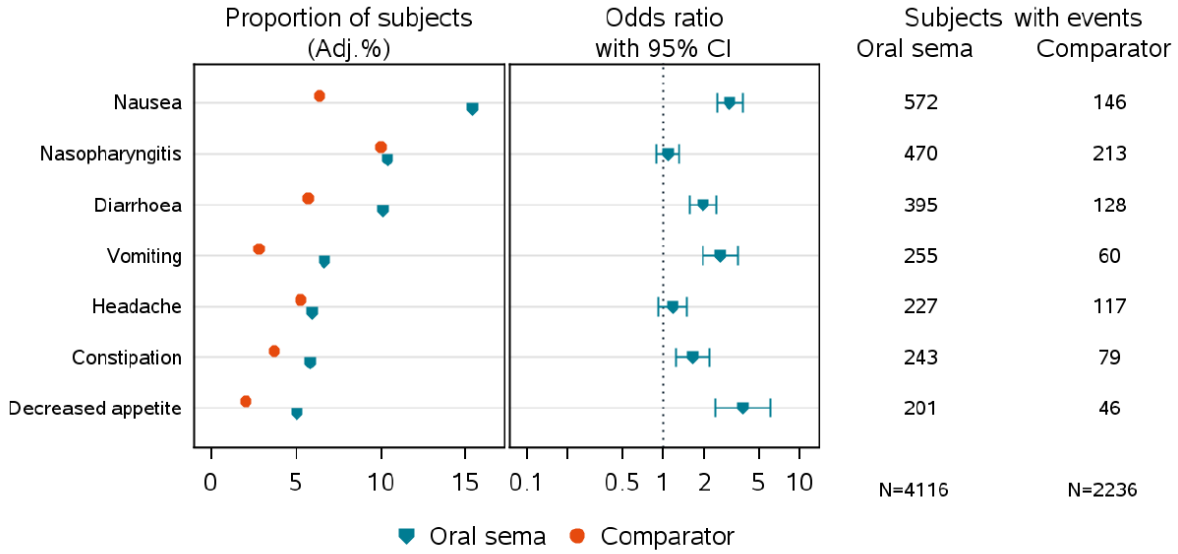
In the phase 3a pool, the most frequent PTs (reported by ≥ 5% of patients) that were more common with oral semaglutide than comparator included: nausea, diarrhea, vomiting, constipation and decreased appetite. Nasopharyngitis and headache were commonly reported by a similar proportion of patients with both oral semaglutide and comparator.

Figure 34 Most Frequent AEs (≥ 5% of Patients) – Statistical Analysis by PT – Phase 3a Pool – On-Treatment



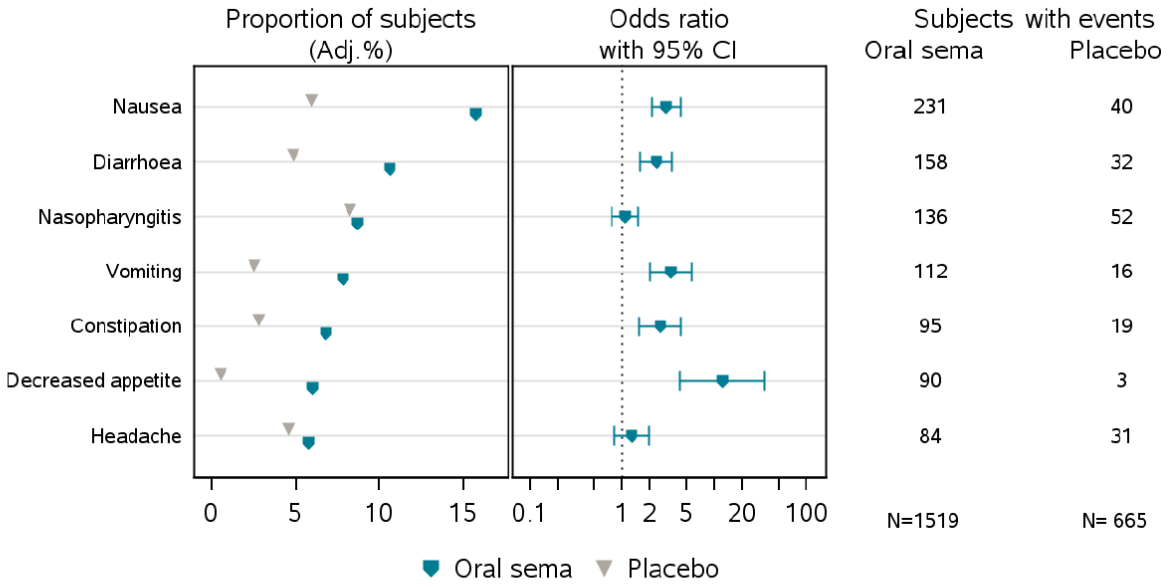
Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
Sorted in descending order by preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%); CI: confidence interval; N: number of subjects.

Source: Figure 2-11 ISS

The data for the placebo pool looks similar as illustrated below.

Reference ID: 4494348

Figure 35 Most Frequent AEs (>=5%) – Statistical Analysis by PT – Placebo Pool – On-Treatment



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

Source: Figure 7.2.27 ISS

In the placebo dose pool, a dose response was seen for nausea, vomiting, diarrhea and decreased appetite.

<u>AEs reported by 1-5% of patients</u>

In the phase 3a pool, of the 39 PTs reported by more than 1% and less than 5% of patients on oral semaglutide, the following were reported by a higher proportion of patients (>0.5%) on oral semaglutide than comparator, respectively:

- Dyspepsia: 4.0% vs 1.6%
- Abdominal pain: 3.3% vs 1.8%
- Abdominal pain upper: 3.3% vs 1.8%
- Abdominal discomfort: 2.7% vs 1.4%
- Gastroesophageal reflux disease: 2.6% vs 0.8%
- Gastroenteritis: 2.1% vs 1.0%
- Abdominal distension: 1.9% vs 1.3%
- Flatulence: 1.3% vs 0.7%

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A similar pattern with the same AEs reported more frequently with oral semaglutide than with placebo was observed in the placebo pool, with the addition of the below PTs being reported more frequently with oral semaglutide than placebo (>0.5%):

- Lipase increased: 2.5% vs 0.6%
- Asthenia:1.7% vs 0 patients
- Fatigue: 1.4% vs 0.5%
- Blood creatinine phosphokinase increased: 1.3% vs 0.6%
- Fall: 1.3% vs 0.7%
- Eructation: 1.2% vs 0 patients

Reviewer comment: The common AEs reported with semaglutide were generally as expected for drugs in the GLP-1 RA class.

8.4.6. Laboratory Findings

Analyses of liver and kidney function tests, calcitonin, lactic acid, and amylase/lipase are presented in section 8.4.5 of this review. Other parameters evaluated in the oral semaglutide program are hematologic and biochemistry parameters. There were no changes to mean hematology or chemistry parameters, no imbalance in the number of outliers between treatment groups, and no imbalance in the laboratory adverse events other than discussed in section 8.4.5.

The rest of this section will focus on the evaluation of lipids, which were evaluated in the PIONEER trials as an efficacy parameter.

<u>Lipids</u>

At baseline, the levels of fasting blood lipids were comparable across treatment groups and within trials for the phase 3a trials. Overall, the blood lipid profiles were improved with oral semaglutide across trials, i.e. with minor reductions in total cholesterol, LDL, and triglycerides, and no change in HDL. The changes were seen mostly with the 14 mg dose of oral semaglutide. Similar changes were observed in PIONEER 6.

While it is unknown whether the magnitude of the observed changes is beneficial, it does not appear that semaglutide has a negative impact on lipids. Additionally, these changes are in line with what was observed for injectable semaglutide, and other GLP-1 RAs.

8.4.7. Vital Signs

<u>Pulse rate</u>
GLP-1RAs are known to increase pulse rate. As expected, an increase in the pulse rate was observed with oral semaglutide, with the greatest increase observed with the 14 mg dose.

Reference ID: 4494748

These changes are presented in the table below, by trial.

Table 87 Pulse Rate (bpm) – Change from Baseline at the End of Treatment – On-Treatment – PIONEER 1–10

	Oral sema 3 mg	Oral sema 7 mg	Oral sema 14 mg	Comparator
PIONEER 1 (placebo)				
N	175	175	175	178
Change from baseline at week 26	0	1	3	-0
Treatment difference [95% CI] at week 26	1 [-1;2]	1 [-1;3]	3 [2;5]*	
PIONEER 2 (empagliflozin)				
N			409	409
Change from baseline at week 52			0	-2
Treatment difference [95% CI] at week 52			2 [1;3]*	
PIONEER 3 (sitagliptin)				
N	466	464	465	466
Change from baseline at week 78	1	1	2	0
Treatment difference [95% CI] at week 78	1 [-0;2]	1 [0;2]*	2 [1;3]*	
PIONEER 4 (liraglutide/placebo)				
N			285	284/ 142
Change from baseline at week 52 (Lira / Placebo)			2	3/ 0
Treatment difference [95% CI] at week 52 vs Lira			-1 [-3;0]	
Treatment difference [95% CI] at week 52 vs Placebo			2 [-0;3]	
PIONEER 5 (placebo)				
N			163	161
Change from baseline at week 26			1	0
Treatment difference [95% CI] at week 26			1 [-1;2]	
PIONEER 7 (sitagliptin)				
N		253		250
Change from baseline at week 52		2		1
Treatment difference [95% CI] at week 52		1 [-0;3]		
PIONEER 8 (placebo)				
N	184	181	181	184
Change from baseline at week 52	0	1	2	-0
Treatment difference [95% CI] at week 52	1 [-1;3]	2 [-0;3]	2 [1;4]*	
PIONEER 9 (placebo/liraglutide)				
N	49	49	48	49 / 48
Change from baseline at week 52	1	3	4	-0 / 3
Treatment difference [95% CI] at week 52 vs PBO	1 [-2;4]	3 [0;6]*	4 [1;7]*	
Treatment difference [95% CI] at week 52 vs Lira	-3 [-6;0]	-0 [-3;3]	1 [-2;4]	
PIONEER 10 (oral antidiabetics)				
N	131	132	130	65
Change from baseline at week 52	2	3	4	2
Treatment difference [95% CI] at week 52	0 [-2;3]	1 [-2;3]	2 [-1;4]	

	Oral sema	Placebo
PIONEER 6		
N	1345	1411
Change from baseline at the end of treatment	4	-0

For trials 1-5 and 7-10, changes from baseline were analysed using a mixed model for repeated measurements model (MMRM) with treatment, strata (P3-P8), interaction between strata (P5 and P8) and region (P1-P8) as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. For PIONEER 6, observed values are presented. CI: confidence interval; 'p-value': unadjusted two-sided p-value for test of no difference from 0. For PIONEER 7, a flexible oral semaglutide dose is used. N: number of subjects contributing to the analysis (P1-5 and 7-10) or summary statistic (P6); CI: confidence interval; *p<0.05

Source: Table 4-1 ISS

In the phase 3a pool, mean pulse rate increased by 2 bpm with oral semaglutide at the end of treatment, whereas there was no change with comparator. The treatment difference was less

Reference ID: 4497478

pronounced in the placebo pool, with a mean increase of 1 bpm at end of treatment with oral semaglutide vs 0 with placebo. In pioneer 6, no difference was seen with placebo, while semaglutide led to an increase in the pulse rate by 4 bpm.

In addition to routine pulse rate measurements in the phase 3 trials, the effects of semaglutide on pulse rate, QT and PR interval have been assessed in a dedicated QTc trial which was reviewed as part of the subcutaneous semaglutide NDA review. A dedicated SNAC QTc trial was performed for a full evaluation of oral semaglutide. Neither semaglutide nor SNAC caused any prolongation of the QTc interval at supra-therapeutic doses.

A MedDRA search was also performed by the applicant for 'heart rate increase' including the PTs 'heart rate increased', 'sinus tachycardia', and 'tachycardia'. There were no notable differences between semaglutide and comparator in the phase 3a pool, but these events were observed more with semaglutide vs placebo in the placebo pool (0.7% vs 0.4% of patients), with no indication of dose-response. However, the numbers are too small to draw any meaningful conclusions.

Table 88 Heart Rate Increased – AEs by SOC and PT – MedDRA search – Phase 3a Pool – On-Treatment

	Oral sema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
All events	24	(0.6)	25	0.7	16	(0.7)	17	0.7
Cardiac disorders	22	(0.6)	23	0.7	11	(0.5)	12	0.5
Tachycardia	16	(0.5)	17	0.6	7	(0.3)	8	0.4
Sinus tachycardia	6	(0.1)	6	<0.1	4	(0.2)	4	0.2
Investigations	2	(<0.1)	2	<0.1	5	(0.2)	5	0.2
Heart rate increased	2	(<0.1)	2	<0.1	5	(0.2)	5	0.2

Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 4-2 ISS

Two heart rate increase SAEs were identified in PIONEER 6, both in patents taking semaglutide. One was in patient (b) (6) who experienced a panic attack. The second one was in patient (b) (6) who was reported with wide complex tachycardia in the context of heart failure exacerbation, hepatic encephalopathy and cellulitis. It is unlikely that either of these events was related to the use of semaglutide.

Reference ID: 4494348

Blood pressure

Across trials, systolic blood pressure (SBP) decreased with semaglutide over time from baseline to end of treatment.

In the phase 3a pool, SBP decreased from baseline to end of treatment with both oral semaglutide and comparator, slightly more so with oral semaglutide (3 mmHg) than with comparator (2 mmHg). In the placebo pool, oral semaglutide resulted in SBP reductions of 4 mmHg at end of treatment compared with a reduction of 1 mmHg with placebo. Results from the placebo dose pool indicated dose-dependent decreases in SBP with oral semaglutide at the end of treatment with mean decreases of 2, 4 and 5 mmHg with oral semaglutide 3, 7 and 14 mg.

In the phase 3a pool, DBP decreased by 1 mmHg with both oral semaglutide and comparator. In the placebo pool, DBP also decreased by 1 mmHg with oral semaglutide, but showed no dose-dependency with oral semaglutide in the placebo dose pool.

In PIONEER 6, the difference between semaglutide and placebo was -3mmHg for systolic blood pressure and +1 mmHg for diastolic blood pressure.

Reviewer comment: Semaglutide treatment was associated with a slight increase in heart rate which was expected with this drug class. Despite some small differences in pulse rate AEs, the body of data does not support an increase in clinical events related to the increase in heart rate. Additionally, a small decrease in systolic blood pressure was observed with oral semaglutide, as expected with the drug class. No meaningful difference was seen for diastolic blood pressure.

8.4.8. Electrocardiograms (ECGs)

In the phase 3a pool, most patients (62.4% with oral semaglutide and 58.4% with comparator) had a normal ECG at baseline. The proportion of patients with abnormal (clinically significant) ECG at baseline was 1.7% for both treatment groups in the phase 3a pool. ECG shifts for the phase 3a pool are presented below. No significant differences are seen between the treatment groups. The results were similar for the placebo pool.

Reference ID: 4494748

Table 89 Overall ECG Investigator Interpretation – Shift Table – Phase 3a Pool

	Normal at baseline			Abnormal NCS at baseline			Abnormal CS at baseline		
	Normal N (%)	Abnormal NCS N (%)	Abnormal CS N (%)	Normal N (%)	Abnormal NCS N (%)	Abnormal CS N (%)	Normal N (%)	Abnormal NCS N (%)	Abnormal CS N (%)
Overall ECG interpretation - on-treatment observation period									
Week 26 visit [1]									
Oral sema	2055 (88.8)	244 (10.5)	15 (0.6)	327 (25.0)	970 (74.2)	10 (0.8)	7 (12.3)	18 (31.6)	32 (56.1)
Comparator	1050 (86.6)	157 (12.9)	6 (0.5)	207 (25.3)	606 (74.1)	5 (0.6)	9 (26.5)	10 (29.4)	15 (44.1)
End-of-treatment visit									
Oral sema	1915 (86.6)	277 (12.5)	19 (0.9)	317 (25.6)	908 (73.3)	13 (1.1)	7 (13.0)	20 (37.0)	27 (50.0)
Comparator	1013 (86.4)	153 (13.1)	6 (0.5)	202 (25.8)	573 (73.1)	9 (1.1)	8 (26.7)	9 (30.0)	13 (43.3)
Overall ECG interpretation - planned follow-up visit									
Follow-up visit									
Oral sema	1833 (86.7)	265 (12.5)	17 (0.8)	305 (26.2)	844 (72.6)	14 (1.2)	9 (17.6)	17 (33.3)	25 (49.0)
Comparator	903 (85.3)	149 (14.1)	6 (0.6)	189 (27.1)	501 (71.9)	7 (1.0)	6 (20.7)	12 (41.4)	11 (37.9)
Overall ECG interpretation - in-trial observation period									
Week 26 visit [1]									
Oral sema	2168 (88.6)	262 (10.7)	16 (0.7)	351 (25.1)	1036 (74.2)	10 (0.7)	9 (13.8)	19 (29.2)	37 (56.9)
Comparator	1084 (86.6)	162 (12.9)	6 (0.5)	213 (25.1)	631 (74.2)	6 (0.7)	9 (24.3)	11 (29.7)	17 (45.9)
End-of-treatment visit									
Oral sema	2074 (86.2)	313 (13.0)	20 (0.8)	356 (26.0)	1000 (73.0)	14 (1.0)	12 (18.5)	23 (35.4)	30 (46.2)
Comparator	1066 (86.5)	160 (13.0)	6 (0.5)	219 (26.1)	612 (72.9)	9 (1.1)	8 (22.2)	11 (30.6)	17 (47.2)

Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. 'End-of-treatment visit': Planned end-of-treatment visit for the trials. PIONEER 1 and 5: Week 26. PIONEER 2, 4, 8-10: Week 52. PIONEER 3: Week 78.
NCS: not clinically significant; CS: clinically significant; N: number of subjects contributing to the summary statistic; %: proportion of subjects; '[1]': For PIONEER 7 the visit was done at week 24.

Source: Table 7.6.11 ISS

In the phase 3a pool, 40 events were sent for adjudication for potential acute coronary syndrome based on ECG readings; of these events, 3 were confirmed as acute coronary syndrome.

In PIONEER 6, ECGs were evaluated in order to identify silent MIs. Eighteen ECGs indicated new ischemia/infarction since last ECG reading, hence 18 potential silent MIs were sent for adjudication; of these, 6 events were confirmed by the EAC.

8.4.9. QT

The effect of semaglutide on the QTc interval, PR interval, and pulse rate has been assessed at the 0.5 mg and 1.0 mg dose levels as well as at the supratherapeutic dose level of 1.5 mg in a dedicated QTc trial for subcutaneous semaglutide (trial 3652). This study was reviewed by Dr Janell Chen from Interdisciplinary Review Team for QT Studies Consultation, and the conclusion was that no significant QTc prolongation effect of semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) was detected in the Thorough QT (TQT) study. The largest upper bounds of the 2-sided 90% CI for the mean difference between semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

An additional SNAC QTc trial was performed (trial 4247), where SNAC was dosed at supra-therapeutic doses of up to 3.6 g, which is 12 times higher than what is administered in an oral semaglutide tablet. No clinically significant QT prolongation was seen with SNAC.

Reference ID: 4497478

8.4.10. Immunogenicity

See section 8.5 for evaluation of immunogenicity concerns.

8.5. Analysis of Submission-Specific Safety Issues

Based on the clinical experience with GLP-1RAs in general, and subcutaneous semaglutide in particular, a number of safety areas have been predefined by the applicant as being of special interest in the evaluation of oral semaglutide. These areas are as follows:

- Gastrointestinal disorders
- Renal disorders
- Hepatic disorders
- Gallbladder-related disorders
- Pancreatitis
- Cardiovascular disorders
- Neoplasms, including thyroid neoplasms
- Hypoglycemia
- Diabetic retinopathy
- Lactic acidosis
- Immunogenicity
- Creatine Kinase (CK)
- Rare events
- Overdose, medication errors, abuse and misuse
- Suspected transmission of an infectious agent
- Hypovolemia

The safety focus areas: renal disorders, pancreatitis, neoplasms, CV disorders and lactic acidosis were all evaluated by means of both MedDRA searches and event adjudication. For these events, the results of the investigator-reported information, and the results of the adjudication will be presented separately.

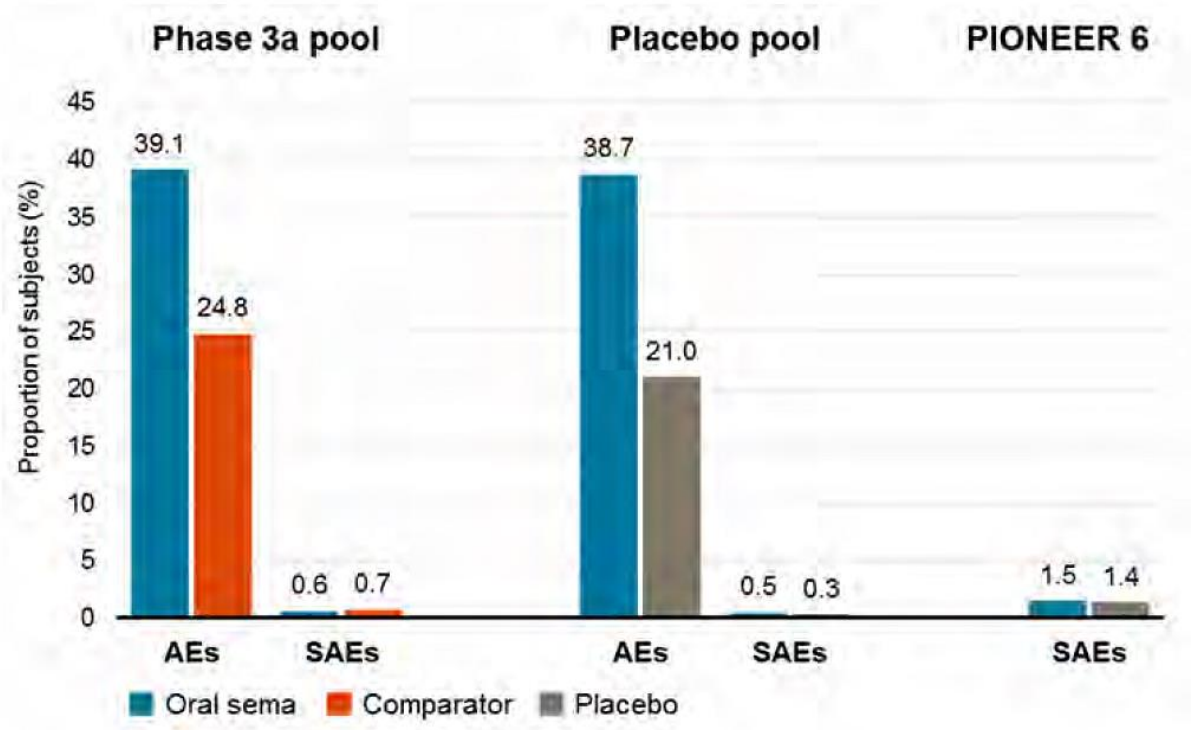
8.5.1. Gastrointestinal disorders

As expected for this class of drugs, GI events were commonly reported with oral semaglutide, in a greater proportion than with comparators or placebo. These AEs were dose-dependent in most trials, except for PIONEER1 and PIONEER 9. In the placebo dose pool, the higher dose of semaglutide was associated with a greater incidence of GI AEs, but the 3 and 7 mg doses did not appear to be different regarding GI AEs. Most of the GI AES reported were non-serious and GI SAEs were balanced between treatment groups in the phase 3a and placebo pools. Because PIONEER 6 employed a targeted safety data collection, only GI SAES were collected, and no significant differences were seen between oral semaglutide and placebo.

Reference ID: 4494748

An overview of GI AEs and SAEs in the various pools and PIONEER 6 is presented in the figure below. SAEs are discussed separately in Section 8.4.2. None of the GI events was fatal.

Figure 36 Overview of Gastrointestinal Disorders – MedDRA Search – Phase 3a, Placebo Pool and PIONEER 6 – On-Treatment



Source: Figure 2-16 ISS

Table 90 Gastrointestinal Disorders – Pre-Defined MedDRA Search – Overview – Phase 3a Trials and Pools – On-Treatment – SAS

	Sema 3 mg	Sema 7 mg	Sema 14 mg	All sema	Comparator	Placebo
Patients and exposure	**N**	**N**	**N**	**N**	**N**	**N**
Phase 3a pool				4116	2236	
Placebo pool				1519		665
Placebo dose pool	359	356	356			362
Patients with events	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Phase 3a pool				1571 (39.1)	540 (24.8)	
Placebo pool				573 (38.7)		138 (21)
Placebo dose pool	116 (32.3)	113 (31.8)	146 (41%)			77 (21.3)
SAEs	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Phase 3a pool				27 (0.6)	15 (0.7)	
Placebo pool				8 (0.5)		2 (0.3)

Reference ID: 4494348

Placebo dose pool	3 (0.8)	0	2 (0.6)			0
Patients with severe events	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Phase 3a pool				57 (1.6)	17 (0.7)	
Placebo pool				22 (1.5)		1 (0.2)
Placebo dose pool	4 (1.1)	2 (0.6)	7 (2)			1 (0.3)
AEs leading to discontinuation	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Phase 3a pool				217 (5.9)	43 (1.8)	
Placebo pool				97 (6.9)		8 (1.1)
Placebo dose pool	12 (3.3)	16 (4.5)	28 (7.9)			2 (0.6)

Source: Excerpted from Table 7.3.1 ISS

Most of the GI AEs were categorized by the investigator as mild, or moderate, with very few events as severe.

A higher proportion of patients on oral semaglutide reported GI AEs leading to treatment discontinuation than with comparator/placebo.

GI AEs were reported throughout the trial, with most reports during the dose escalation period. A breakdown of common GI AEs by PT in the phase 3a and placebo pools is presented in Section 8.4.5 under AEs reported by ≥5% of patients with oral semaglutide.

Reviewer comment: The GI AEs are expected with oral semaglutide, and this information will be reflected in the prescribing information in a similar manner as for other GLP-1RAs.

8.5.2. Renal Disorders

Acute renal failure (ARF) was designated as AE of interest because GI AEs associated with the use of semaglutide may lead to dehydration, and acute kidney disease.

PIONEER 5 investigated the safety and efficacy of oral semaglutide in patients with moderate renal impairment (eGFR 30 to <60 ml/min). In this trial the urinary albumin to creatinine ratio (UACR) was collected in addition to eGFR which was collected in most other trials.

AKI events were identified via MedDRA search and were adjudicated by EAC for confirmation. The EAC confirmation was based on pre-defined diagnostic and staging criteria. For PIONEER 6, the MedDRA search was performed on SAEs only.

Table 91 Adjudication of AKI

Reference ID: 4494748

Event category	Details	Adjudication outcome(s)
Acute kidney injury	Acute kidney injury was defined[28] as any of the following (not graded): Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours Increase in serum creatinine ≥1.5x baseline, which is known or presumed to have occurred within the previous 7 days Urine volume <0.5 mL/kg/h for 6 hours	Acute kidney injury

Source: Table 2-24 ISS

MedDRA search

In the phase 3a pool, there was a slightly higher proportion of patients on semaglutide who experienced renal events vs comparator, however the number of events was small (0.8% vs 0.5%). The same was true of the placebo pool (0.7% vs 0.5%). SAEs were rare, but more common with semaglutide in the phase 3a pool (0.2% vs 0.1%). Only SAEs were captured in PIONEER 6, and SAEs were less common with semaglutide vs placebo (0.9% vs 1.1%).

Table 92 AKI AEs and SAEs – MedDRA Search

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	31	(0.8)	34	1.0	13	(0.5)	13	0.6
SAEs	8	(0.2)	8	0.2	4	(0.1)	4	0.2
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	9	(0.7)	11	1.5	4	(0.5)	4	0.9
SAEs	3	(0.2)	3	0.3	2	(0.2)	2	0.4
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
SAEs	15	(0.9)	16	1	18	(1.1)	22	1

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

Source: Table 2-2 5 ISS

The most common preferred terms in the phase 3 pool are presented in the table below. The preferred term that accounts for the difference in AEs between treatment arms is "renal

Reference ID: 4494348

impairment". The clinical significance of this small difference is unclear. For SAEs, the PT acute kidney injury accounted for almost all events.

Notably, most renal events in the phase 3 and placebo pool come from the renal impairment trial PIONEER 5.

Table 93 Renal Disorder AEs by SOC and PT – MedDRA Search – Phase 3a Pool –On-Treatment

	Oral sema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
Renal and urinary disorders	31	(0.8)	34	1.0	13	(0.5)	13	0.6
Renal impairment	15	(0.4)	17	0.5	3	(0.1)	3	0.1
Acute kidney injury	13	(0.3)	13	0.4	8	(0.4)	8	0.4
Renal failure	3	(<0.1)	3	<0.1	2	(<0.1)	2	<0.1
Azotaemia	1	(<0.1)	1	<0.1	0			

Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 2-26 ISS

PIONEER 6

The PT acute kidney injury accounted for most of the events in both treatment groups. An overview of the reported PTs for renal disorders (MedDRA search) in PIONEER 6 is presented in the table below.

Table 94 Renal Disorder AEs by SOC and PT – MedDRA Search – PIONEER 6

	Oral sema				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
Renal and urinary disorders	15	(0.9)	16	1	18	(1.1)	22	1
Acute kidney injury	13	(0.8)	14	1	14	(0.9)	18	1
Renal failure	1	(0.1)	1	0	2	(0.1)	2	0
Renal impairment	1	(0.1)	1	0	0			
Acute prerenal failure	0				1	(0.1)	1	0
Azotaemia	0				1	(0.1)	1	0

The summary includes a subset of all preferred terms within each system organ class. The listed preferred terms were identified by a pre-defined MedDRA search and contribute to the total for each system organ class. Table is sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide arm.
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 exposure.

Source: Table 2-28 ISS

Reference ID: 4494748

EAC-confirmed events of acute kidney injury

In the phase 3a pool, 39 events of potential acute kidney injury were sent for adjudication; 31 events identified by the investigator and 8 events identified by the preferred term query (PTQ) search. Of these 39 events, 29 were confirmed by the EAC: 23 occurred in the on-treatment period and 6 occurred outside the on-treatment period. For the events reported during the on-treatment period, the proportion of patients experiencing an event was similar in the semaglutide group vs comparator. The proportions and rates of stage 2 and 3 acute kidney injury were similar between oral semaglutide and comparator, while stage 1 events were only present in the oral semaglutide group (0.2% with oral semaglutide vs 0 patients with comparator).

Table 95 EAC-Confirmed Events of AKI – Phase 3a Pool – On-Treatment

	Oral sema			Comparator		
	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R
Number of subjects	4116			2236		
Exposure time (years)	4379			2335		
EAC-confirmed events						
Acute kidney injury	16 (0.4)	17	0.5	6 (0.3)	6	0.3
Stage 3	5 (0.1)	5	0.1	4 (0.2)	4	0.2
Stage 2	3 (<0.1)	3	<0.1	2 (<0.1)	2	0.1
Stage 1	8 (0.2)	9	0.3	0		

Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. 'Stage': the Acute Kidney Injury Network criteria, stage 3 being the most severe.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events; EAC: event adjudication committee.

Source: Table 2-27 ISS

In the placebo pool, AKI observed in 0.4% of patients on oral semaglutide, and 0.3% of patients on placebo. The event rate appears to be higher with semaglutide vs placebo, although events are still very rare.

Table 96 EAC-Confirmed Events of AKI – Placebo Pool – On-Treatment

Reference ID: 4494748

	Oral sema N	(Adj.%)	E	Adj.R	Placebo N	(Adj.%)	E	Adj.R
Number of subjects	1519				665			
Exposure time (years)	1197				523			
Acute kidney injury	6	(0.4)	7	0.9	2	(0.3)	2	0.5
Stage 3	0				1	(0.2)	1	0.3
Stage 2	1	(<0.1)	1	<0.1	1	(0.1)	1	0.2
Stage 1	5	(0.4)	6	0.8	0			

Placebo pool: PIONEER 1, 4, 5 and 8.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).
EAC: event adjudication committee; 'Stage': the Acute Kidney Injury Network criteria; N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 7.3.46 ISS

In the renal impairment trial PIONEER 5, 4 EAC-confirmed events of AKI were reported, 3 events in 2 patients with oral semaglutide 14 mg and 1 event with placebo. None of the events was reported as SAEs.

In the phase 3a pool, 6 of the EAC-confirmed events occurred outside the on-treatment period; 4 events in PIONEER 3 (two events with oral semaglutide 7 mg, one event with oral semaglutide 14 mg and one event with sitagliptin), and one event each in PIONEER 2 and 5 (oral semaglutide 14 mg and placebo, respectively). The events in PIONEER 2 and 5 were also outside the in-trial period. All 6 of these events were reported as stage 1 acute kidney injury.

In total, 108 events of potential AKI were evaluated by the EAC in PIONEER 6. Of these, 88 were confirmed as AKI by the EAC, of which 78 had onset during the on-treatment observation period. The EAC-confirmed events of AKI were reported by a similar proportion of patients with events and rate of events with oral semaglutide and placebo (2.0% vs 2.3% of patients).

Table 97 EAC-Confirmed Events of AKI – PIONEER 6

	Oral sema N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
EAC-confirmed events								
Acute kidney injury	32	(2.0)	36	1.9	37	(2.3)	42	2.1
Stage 3	4	(0.3)	4	0.2	5	(0.3)	5	0.3
Stage 2	2	(0.1)	2	0.1	10	(0.6)	10	0.5
Stage 1	26	(1.6)	30	1.6	23	(1.4)	27	1.4

'Stage': the Acute Kidney Injury Network criteria, stage 3 being the most severe.
N: number of subjects with at least one event; %: proportion of subjects with at least one event; E: number of events; EAC: event adjudication committee; R: events per 100 years of exposure.

Source: Table 2-29 ISS

Reference ID: 4494748

The applicant evaluated the co-reporting of GI and renal adverse events. In the phase 3a pool, a similar proportion of patients with or without renal disorders reported GI adverse events of nausea/vomiting/diarrhea during the on-treatment period.

Renal function parameters

eGFR, creatinine and urine albumin to creatinine ration (UACR)

In the phase 3a pool, mean baseline eGFR values (92 vs 90 mL/min/1.73 m2) and creatinine values were similar with oral semaglutide and comparator. Generally renal function parameters were stable over time across trials.

Reviewer comment: In conclusion, no significant increase in renal events was observed with semaglutide, despite an increase in GI AEs that could lead to dehydration and AKI. This is in line with what was observed with subcutaneous semaglutide.

8.5.3. Hepatic Disorders

Marketed GLP-1RAs are not known to be hepatotoxic, and no indication of hepatic toxicity was seen in toxicology studies with semaglutide.
The hepatic toxicity of oral semaglutide was evaluated by MedDRA search, and evaluation of liver function tests.

In PIONEER 6, systematic collection of data on AEs was limited to SAEs, AEs leading to treatment discontinuation and a few other AE categories of special interest (hepatic events: ALT or AST >5xULN with concurrent TBL ≤2xULN; or ALT or AST >3xULN with concurrent TBL >2xULN; or hepatic events leading to premature discontinuation of trial product).

Liver events MedDRA search
The proportion of patients experiencing liver events captured by the MedDRA search was similar between treatment arms in the phase 3a and placebo pools, as were the liver SAEs captured in PIONEER 6. Generally liver SAEs were rare and balanced between treatment groups in all pools.

Table 98 Total Hepatic Disorders – MedDRA Search – Phase 3a, Placebo Pool and PIONEER 6 – On-Treatment

Reference ID: 4494748

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	141	(3.4)	173	3.7	73	(3.3)	94	4.0
SAEs	6	(0.2)	7	0.2	6	(0.3)	6	0.2
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	30	(2.0)	36	2.8	8	(1.3)	15	3.2
SAEs	2	(0.1)	2	0.1	0			
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
SAEs	4	(0.3)	4	0	6	(0.4)	6	0

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

Source: Table 2-34 ISS

Hepatic steatosis was the most common PT reported in both phase 3a and placebo pool, and it appeared to be slightly more prevalent in the semaglutide arm vs comparator in both pools. Other commonly reported PTs were liver enzyme abnormalities, which were slightly more common in the comparator arm vs semaglutide. Overall these differences are small, and not likely to be clinically significant.

Table 99 Hepatic Disorders (≥0.1%) by SOC and PT – MedDRA Search – Phase 3a Pool –On-Treatment

Reference ID: 4494348

	Oral sema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
Events	141	(3.4)	173	3.7	73	(3.3)	94	4.0
Hepatobiliary disorders	90	(2.2)	100	2.2	42	(2.0)	49	2.1
Hepatic steatosis	60	(1.5)	60	1.5	26	(1.2)	26	1.2
Hepatomegaly	7	(0.1)	7	0.1	2	(<0.1)	2	<0.1
Hyperbilirubinaemia	4	(0.1)	4	<0.1	3	(0.1)	3	0.1
Hepatic function abnormal	4	(<0.1)	4	<0.1	3	(0.1)	3	0.1
Hepatic cirrhosis	2	(<0.1)	2	<0.1	2	(0.1)	2	<0.1
Steatohepatitis	1	(<0.1)	1	<0.1	3	(0.2)	3	0.1
Investigations	50	(1.1)	66	1.3	33	(1.5)	45	1.9
Alanine aminotransferase increased	21	(0.5)	22	0.5	13	(0.6)	14	0.7
Aspartate aminotransferase increased	14	(0.3)	15	0.3	11	(0.5)	12	0.5
Hepatic enzyme increased	13	(0.3)	13	0.2	8	(0.3)	8	0.3
Blood bilirubin increased	3	(<0.1)	3	<0.1	3	(0.1)	3	<0.1
Liver function test abnormal	3	(<0.1)	3	<0.1	2	(0.1)	2	<0.1
Liver function test increased	3	(<0.1)	3	<0.1	4	(0.2)	4	0.2
Blood alkaline phosphatase increased	2	(<0.1)	2	<0.1	2	(0.1)	2	<0.1

Phase 3a pool: PIONEER 1-5 and 7-10. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin,empagliflozin, liraglutide, dulaglutide and placebo. Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group. This table includes SOCs and PTs, where PTs were reported by ≥ 0.1% of subjects in either treatment group. The numbers in the SOC row represent the total number for the SOC. All PTs can be found in the referenced table.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 2-35 ISS

Reference ID: 4497478

Table 100 Hepatic disorders – AEs by SOC and PT – Pre-Defined MedDRA Search – Placebo Pool – On-Treatment

	Oral sema N	(Adj.%)	E	Adj.R	Placebo N	(Adj.%)	E	Adj.R
Number of subjects	1519				665			
Exposure time (years)	1197				523			
All events	30	(2.0)	36	2.8	8	(1.3)	15	3.2
Hepatobiliary disorders	20	(1.4)	22	1.9	3	(0.5)	4	1.2
Hepatic steatosis	13	(0.9)	13	1.1	3	(0.5)	3	0.9
Hyperbilirubinaemia	2	(0.1)	2	0.1	0			
Hepatosplenomegaly	1	(0.1)	1	0.2	1	(0.2)	1	0.3
Drug-induced liver injury	1	(<0.1)	1	<0.1	0			
Non-alcoholic steatohepatitis	1	(<0.1)	1	0.1	0			
Hepatic function abnormal	1	(<0.1)	1	<0.1	0			
Hepatomegaly	1	(<0.1)	1	<0.1	0			
Liver disorder	1	(<0.1)	1	<0.1	0			
Liver injury	1	(<0.1)	1	<0.1	0			
Investigations	10	(0.6)	14	0.9	5	(0.8)	11	2.0
Alanine aminotransferase increased	7	(0.4)	7	0.4	4	(0.6)	4	0.8
Aspartate aminotransferase increased	4	(0.2)	4	0.2	2	(0.3)	3	0.6
Hepatic enzyme increased	1	(<0.1)	1	0.1	2	(0.3)	2	0.3
Liver function test abnormal	1	(<0.1)	1	0.1	0			
Blood alkaline phosphatase increased	1	(<0.1)	1	<0.1	1	(0.2)	1	0.2
Liver function test increased	0				1	(0.2)	1	0.2

Placebo pool: PIONEER 1, 4, 5 and 8.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).
Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.
MedDRA version 20.1

Source: Table 7.3.52 ISS

In PIONEER 6, the number of liver SAES was small and they were balanced between treatment groups, no clustering of PT terms was observed.

<u>Drug induced liver injury</u>

Two SAEs of 'drug-induced liver injury' were reported in the oral semaglutide program: one in PIONEER 4 (oral semaglutide 14 mg) and one in PIONEER 6 (placebo).

The event in PIONEER 4 was reported in the oral semaglutide 14 mg group. It occurred 3 weeks after premature trial product discontinuation, while the patient was being treated with clarithromycin, amoxicillin and metronidazole for a duodenal ulcer.

The event in PIONEER 6 was reported to be caused by azithromycin used for treating acute bronchitis.

Reference ID: 4494748

One patient in the sitagliptin group of PIONEER 3 died due to hepatic disorders (alcoholic cirrhosis and chronic hepatic failure)

Liver laboratory parameters

Markers of liver function (AST, ALT, ALP and TBL) were assessed in all phase 3a trials at regular intervals. The applicant reports that there was no effect of oral semaglutide versus comparators on the mean levels of these parameters. There was no difference in the proportion of patients with various levels of elevation in liver function enzymes between the treatment arms in the phase 3a pool, as seen in the Table 101 below.

Table 101 Categorical Summary of Max Post-Baseline Values Phase 3a Pool SAS On Treatment

	Oral sema N=4116	**Comparator N=2236**
AST		
N	4024	2186
Normal	3176 (79.4)	1716 (78.2)
High	848 (20.6)	470 (21.8)
>2XULN	134 (3.1)	82 (4)
>3XULN	34 (0.8)	24 (1.1)
>5XULN	8 (0.2)	8 (0.4)
>10XULN	1 (<0.1)	0
ALT		
N	4026	2186
Normal	3418 (85.4)	1863 (84.8)
High	608 (14.6)	323 (15.2)
>2XULN	80 (1.9)	52 (2.4)
>3XULN	22 (0.6)	15 (0.7)
>5XULN	4 (<0.1)	7 (0.3)
>10XULN	0	0
TBL		
N	4026	2186
Normal	3565 (89.3)	1955 (89.4)
High	461 (10.7)	231 (10.6)
>2XULN	22 (0.6)	7 (0.4)
>3XULN	2 (<0.1)	1 (<0.1)
>5XULN	0	0
>10XULN	0	0

Source: Modified from table 7.5.2 ISS

Hy's law

No patients in the phase 3a pool had AST or ALT concentrations >3xULN with concurrent total bilirubin concentrations >2xULN. In PIONEER 6, there were two such cases (one with oral semaglutide and one with placebo); however, in both cases an alternative etiology was present. Details are presented below:

Reference ID: 4494748

- Patient no (b) (6) 74 year old male receiving oral semaglutide has elevated AST throughout the trial and developed elevated bilirubin at week 62. He was diagnosed with hepatocellular carcinoma on trial day 357, followed by septic shock with fatal outcome on trial day 507
- Patient no (b) (6): 71 year old male on placebo had normal AST, ALT and bilirubin throughout the trial, but they were found to be elevated at week 62, and he was subsequently diagnosed with pancreatic adenocarcinoma on trial day 431, which lead to permanent treatment discontinuation.

Reviewer comment: Both cases of Hy's law had alternate etiologies that appeared to be unrelated to the study treatment. Overall it does not appear that semaglutide causes liver dysfunction based on the results of the oral semaglutide clinical program. This is in line with the safety information known for other members of the class.

8.5.1. Gallbladder-related Disorders

A general link between incretin-based therapies (and specifically GLP-1 receptor agonists) and gallbladder-related AEs (cholelithiasis and cholecystitis) has been suggested, as gallbladder emptying appears to be slower with this class of drugs.

A higher rate of gallbladder-related AEs (especially cholelithiasis and cholecystitis) was noted in the liraglutide program for the weight management indication (3 mg, marketed as Saxenda), but not in the T2DM program (1.2 and 1.8 mg, marketed as Victoza). In the semaglutide sc program, no increased risk of cholecystitis was observed.

The risk of gallbladder-related disorders was evaluated based on an integrated evaluation of investigator reported events captured by a MedDRA search and case evaluation of narratives, medical history and additional data collection forms.

In the phase 3a pool, there was no difference in the rate or proportion of patients with gallbladder-related disorders between oral semaglutide and comparators. In the placebo pool, the rate and proportion of patients with gallbladder-related disorders was higher with oral semaglutide than with placebo.

Reference ID: 4497478

Table 102 Total Gallbladder-Related Disorders – MedDRA Search – Phase 3a Pool, Placebo Pool and PIONEER 6 – On-Treatment

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	55	(1.3)	65	1.5	28	(1.3)	35	1.3
SAEs	12	(0.3)	15	0.4	9	(0.4)	14	0.5
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	19	(1.3)	20	1.6	1	(0.1)	1	0.1
SAEs	4	(0.3)	5	0.5	0			
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
SAEs	8	(0.5)	10	1	11	(0.7)	13	1

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

Source: Table 2-40 ISS

Cholelithiasis was the most common PT reported within this MedDRA search with all treatment groups in both the phase 3a pool and the placebo pool. In the phase 3a pool, cholelithiasis was reported by a similar rate and proportion of patients in both treatment groups (oral semaglutide: 0.7 AEs/100 PYE and 0.7% of patients; comparator: 0.7 AEs/100 PYE and 0.8% of patients). Seventeen of 18 events in 18 patients in the comparator group were reported with active comparators: 7 with a DPP-4i (sitagliptin), 5 with an SGLT-2i (empagliflozin), and 5 with GLP-1 RAs (liraglutide or dulaglutide). In the placebo pool, the difference in gallbladder-related disorder was driven by cholelithiasis, which was reported by a higher number, rate and proportion of patients with oral semaglutide (10 events, 0.7 AEs/100 PYE and 0.6% of patients) versus placebo (1 event). Seven of the 10 cholelithiasis events with oral semaglutide were reported in PIONEER 8. Cholecystitis was rare but was reported by a larger proportion of patients in the semaglutide arm vs comparator in the phase 3a and placebo (4 events with semaglutide vs 0 with placebo) pools.

Reference ID: 4497478

Table 103 Gallbladder-Related Disorders – by SOC and PT – MedDRA Search – Phase 3a Pool – On-Treatment

	Oral sema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
Events	55	(1.3)	65	1.5	28	(1.3)	35	1.3
Hepatobiliary disorders	51	(1.2)	60	1.3	25	(1.1)	31	1.2
Cholelithiasis	30	(0.7)	31	0.7	18	(0.8)	18	0.7
Cholecystitis	5	(0.2)	5	0.2	2	(<0.1)	2	<0.1
Hyperbilirubinaemia	4	(0.1)	4	<0.1	3	(0.1)	3	0.1
Cholecystitis chronic	5	(<0.1)	5	<0.1	1	(<0.1)	1	<0.1
Hyperplastic cholecystopathy	3	(<0.1)	3	<0.1	0			
Gallbladder disorder	2	(<0.1)	2	<0.1	0			
Gallbladder cholesterolosis	1	(<0.1)	1	<0.1	0			
Cholecystitis acute	2	(<0.1)	2	<0.1	5	(0.2)	5	0.2
Biliary dyskinesia	2	(<0.1)	2	<0.1	0			
Biliary colic	1	(<0.1)	1	<0.1	0			
Bile duct stone	1	(<0.1)	2	<0.1	1	(<0.1)	1	<0.1
Biliary cirrhosis primary	1	(<0.1)	1	<0.1	0			
Cholestasis	1	(<0.1)	1	<0.1	0			
Cholangitis acute	0				1	(<0.1)	1	<0.1
Investigations	3	(<0.1)	3	<0.1	3	(0.1)	3	<0.1
Blood bilirubin increased	3	(<0.1)	3	<0.1	3	(0.1)	3	<0.1
Surgical and medical procedures	1	(<0.1)	1	<0.1	0			
Cholecystectomy	1	(<0.1)	1	<0.1	0			
Infections and infestations	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Biliary sepsis	1	(<0.1)	1	<0.1	0			
Cholecystitis infective	0				1	(<0.1)	1	<0.1

Phase 3a pool: PIONEER 1-5 and 7-10. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.

Source: Table 2-41 ISS

Reviewer comment: The increased incidence of cholelithiasis is expected with this class of drugs and described in the prescribing information for other members of the class.

8.5.2. Pancreatitis

A class labelling *Warnings and Precautions* exists for all incretin-based therapies concerning the risk of pancreatitis. Patients with a history of pancreatitis were therefore excluded from the phase 3 trials. The risk of pancreatitis was evaluated as a safety focus area based on a pre-defined MedDRA search for pancreatitis and on the outcome of the adjudication of suspected cases of acute pancreatitis. Acute pancreatitis was diagnosed, adjudicated and categorized by severity as described below.

Table 104 Adjudication of Acute Pancreatitis

Reference ID: 4494748

Event category	Details	Adjudication outcome(s)
Acute pancreatitis	The diagnosis of acute pancreatitis required two of the following three criteria: • Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) • Serum lipase activity (and/or amylase activity) at least three times greater than the ULN • Characteristic findings of acute pancreatitis on imaging	Acute pancreatitis by severity (Atlanta classification[35]): • Mild • Moderate • Severe

Source: Table 2-43 ISS

In PIONEER 6, only SAEs of pancreatitis were captured systematically.

MedDRA search

Few events were identified in the oral semaglutide clinical program, as seen below.

Table 105 Pancreatitis AEs MedDRA Search

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	8	(0.2)	8	0.2	5	(0.2)	5	0.2
SAEs	6	(0.1)	6	0.1	1	(<0.1)	1	0.0
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	1	(<0.1)	1	<0.1	1	(0.1)	1	0.1
SAEs	1	(<0.1)	1	<0.1	0			
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
SAEs	1	(0.1)	1	0	3	(0.2)	3	0

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

Source: Table 2-44 ISS

In the phase 3a pool, 13 events of investigator-reported pancreatitis or acute pancreatitis were reported. These were characterized as follows:

- Seven of the events were SAEs: 6 with oral semaglutide and 1 with comparator

Reference ID: 4494348

- As per protocol, all AEs of pancreatitis led to premature treatment discontinuation, except for two patients who already had discontinued trial product prior to the event for other reasons (1 patient on sitagliptin and 1 patient on empagliflozin).
- Ten (10) events of pancreatitis or acute pancreatitis were recovered by the end of the trial 6 with oral semaglutide and 4 with comparator) 2 events were recovered with sequelae (with oral semaglutide) and 1 was not recovered (comparator).

EAC-confirmed acute pancreatitis

In the phase 3a pool, a total of 19 pancreatitis events were sent for adjudication: 17 investigator identified events of pancreatitis or acute pancreatitis and 2 events captured via PTQ identification.

Eight of the 19 adjudicated events were confirmed by the EAC as acute pancreatitis. Of the 8 confirmed events, 7 had onset during the on-treatment period. Details regarding these events are presented below:

- Patient (b) (6) from study 4222: 69 year old male on oral semaglutide 3 mg was reported with SAE of acute pancreatitis on trial day 293, confirmed by imaging. Cholelithiasis was reported on day 305. The patient experienced other serious events in the same time, as follows; AKI, respiratory failure, sepsis, and ultimately died.
- Patient (b) (6) from study 4222: 69 year old male on oral semaglutide 14 mg was reported with acute pancreatitis SAE on trial day 516, confirmed by imaging. The patient was reported to have a history of cholelithiasis, cholecystitis, and cholecystectomy. The study drug was withdrawn as a result of the event of acute pancreatitis.
- Patient (b) (6) from study 4223, 69 year old female on oral semaglutide 14 mg, presented with severe acute upper abdominal pain, diagnosed with acute pancreatitis on trial day 192, confirmed by imaging. The event was an SAE, and the study drug was withdrawn as a result of the event of acute pancreatitis.
- Patient (b) (6) from study 4222: 48 year old female on sitagliptin 100 mg, presented with severe acute upper abdominal pain and elevation of pancreatic enzymes on day 256. It is not clear whether imaging was performed. The study drug was withdrawn as a result of the event of acute pancreatitis.
- Patient (b) (6) from study 4223: 64 year old male on empagliflozin 25 mg, reported severe acute abdominal pain and elevated pancreatic enzymes on day 356, without any characteristic imaging findings. The event was an SAE.
- Patient (b) (6) from study 4224: 70 year old female on liraglutide reported severe acute abdominal pain and elevated pancreatic enzymes on day 211. Ultrasound was performed and imaging results were not consistent with gallstones or acute/chronic pancreatitis. Relevant confounding factor included hypertriglyceridemia. The study drug was withdrawn because of this event. The event was non-serious.

Reference ID: 4494748

- - Patient (b) (6) from study 4224: 61 year old female on placebo reported severe acute abdominal pain and elevated pancreatic enzymes on day 52, no imaging was performed. The event was non-serious, but the study drug was withdrawn due to the event.

The adjudicated pancreatitis events were balanced between treatment arms in both the phase 3a and placebo pools.

For the phase 3a pool, the following patients were sent for adjudication but not positively adjudicated due to diagnostic criteria not met:

- Pt (b) (6) 60 year old male study 4222 presented with elevated amylase and upper abdominal pain after almost 5 months of treatment with semaglutide 14 mg, imaging was not consistent with pancreatitis. He received dexamethasone for sensorineural hearing loss the week prior to the abdominal symptoms. Semaglutide was discontinued due to this event.
- Pt (b) (6) study 4222 49 year old male with suspected chronic pancreatitis on imaging, on sitagliptin 100 mg
- Pt (b) (6) study 4222 72 year old female on semaglutide 14 mg was diagnosed with pancreatic neuroendocrine tumor in the tail of the pancreas, which was biopsied, and the patient continued to have pain and presented to the emergency room. A diagnosis of acute pancreatitis was reported. The results of imaging are not known but the patient was reported to be experiencing abdominal pain, and lipase was elevated to 1032 U/L.
- Patient (b) (6) study 4222 64 year old male on oral semaglutide 7 mg was reported with an event of acute pancreatitis on trial day 435
- Patient (b) (6) study 4223 67 year old female on semaglutide 14 mg who presented acute pancreatitis on day 275 of treatment. The study drug was discontinued due to this adverse event. A narrative was not submitted by the sponsor for this patient. As a result, it is unclear why this event was not positively adjudicated as acute pancreatitis
- Patient (b) (6) study 4233 47 year old female on semaglutide 3 mg. A week before initiation of the study drug, she experienced abdominal pain, was admitted to the hospital where liver enzymes and lipase were reported as elevated. Imaging was not performed but she was not diagnosed with acute pancreatitis. About 2 months after the initiation of the study drug, the patient was admitted to the hospital with abdominal pain and nausea (lipase 109 U/L, amylase 63 U/L), but no fever or vomiting. The discharge diagnosis was acute pancreatitis although no imaging was performed, and the trial drug was discontinued due to this event.
- Patient (b) (6) study 4257 60 year old male on sitagliptin 100 mg with pancreatic calcification. It is not clear why the imaging was performed; pancreatic enzymes were not reported to be elevated.

The remaining 4 patients were duplicates.

Reference ID: 4494748

Reviewer comment: The lack of data for the patients who were not positively adjudicated is somewhat concerning, and it appears that there were more events on semaglutide who were submitted for adjudication but not positively adjudicated. There were some events which in the opinion of this reviewer, were consistent with pancreatitis, but which were not adjudicated as pancreatitis events, for reasons which were unclear. At least in some of these cases it is possible that the pancreatitis was caused by study drug, in this case by oral semaglutide. I believe that there may have been a small imbalance in events of pancreatitis, not favoring semaglutide in the phase 3a pool.

In PIONEER 6, the MedDRA search identified 4 patients with pancreatitis SAEs (4 events), one with semaglutide, and 3 with placebo.

In total, 7 events were evaluated by the EAC, 5 investigator-identified, and 2 were PTQ-identified. Of these, 5 were positively adjudicated, 4 during the in-trial period (one with semaglutide and 3 with placebo). The one event that was not during the in trial period occurred in a patient with an already positively adjudicated event – the patient was on semaglutide.

Overall, events of pancreatitis were balanced in PIONEER 6.

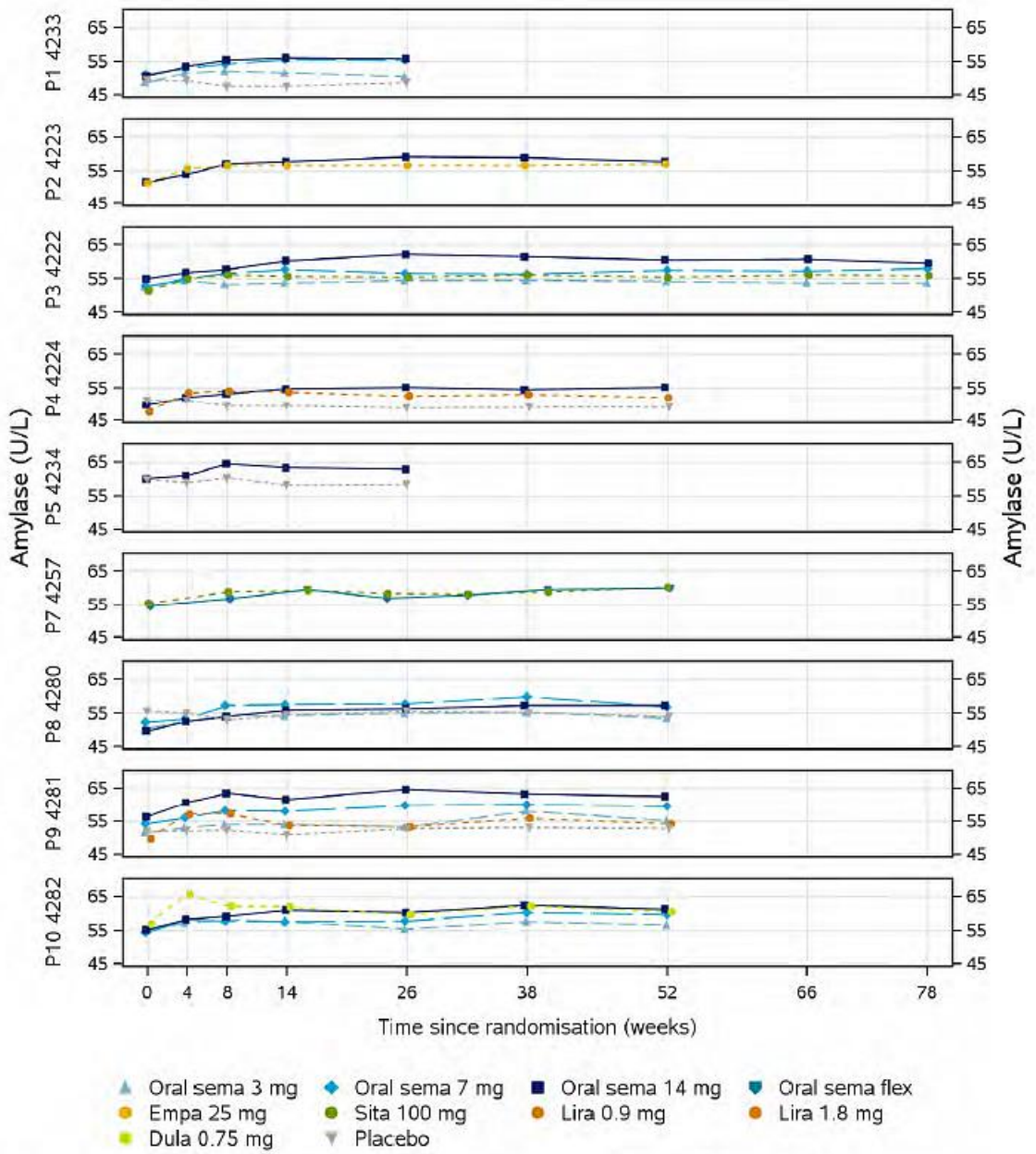
<u>Pancreatic enzymes</u>

Amylase and lipase levels were monitored in all phase 3 clinical trials.

Mean serum lipase and amylase activities increased with oral semaglutide during the initial 14 weeks of the clinical trials, similar to what has been described with other incretin-based therapies. In general, lipase and amylase levels were statistically significantly higher for oral semaglutide than for placebo in all 5 placebo-controlled trials. After the initial 14 weeks, lipase and amylase levels plateaued. At the follow-up visit (when trial drug was discontinued in all patients), mean levels of amylase and lipase in patients treated with oral semaglutide approached baseline levels.

Reference ID: 4494748

Figure 37 Amylase by Trial – Geometric Mean Plot – On-Treatment

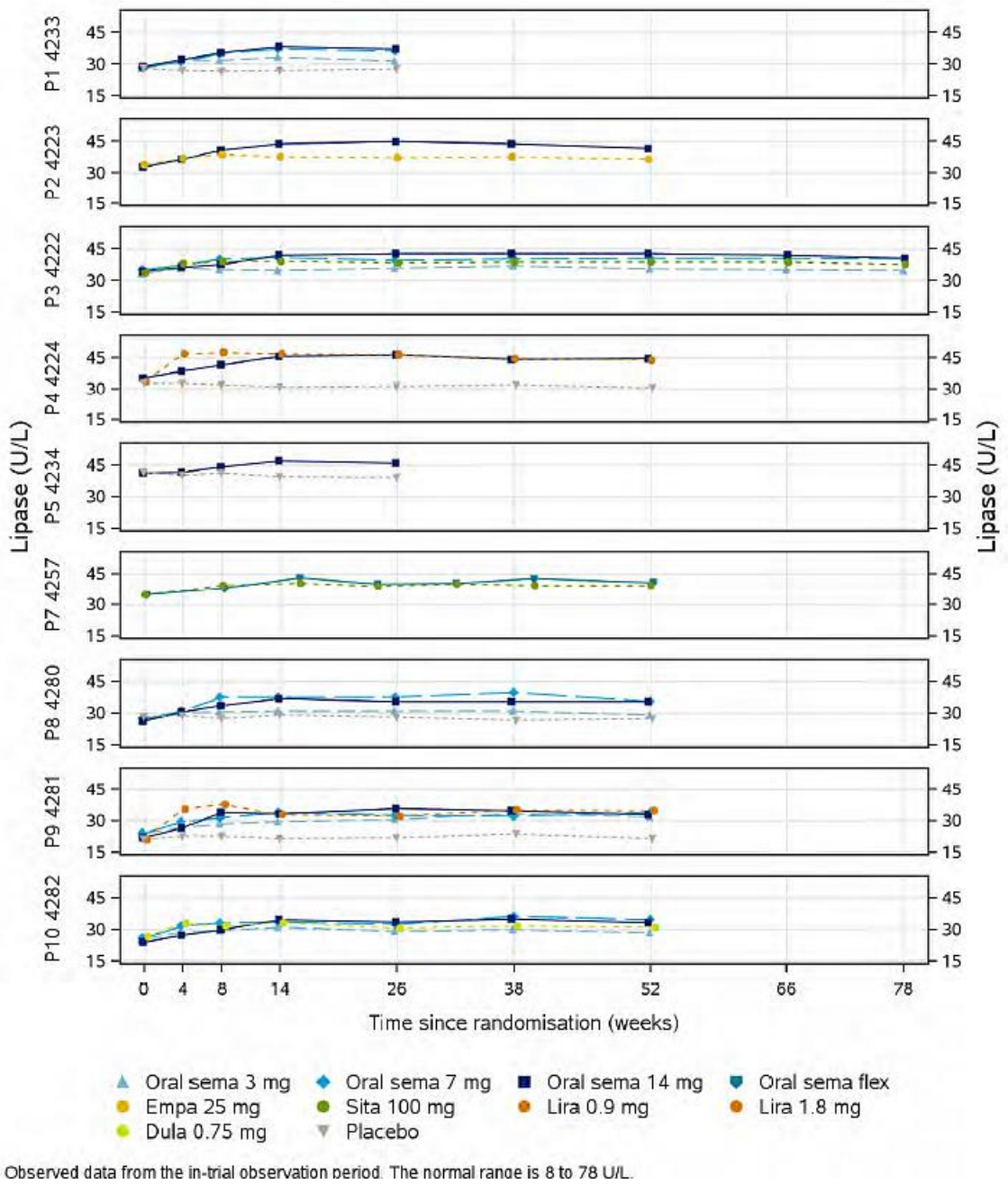


Observed data from the on-treatment observation period. The normal range is 25 to 125 U/L for age group 18-71 years and 20 to 160 U/L for age group 71-120 years.

Source: Figure 7.5.36 ISS

Reference ID: 4494348

Figure 38 Lipase by Trial – Geometric Mean Plot – On-Treatment



Observed data from the in-trial observation period. The normal range is 8 to 78 U/L.
Source: Figure 7.5.40 ISS

The same pattern of increases in amylase and lipase with oral semaglutide versus placebo was seen in PIONEER 6.

Reference ID: 4494348

The increase in pancreatic enzymes was observed with other incretin therapies, and it is not clear that it is predictive of an increase in events of pancreatitis with oral semaglutide.

8.5.3. Cardiovascular Adverse Events

CV disorders were therefore defined as a safety focus area in the oral semaglutide phase 3a trials. The CV safety of oral semaglutide was evaluated in a dedicated pre-market CVOT (PIONEER 6) in patients with T2DM at high risk of CV events. The risk of CV disorders was evaluated based on a pre-defined MedDRA search for CV events among investigator reported AEs (SAEs for PIONEER 6 and AEs for the other phase 3a trials) and based on the outcome of adjudication of selected pre-defined CV events.

Table 106 Adjudication of CV Events

Event category	Details	Adjudication outcome(s)
Death	All-cause death	Cardiovascular death Non-cardiovascular death Undetermined cause of death
Acute coronary syndrome	ST-elevation acute myocardial infarction (STEMI Non-ST elevation acute myocardial infarction (NSTEMI) Silent MI Unstable angina pectoris (UAP) requiring hospitalisation	AMI (STEMI/NSTEMI) Silent MI UAP requiring hospitalisation
Cerebrovascular event	Episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction TIA defined as a transient episode (<24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction	Ischaemic stroke Haemorrhagic stroke Undetermined stroke TIA
Heart failure requiring hospitalisation	Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	Heart failure requiring hospitalisation

Source: Table 2-50 ISS

The in-trial period was used for all evaluations of CV safety due to the potentially long latency between onset and diagnosis.

Since PIONEER 6 was a dedicated CVOT, most of the CV safety data comes from this study. The primary endpoint was time to first MACE event, a composite of EAC-confirmed CV death (including undetermined cause of death), non-fatal MI, and non-fatal stroke. Additional expanded MACE endpoints were defined in PIONEER 6.

The primary analysis for PIONEER 6 shows that treatment with semaglutide is not associated with an increase in CV events. It appears that semaglutide may be associated with a reduction in 3-point MACE composite endpoint, mainly due to a reduction in CV death. Non-fatal stroke

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also had a lower incidence in the semaglutide arm, and non-fatal MI appeared to be slightly more common with semaglutide vs placebo.

Table 107 First EAC-Confirmed MACE – PIONEER 6 – In-Trial

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

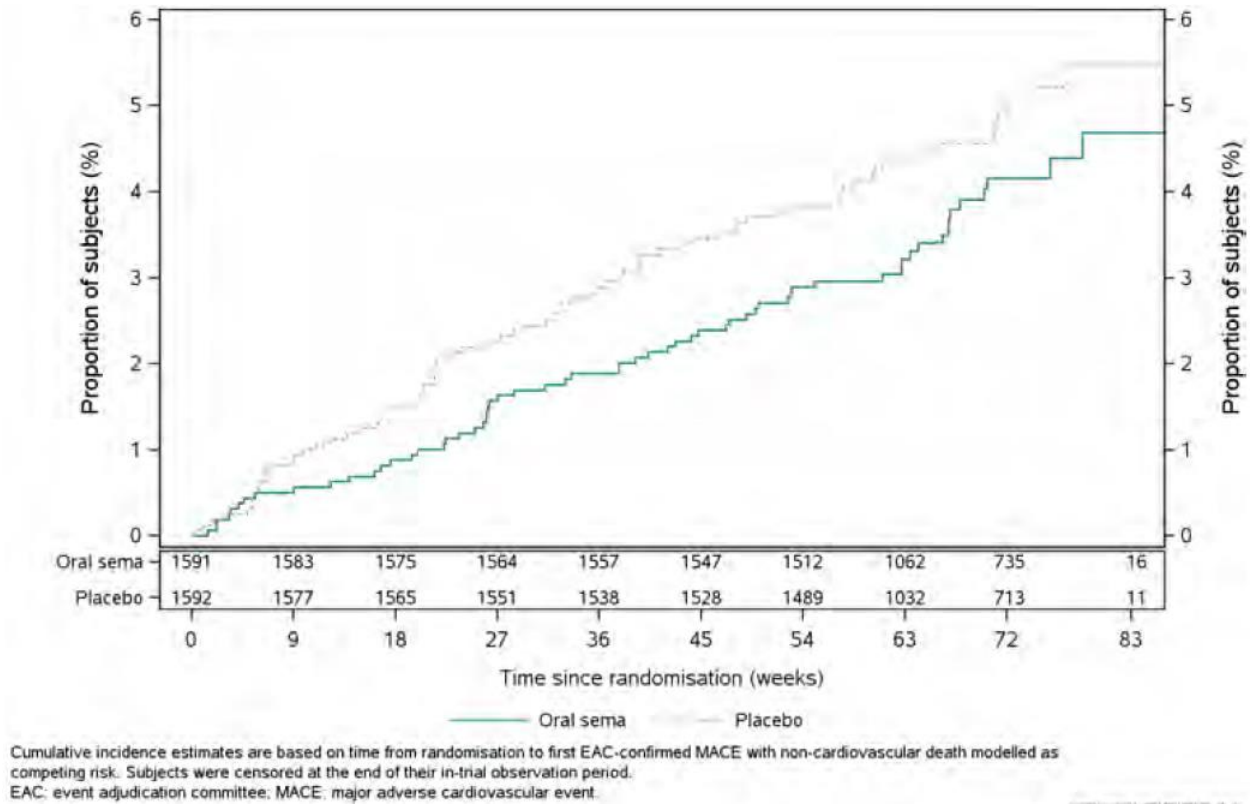
Abbreviations: EAC: event adjudication committee; MACE: major adverse cardiovascular event, N: number of subjects; PYO: patient-years of observation; R: event rate per 100 PYO; %: percentage of subjects.

Source: Table 2-53 ISS

The difference in MACE events was apparent from the beginning of the trial, and was sustained, as shown below.

Reference ID: 4494748

Figure 39 Time to First-EAC-Confirmed MACE – Cumulative Incidence Plot – PIONEER 6 – In-Trial



Source: Figure 2-27 ISS

The primary analysis of the time to first MACE event resulted in an estimated HR of 0.79 with a 95% CI 0.57 to 1.11, therefore excluding an increase in CV risk with oral semaglutide.

A total of 68 first MACE events with onset during the in-trial period were identified in the phase 3a pool, and the proportion of patients with events was lower with semaglutide (1%) vs comparator (1.2%). The same was true of the placebo pool, with 1.3% of patients in the semaglutide arm vs 1.7% in placebo. There was no increased incidence in non-fatal MI with semaglutide in either phase 3a or placebo pools.

Reference ID: 4494348

Table 108 First EAC-Confirmed MACE – Phase 3a Pool and Placebo Pool – In Trial

	Oral sema N (Adj.%)	Comparator or Placebo N (Adj.%)
Phase 3a pool		
Number of subjects	4116	2236
Observation time (years)	4719	2452
First EAC-confirmed MACE	42 (1.0)	26 (1.2)
Myocardial infarction, non-fatal		
Acute myocardial infarction	14 (0.3)	6 (0.3)
Silent myocardial infarction	2 (<0.1)	2 (0.1)
Stroke, non-fatal	15 (0.3)	10 (0.5)
Cardiovascular and undetermined cause of death	11 (0.3)	8 (0.3)
Cardiovascular death	5 (0.1)	5 (0.2)
Undetermined cause of death	6 (0.1)	3 (0.1)
Placebo pool		
Number of subjects	1519	665
Observation time (years)	1292	548
First EAC-confirmed MACE	19 (1.3)	11 (1.7)
Myocardial infarction, non-fatal		
Acute myocardial infarction	5 (0.3)	2 (0.3)
Silent myocardial infarction	1 (<0.1)	1 (0.2)
Stroke, non-fatal	7 (0.5)	6 (1.0)
Cardiovascular and undetermined cause of death	6 (0.4)	2 (0.2)
Cardiovascular death	2 (0.2)	1 (0.1)
Undetermined cause of death	4 (0.2)	1 (0.1)

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

Source: Table 2-54 ISS

Individual components of the CV endpoints

CV death

- PIONEER 6: a total of 15 patients on oral semaglutide died during the trial due to CV events versus 30 patients on placebo, resulting in a HR of 0.49 with a 95% CI 0.27; 0.92. Most common causes of death were sudden death, and death due to MI.
- In the phase 3a pool, few CV deaths occurred (5 events in each treatment group) and in a similar proportion of patients with oral semaglutide (0.1%) and comparators (0.2%). There were even fewer CV deaths (3 deaths) in the placebo pool and no apparent difference between treatment groups was noted (2 vs 1 deaths).

Myocardial infarction

- In PIONEER 6, a total of 72 patients had MIs (fatal and non-fatal) confirmed by the EAC, 37 with oral semaglutide and 35 with placebo. There were 4 patients with fatal MI, all

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treated with placebo. Silent MIs were included in these events, an occurred in 6 patients on semaglutide, and one in placebo.
- In the phase 3a pool, EAC confirmed 26 total MI events, 17 with semaglutide, and 9 with placebo. The proportion of patients with events was similar in both treatment groups (0.4%). In the placebo pool, 10 events were EAC -confirmed, 7 with semaglutide (o.5%) and 3 with placebo (0.5%).

Stroke

- PIONEER 6: 30 patients had confirmed stroke events, 13 with semaglutide and 17 with placebo. Two of the 30 were fatal events, one in each treatment arm.
- Phase 3a pool: 30 confirmed events, 18 with semaglutide (0.4%), and 11 with comparator (0.5%).
- Placebo pool: 14 events, 8 with semaglutide (0.5%) and 6 with placebo (1%).

Heart failure requiring hospitalization

- PIONEER 6: 21 confirmed events with semaglutide vs 24 on placebo. Two deaths were both with placebo.
- Phase 3a pool: 17 events, 10 with semaglutide (0.2%) and 7 with comparator (0.3%).
- Placebo pool: 4 events, 3 with semaglutide (0.2%) and one with placebo (0.1%).

Unstable angina

- PIONEER 6: 11 patients with semaglutide and 7 with placebo.
- Phase 3a pool: 11 events were confirmed, 10 with semaglutide (0.3%) vs 1 with comparator (<0.1%).
- Placebo pool: 3 events, all with semaglutide (0.3%).

MedDRA search for investigator reported CV events also did not show an increase in CV risk with semaglutide in either PIONEER 6 or either of the pools. The most commonly reported PTs were acute myocardial infarction, angina unstable, coronary artery disease for PIONEER 6, and atrial fibrillation, angina pectoris, and angina unstable for the phase 3 pool.

Table 109 CV Disorders AEs MedDRA Search, In-Trial

	Oral semaglutide	**Comparator/placebo**
Phase 3a pool		
CV AEs	245 (5.9)	143 (6.5)
CV SAEs		
Placebo pool		
CV AEs	84 (6)	34 (5)
PIONEER 6		

Reference ID: 4494748

CV SAEs	130 (8.2)	155 (9.7)

Source: Tables 7.3.84, 2-57 and 2-58 ISS

Reviewer comment: Based on premarket evaluation, including a CVOT, semaglutide does not appear to increase the risk of 3-point MACE vs standard of care. On the contrary, a nominally significant reduction in CV death was seen with semaglutide in PIONEER 6, although this as was not prespecified and controlled for type 1 error, and the study failed to demonstrate superiority for MACE. While it is possible that this finding was due to chance as the number of events was small and the exposure time was not long enough to be conclusive for such events, there is no evidence to demonstrate an increase in CV risk with oral semaglutide. No significant differences between treatment arms were seen regarding MI, stroke, or hospitalization for heart failure. Unstable angina appears to be more common with semaglutide, but the numbers are too small to be conclusive.

8.5.4. Neoplasms

In general, GLP-1 receptor agonists have not been associated with an increased risk of neoplasms in humans. Non-clinical data for semaglutide did not suggest any mutagenicity or genotoxicity. Thyroid C-cell neoplasia has been seen in the mouse and rat semaglutide carcinogenicity studies, preceded by an increase in serum calcitonin. This is in line with what was observed with other long acting GLP-1 receptor agonists, however, no clinical implications of this finding have been detected so far despite increased surveillance for approved long acting GLP-1 receptor agonists (including post-approval REMS).

A series of animal studies have suggested a potential association between incretin-based therapy and both pancreatic exocrine (pancreatic ductal adenocarcinomas) and pancreatic islet cell (glucagonomas) neoplasms. After an extensive review of all available nonclinical and clinical trial data, FDA and EMA published a joint commentary stating that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer were inconsistent with the then available data. Nonetheless, assessment of pancreatic neoplasms in clinical trials with incretin-based therapies remains an area of special interest.

Thyroid C-cell and pancreatic cancers are specific focus areas for GLP-1 RAs, and breast cancer and benign colon adenomas were also included for semaglutide as areas of interest due to higher frequencies with liraglutide than with placebo in the Saxenda weight management clinical development program.

Patients with a diagnosis of malignant neoplasm in the previous 5 years prior to enrollment in the trials (except basal and squamous cell skin cancer and carcinoma in situ) or known personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 were excluded from the phase 3 trials in the semaglutide development program.

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Due to the anticipated long lead-time for potential treatment-related neoplasms, events were evaluated based on the in-trial period.

Neoplasms were based on a MedDRA search (for all neoplasms, and for malignant neoplasms specifically), and EAC-confirmed malignant neoplasms. All events of suspected malignant neoplasm were sent for adjudication in one of two categories represented in the table below.

Table 110 Adjudication of Malignant Neoplasms

Event category	Details	Adjudication outcome(s)
Malignant neoplasm	Malignant neoplasms were defined as neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems. Thyroid neoplasms were not included in this event category.	Malignant neoplasm
Malignant thyroid neoplasm or C-cell hyperplasia	Suspected cases of the following neoplasms were considered in this event category: 1) Thyroid neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems 2) C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland	Malignant thyroid neoplasm C-cell hyperplasia

Source: Table 2-60 ISS

Blood levels of calcitonin, which is considered a biomarker associated with thyroid C-cell hyperplasia, were monitored throughout the trials. Calcitonin levels were reported for the on-treatment period. The investigator was to act according to the following:

- For calcitonin levels ≥10 ng/L and <50 ng/L; investigate potential confounding factors and continue sampling of calcitonin
- For calcitonin levels ≥50 ng/L (or ≥10 ng/L if it was the last measurement in the trial); refer the patient to a thyroid specialist
- If calcitonin levels reached ≥100 ng/L; discontinue trial product prematurely for the patient and refer the patient to a thyroid specialist

Neoplasms (malignant and benign)

Neoplasm AEs and SAEs were reported more commonly with semaglutide vs placebo/comparator in the phase 3a and placebo pools, but no difference was observed in PIONEER 6 (SAEs).

Reference ID: 4494748

Table 111 All Neoplasms MedDRA Search – In-Trial

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Observation time (years)	4719				2452			
AEs	267	(6.4)	336	7.0	122	(5.7)	143	6.2
SAEs	62	(1.7)	66	1.6	29	(1.3)	29	1.3
Placebo pool								
Number of subjects	1519				665			
Observation time (years)	1292				548			
AEs	69	(4.7)	77	5.7	28	(4.2)	32	6.5
SAEs	17	(1.2)	18	1.4	7	(1.0)	7	1.5
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Observation time (years)	2101				2081			
SAEs	39	(2.5)	42	2	42	(2.6)	44	2

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

Source: Table 2-61 ISS

Malignant neoplasms

In the phase 3a and placebo pools, there was a trend towards increase in malignant neoplasms with semaglutide, both in MedDRA search and EAC-confirmed. This was not observed in PIONEER 6 where events were balanced between the treatment arms.

Reference ID: 4494348

Table 112 Malignant Neoplasms MedDRA Search and EAC-Confirmed, In-Trial

	Oral sema N	(Adj.%)	E	Adj.R	Comparator or Placebo N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Observation time (years)	4719				2452			
MedDRA search								
AEs	57	(1.5)	62	1.6	23	(1.1)	24	1.1
SAEs	42	(1.1)	43	1.1	20	(0.9)	20	0.9
EAC confirmed events								
Malignant neoplasms excl. thyroid	52	(1.4)	56	1.4	22	(1.0)	23	1.1
Malignant thyroid neoplasms	2	(<0.1)	2	<0.1	1	(<0.1)	1	<0.1
Placebo pool								
Number of subjects	1519				665			
Observation time (years)	1292				548			
MedDRA search								
AEs	17	(1.2)	19	1.6	6	(0.8)	6	1.4
SAEs	11	(0.8)	12	1.0	5	(0.7)	5	1.1
EAC confirmed events								
Malignant neoplasms excl. thyroid	14	(1.0)	15	1.2	6	(0.8)	6	1.4
Malignant thyroid neoplasms	1	(<0.1)	1	<0.1	0			
PIONEER 6								
Number of subjects	1591				1592			
Observation time (years)	2101				2081			
MedDRA search								
SAEs	31	(1.9)	33	2	38	(2.4)	40	2
EAC confirmed events								
Malignant neoplasms excl. thyroid	41	(2.6)	50	2.4	48	(3.0)	61	2.9
Malignant thyroid neoplasms	2	(0.1)	3	0.1	0			

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

Source: Table 2-64 ISS

In the phase 3a pool, most of the neoplasms in the MedDRA search were reported in one patient in each treatment group with the following exceptions:

- Skin cancer (non-melanoma): 10 patients with semaglutide and 4 with comparator.
- Breast cancer: 6 patients in each treatment group.
- Prostate cancer: 8 with semaglutide and none with comparator.
- Lung cancer: 3 with semaglutide and 1 with comparator.
- Colorectal malignant neoplasms: 9 with semaglutide and 1 with comparator.
- Thyroid: 4 with semaglutide and 1 with comparator.

Five patients died from a malignancy in the phase 3a pool, and they are represented in the table below:

Reference ID: 4494748

Table 113 Malignant Neoplasms – MedDRA Search – with Fatal Outcome – Phase 3a Pool – In-Trial

Actual Treatment	Subject ID	Sex/age/BMI	Preferred term / Reported term	Trial day of AE onset	EAC Trial day of death (In-trial)
Oral sema 14 mg	(b) (6)	M/52/34.3	Lung adenocarcinoma / Lung adenocarcinoma metastatic	44	134 (Y)
Lira 1.8 mg		M/78/29.9	Pancreatic carcinoma / Cancer of head of pancreas	87	241 (Y)
Lira 1.8 mg		F/56/23.5	Ovarian cancer metastatic / Metastatic ovarian malignant neoplasm	58	146 (Y)
Sita 100 mg		M/60/29.0	Pancreatic carcinoma metastatic/ Pancreatic adenocarcinoma metastatic	228	315 (Y)
Sita 100 mg		M/56/38.8	Adenocarcinoma gastric / Gastric adenocarcinoma	514	523 (Y)[a]

a: EAC evaluation of death: Non-cardiovascular events/death (related to the PT: chronic hepatic failure)
Source: Table 2-65 ISS

EAC-confirmed events in the phase 3a pool: 106 events of malignant neoplasms (excluding malignant thyroid neoplasms) were sent for adjudication; 79 events identified by the investigator and 27 events identified by the PTQ search. Of these, 82 events were confirmed by the EAC, 79 of which were in-trial. Of the 6 events of potential thyroid-related events including malignant thyroid neoplasms sent for adjudication (all events were identified by the investigator), 4 events were confirmed by the EAC, 3 of which were in-trial. Generally, evaluation of the EAC-confimed events is similar to the MedDRA search, with imbalances not favoring semaglutide noted for the same types of cancers.

Reference ID: 4497478

Table 114 EAC-Confirmed Malignant Neoplasms (Including Malignant Thyroid Neoplasms) – MedDRA Search – Phase 3a Pool – In-Trial

	Oral sema N	(Adj.%)	E	Adj.R	Comparator N	(Adj.%)	E	Adj.R
Number of subjects	4116				2236			
Observation time (years)	4719				2452			
Malignant neoplasms	52	(1.4)	56	1.4	22	(1.0)	23	1.1
Skin cancer	15	(0.4)	19	0.5	5	(0.2)	5	0.2
Skin cancer other than melanoma	14	(0.4)	18	0.4	5	(0.2)	5	0.2
Malignant melanoma	1	(<0.1)	1	<0.1	0			
Breast cancer	6	(0.2)	6	0.2	6	(0.3)	6	0.3
Colorectal cancer	9	(0.2)	9	0.2	2	(0.1)	2	<0.1
Gastrointestinal cancer	4	(0.1)	4	<0.1	5	(0.3)	5	0.2
Pancreas	2	(<0.1)	2	<0.1	2	(<0.1)	2	<0.1
Stomach	1	(<0.1)	1	<0.1	3	(0.2)	3	0.1
Liver	1	(<0.1)	1	<0.1	0			
Prostate cancer	8	(0.2)	8	0.1	0			
Lung and pleura cancer	3	(0.1)	3	0.1	2	(0.1)	2	0.1
Lung cancer	3	(0.1)	3	0.1	2	(0.1)	2	0.1
Genitourinary cancer	1	(<0.1)	1	<0.1	2	(<0.1)	2	0.1
Kidney	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Bladder	0				1	(<0.1)	1	<0.1
Gynecologic cancer	2	(<0.1)	2	<0.1	0			
Other gynecologic sites	1	(<0.1)	1	<0.1	0			
Uterus	1	(<0.1)	1	<0.1	0			
Hematological malignancies	2	(<0.1)	2	<0.1	0			
Lymphoid neoplasm	2	(<0.1)	2	<0.1	0			
Unknown primary site	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Other primary site	1	(<0.1)	1	<0.1	0			
Malignant thyroid neoplasms	2	(<0.1)	2	<0.1	1	(<0.1)	1	<0.1
C-cell hyperplasia	0				0			

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

Source: Table 2-66 ISS

On PIONEER 6, the proportion of patients with malignant neoplasms SAEs was similar between the treatment groups. There were 31 events in the semaglutide group (1.9%) vs 38 with comparator (2.4%). Most of the imbalances noted in the phase 3a pool were not seen to the same extent in PIONEER 6, and no new imbalances were noted.

- Skin cancer (non-melanoma): 0 with semaglutide and 2 with placebo
- Breast cancer: 1 with semaglutide vs 0 with placebo
- Prostate cancer: 5 with semaglutide and 4 with placebo
- Lung cancer: 6 with semaglutide, and 2 with placebo
- Colorectal malignant neoplasms: 5 with semaglutide and 2 with placebo
- Thyroid: 2 with semaglutide and 0 with placebo

Sixteen of the malignant neoplasms had a fatal outcome, 7 with semaglutide and 9 with placebo, with no particular clustering for any malignancy type.

Reference ID: 4494748

EAC-confirmed neoplasms for PIONEER 6: 140 events sent for adjudication, 119 confirmed, 111 in-trial.

Table 115 EAC-Confirmed Malignant Neoplasms (Including Malignant Thyroid Neoplasms) – PIONEER 6 – In-Trial

	Oral sema				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1591				1592			
Observation time (years)	2101				2081			
Malignant neoplasms	41	(2.6)	50	2.4	48	(3.0)	61	2.9
Skin cancer	10	(0.6)	18	0.9	12	(0.8)	23	1.1
Skin cancer other than melanoma	9	(0.6)	17	0.8	12	(0.8)	23	1.1
Malignant melanoma	1	(0.1)	1	0.0	0			
Gastrointestinal cancer	9	(0.6)	9	0.4	10	(0.6)	10	0.5
Pancreas	5	(0.3)	5	0.2	4	(0.3)	4	0.2
Gall bladder and bile ducts	0				3	(0.2)	3	0.1
Liver	2	(0.1)	2	0.1	1	(0.1)	1	0.0
Stomach	1	(0.1)	1	0.0	2	(0.1)	2	0.1
Other gastrointestinal malignancy	1	(0.1)	1	0.0	0			
Hematological malignancies	4	(0.3)	4	0.2	6	(0.4)	6	0.3
Lymphoid neoplasm	4	(0.3)	4	0.2	5	(0.3)	5	0.2
Other hematological malignancy	0				1	(0.1)	1	0.0
Prostate cancer	5	(0.3)	5	0.2	5	(0.3)	5	0.2
Lung and pleura cancer	6	(0.4)	6	0.3	3	(0.2)	3	0.1
Lung cancer	6	(0.4)	6	0.3	2	(0.1)	2	0.1
Pleural mesothelioma	0				1	(0.1)	1	0.0
Colorectal cancer	5	(0.3)	5	0.2	2	(0.1)	2	0.1
Genitourinary cancer	2	(0.1)	2	0.1	4	(0.3)	4	0.2
Kidney	2	(0.1)	2	0.1	1	(0.1)	1	0.0
Bladder	0				2	(0.1)	2	0.1
Other genitourinary malignancy	0				1	(0.1)	1	0.0
Head and neck cancer	0				3	(0.2)	3	0.1
Pharynx or mouth	0				3	(0.2)	3	0.1
Breast cancer	0				1	(0.1)	2	0.1
Brain and spinal cord cancer	1	(0.1)	1	0.0	0			
Gynecologic cancer	0				1	(0.1)	1	0.0
Ovary	0				1	(0.1)	1	0.0
Other primary site	0				1	(0.1)	1	0.0
Unknown primary site	0				1	(0.1)	1	0.0
Malignant thyroid neoplasms	2	(0.1)	3	0.1	0			
Other	2	(0.1)	2	0.1	0			
Medullary thyroid microcarcinoma	1	(0.1)	1	0.0	0			
C-cell hyperplasia	0				0			

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.

Source: Table 2-68 ISS

Skin cancers and gastrointestinal cancers were the most frequent types of neoplasms, and they were observed in both treatment arms. Prostate cancer was also balanced between treatment groups. Colorectal and lung cancers were more commonly seen with semaglutide vs placebo; however, the small event numbers preclude any systematic conclusions. Overall, there were no significant differences in any neoplasm type when comparing semaglutide and placebo in PIONEER 6.

Reference ID: 4494348

Additionally, 3 thyroid events were sent for adjudication, all confirmed and in-trial, all on semaglutide (one was medullary microcarcinoma in the semaglutide arm). The 3 events occurred in 2 patients described below:

- Patient no (b) (6) had 2 events of thyroid neoplasm confirmed by the EAC, one of which was a thyroid microcarcinoma. The patient had thyroid nodules diagnosed about 1 year prior to trial enrollment, and calcitonin level was elevated at baseline (30.3 ng/L, with normal range <8.5 ng/L), however fine needle aspiration results were inconclusive. About one year into the trial, another fine needle aspiration showed multiple areas of medullary microcarcinoma and papillary thyroid cancer, and thyroidectomy was performed.
- Patient no (b) (6) had one event of metastatic follicular thyroid carcinoma. In 2000, 17 years prior to study enrollment, the patient underwent a total thyroidectomy for thyroid carcinoma. About one year into the study, a pulmonary nodule was noted during a routine primary care yearly exam. The diagnosis was confirmed by biopsy, and the lung nodule was surgically removed, followed by radioactive iodine ablation. Semaglutide was discontinued due to this event.

While there is an imbalance in thyroid cancer with semaglutide, evaluation of the narratives for the 2 patients suggests that these cancers were likely present prior to semaglutide initiation, and therefore, likely unrelated.

<u>Calcitonin</u>

Phase 3a and placebo pool

Calcitonin levels were similar at baseline between the treatment groups, and remained relatively unchanged at week 26, and end of treatment. No major differences in calcitonin outliers were seen in either of the pools. The summary of maximum post baseline values is presented below. In the phase 3a pool, calcitonin values above 50 ng/dL were seen in more patients on semaglutide (8 patients, 0.2%) vs 1 patient on comparator (<0.1%). No patients on semaglutide had calcitonin >100 ng/L. It is unclear whether this small numerical imbalance is clinically significant as the duration of the trials is relatively short.

Reference ID: 4494748

Table 116 Calcitonin (ng/L) – Categorical Summary of Maximum Post-Baseline Values – Phase 3a Pool and Placebo Pool – On-Treatment

	Oral sema N (Adj.%)	Comparator or Placebo N (Adj.%)
Phase 3a pool		
Number of subjects	4116	2236
N	3874	2145
Normal	3539 (90.8)	1950 (91.0)
High (>ULN)	335 (9.2)	195 (9.0)
>50 ng/L	8 (0.2)	1 (<0.1)
>100 ng/L	0	1 (<0.1)
Placebo pool		
Number of subjects	1519	665
N	1409	634
Normal	1295 (90.6)	575 (91.1)
High (>ULN)	114 (9.4)	59 (8.9)
>50 ng/L	2 (0.1)	1 (0.2)
>100 ng/L	0	1 (0.2)

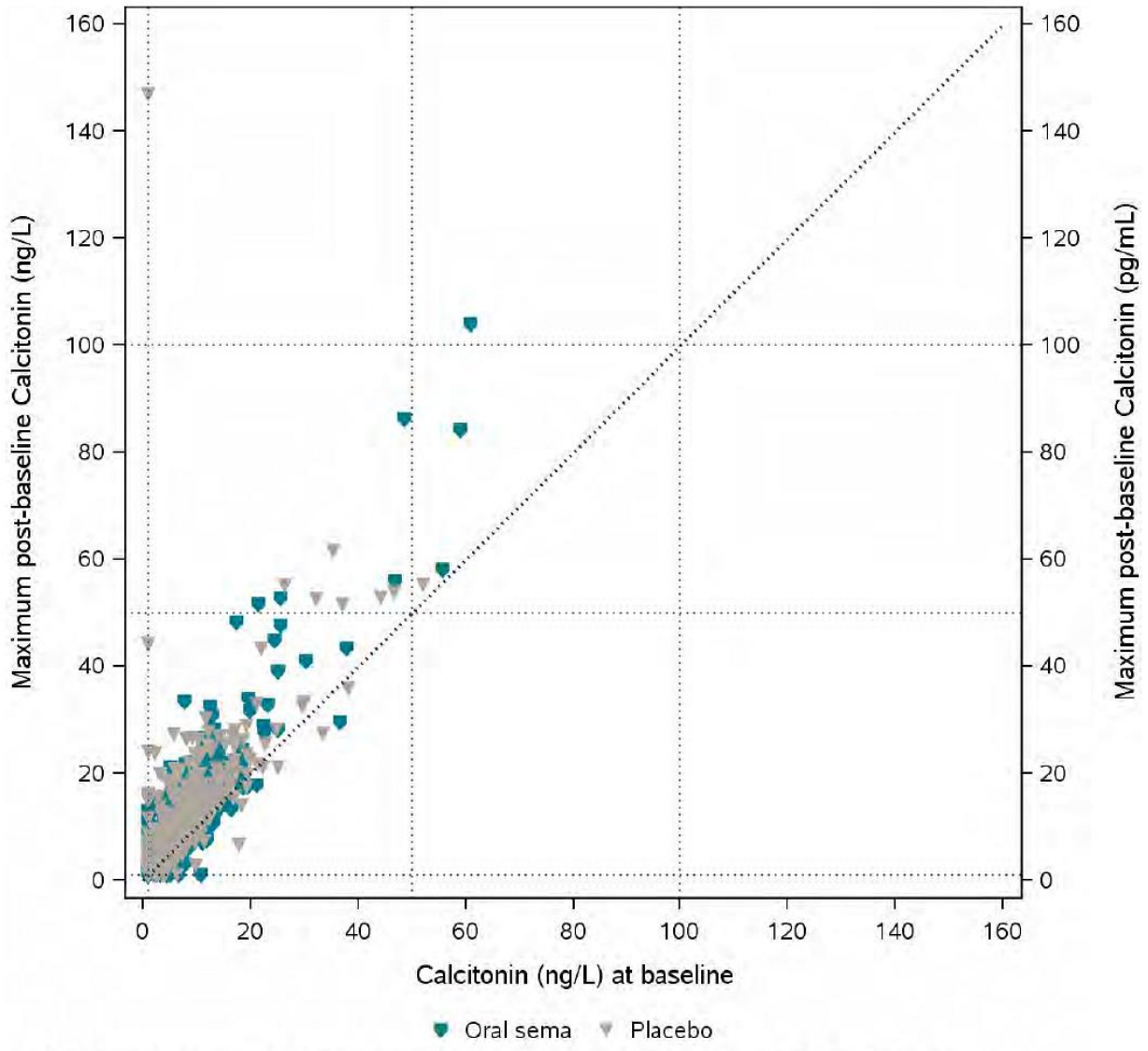
Phase 3a pool: PIONEER 1-5 and 7-10. Placebo pool: PIONEER 1, 4, 5 and 8.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). Phase 3a pool comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. Placebo pool comparator: placebo.
The maximum value from all post-baseline observations in the observation period was used.
N: number of subjects contributing to the summary statistic; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects; ULN: upper limit of the normal.

Source: Table 2-70 ISS

In PIONEER 6, the mean calcitonin levels were also stable over time, and similar between the two treatment groups. At baseline, 9.5% of patients in the oral semaglutide group and 8.5% of patients in the placebo group had calcitonin levels elevated above ULN, and a similar pattern was observed during the trial, where 10.3% with oral semaglutide and 9.8% with placebo had calcitonin levels elevated above ULN.

Reference ID: 4494748

Figure 40 Calcitonin Maximum Post Baseline Value – Shift Plot



Source: Figure 14.3.5.116 CSR PIONEER 6

Two (2) patients had values above 100 ng/L during the trial, one in each treatment group. Both patients were referred to a thyroid specialist (no thyroid malignancy identified), and the study drug was discontinued per protocol.

- Patient no (b) (6) traded with oral semaglutide had a calcitonin level of 104 ng/L at week 26, followed by a decrease to below 50 ng/L at the end of trial
- Patient no (b) (6) on placebo had a calcitonin value of 147 ng/L at week 50 (all previous values were normal)

Reference ID: 4494748

Reviewer's comment: While an imbalance not favoring semaglutide was seen for skin, lung, prostate, thyroid, and colorectal cancers, particularly in the phase 3a pool, the numbers are too small to be conclusive. It is not clear how such a short semaglutide exposure could have caused the imbalance given the usual long latency for these malignancies, and the imbalances were not seen in PIONEER 6 which followed patients longer than most studies in the phase 3a pool. Additionally, confounding factors are present in most cases. Pancreatic cancer was rare, and no imbalance not favoring semaglutide was observed. Calcitonin levels were generally stable throughout the trials regardless of the treatment arm, and no significant imbalances were seen regarding outliers.

8.5.1. Hypoglycemia

For the phase 3a pool, the placebo pool and the placebo dose pool, hypoglycemic episodes were summarized by the applicant according to the ADA 2018/IHSG 2017 classification below:

Table 117 ADA 2018 and IHSG 2017 classification of hypoglycemia

Level		Glycaemic criteria	Description
Level 1	Hypoglycaemia alert value	≤3.9 mmol/L (70 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Level 2	Clinically significant hypoglycaemia	<3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Level 3	Severe hypoglycaemia	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

Source: Table 1-8 ISS

In PIONEER 6, only severe hypoglycemic episodes were collected systematically; and these will be presented based on the on-treatment period.

Hypoglycemic episodes were summarized for subsets of patients across trials based on each patient's baseline background diabetes medication:

- No background medication
- Trial product in combination with an SU with or without metformin
- Trial product in combination with insulin with or without OADs (including SUs)
- Trial product in combination with other OADs (excluding SU)

An overview of these different background medications by trial in the phase 3a pool is presented in the table below:

Reference ID: 4494748

Table 118 Background Medications by Trial

Contributing trials	No background medication	SU as background medication	Insulin as background medication	Other OADs as background medication
PIONEER 1	X			
PIONEER 2				X
PIONEER 3		X		X
PIONEER 4				X
PIONEER 5		X	X	X
PIONEER 7		X		X
PIONEER 8			X	
PIONEER 9	X			
PIONEER 10		X		X

Source: Table 1-9 ISS

Reference ID: 4494748

Table 119 Hypoglycemia in Phase 3a, Placebo Pools, and PIONEER 6

	Oral sema N (Adj.%)	E	Adj.R	Comparator or Placebo N (Adj.%)	E	Adj.R
Phase 3a pool (On-treatment without rescue medication)						
Number of subjects	4116			2236		
Exposure time (years)	3697			1945		
ADA 2018 classification	776 (17.1)	3820	95.4	321 (15.7)	1301	75.8
Level 3 - Severe	11 (0.2)	11	0.3	2 (0.1)	2	0.1
Level 2 - Clinically significant	292 (6.1)	813	19.9	124 (6.3)	299	17.8
Level 1 - Alert value	723 (16.0)	2996	75.2	287 (14.1)	1000	57.8
Placebo pool (On-treatment without rescue medication)						
Number of subjects	1519			665		
Exposure time (years)	995			410		
ADA 2018 classification	368 (23.0)	2327	184.0	115 (18.3)	654	137.7
Level 3 - Severe	8 (0.5)	8	0.6	1 (0.2)	1	0.2
Level 2 - Clinically significant	162 (9.7)	551	42.1	56 (9.2)	163	34.4
Level 1 - Alert value	346 (21.7)	1768	141.3	106 (17.0)	490	103.1
	N (%)	E	R	N (%)	E	R
PIONEER 6 (On-treatment)						
Number of subjects	1591			1592		
Observation time (years)	1932			1987		
ADA 2013 classification						
Severe	23 (1.4)	28	1	13 (0.8)	17	1

Phase 3a pool: PIONEER 1-5 and 7-10, Phase 3a pool comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. Placebo pool and PIONEER 6 comparator: placebo.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). Placebo pool: PIONEER 1, 4 and 8. 'on-treatment without rescue medication': For hypoglycaemia the on-treatment without rescue medication period is defined as the period from date of first dose of trial product to date of last dose of trial product or initiation of rescue medication whichever comes first. N: number of subjects with at least one episode; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one episode (%) and rate per 100 patient-years of exposure (R); E: number of episodes; ADA: American Diabetes Association
'ADA 2018 classification': 'Severe': requiring assistance from another person for recovery; 'Clinically significant': plasma glucose < 3.0 mmol/L (54 mg/dL); 'Alert value': plasma glucose <=3.9 mmol/L (70 mg/dL).

Source: Table 2-72 ISS

Severe hypoglycemia was more common with semaglutide vs comparator in all pools, and PIONEER 6, although the events were rare, and the differences were numerically small. Of the episodes of severe hypoglycemia in the phase 3a pool, two episodes of hypoglycemic unconsciousness with oral semaglutide 3 mg (2 patients, both from PIONEER 8 having insulin as background diabetes medication) were also reported as SAEs.

Level 2, clinically significant hypoglycemia, was balanced between the treatment groups in the placebo and phase 3a pools. No dose dependence was observed for the three doses of semaglutide as evidenced by the results of the placebo dose pool.

Reference ID: 4494748

Table 120 Hypoglycemia – ADA 2018 Classification – Placebo Dose Pool – On-Treatment Without Rescue Medication

	Oral sema 3 mg			Oral sema 7 mg			Oral sema 14 mg			Placebo		
	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R
Number of subjects	359			356			356			362		
Exposure time (years)	232			227			222			227		
ADA 2018 classification	111 (30.8)	773	265.2	99 (27.9)	709	248.9	102 (28.7)	705	254.2	95 (26.3)	614	211.6
Level 3 - Severe	5 (1.4)	5	1.7	1 (0.3)	1	0.6	2 (0.6)	2	0.7	1 (0.3)	1	0.3
Level 2 - Clinically significant	57 (15.8)	208	71.6	46 (12.9)	180	62.5	48 (13.5)	144	51.5	52 (14.4)	159	55.1
Level 1 - Alert value	99 (27.4)	560	191.9	95 (26.7)	528	185.8	99 (27.9)	559	201.9	89 (24.6)	454	156.1

Placebo dose pool: PIONEER 1 and 8.
'on-treatment without rescue medication': For hypoglycaemia the on-treatment without rescue medication period is defined as the period from date of first dose of trial product to date of last dose of trial product or initiation of rescue medication whichever comes first.
N: number of subjects with at least one episode; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one episode (%) and rate per 100 patient-years of exposure (R); E: number of episodes; ADA: American Diabetes Association
'ADA 2018 classification': 'Severe': requiring assistance from another person for recovery; 'Clinically significant': plasma glucose < 3.0 mmol/L (54 mg/dL); 'Alert value': plasma glucose <= 3.9 mmol/L (70 mg/dL).

Source: Table 7.3.181 ISS

On the contrary, it is notable that all hypoglycemia, as well as severe, and clinically significant hypoglycemia were more common with the lowest dose of semaglutide, 3 mg, compared to either the 7 or 14 mg semaglutide, or placebo. It is not reasonable to conclude that the lowest semaglutide dose is most likely to cause hypoglycemia. Since this analysis is based on the on-treatment without rescue events, it is not likely that needing more rescue medications contributed to hypoglycemia, and the differences in hypoglycemia may be due to chance.

Because the trials designs were designed differently regarding the background antidiabetic medications, and adjustment of background therapies, these aspects will have to be considered in the hypoglycemia analyses.

In PIONEER 3, which was the other study using all three semaglutide doses, but not included in the placebo dose pool, dose dependence was observed for semaglutide regarding all hypoglycemic episodes, and clinically significant hypoglycemia (5.4% patients with semaglutide 3 mg, 6% with 7 mg, 8.8% with 14 mg vs 7.5% with comparator sitagliptin).

The table below presents an overview of hypoglycemic episodes by background medication in the phase 3a pool.

Reference ID: 4494748

Table 121 Hypoglycemia by Anti-Diabetic Background Medication– Phase 3a Pool – On-Treatment Without Rescue Medication

	Oral sema N (Adj.%)	E	Adj.R	Comparator N (Adj.%)	E	Adj.R
No background medication						
Number of subjects	671			275		
Exposure time (years)	374			165		
ADA 2018 classification	31 (4.4)	40	11.1	6 (2.0)	7	4.1
Level 3 - Severe	1 (0.1)	1	0.3	0		
Level 2 - Clinically significant	5 (0.7)	5	1.4	4 (1.4)	4	2.5
Level 1 - Alert value	27 (3.9)	34	9.4	3 (1.0)	3	1.6
SU +/- Metformin						
Number of subjects	970			428		
Exposure time (years)	994			410		
ADA 2018 classification	284 (29.0)	1098	120.2	114 (27.6)	472	109.2
Level 3 - Severe	1 (<0.1)	1	<0.1	1 (0.3)	1	0.2
Level 2 - Clinically significant	105 (10.7)	234	24.5	46 (11.2)	110	24.9
Level 1 - Alert value	265 (27.2)	863	95.6	100 (24.3)	361	84.0
Insulin +/- OADs						
Number of subjects	605			240		
Exposure time (years)	465			172		
ADA 2018 classification	307 (49.6)	2225	453.2	102 (44.6)	627	352.2
Level 3 - Severe	7 (1.1)	7	1.3	1 (0.4)	1	0.6
Level 2 - Clinically significant	153 (24.2)	541	108.6	52 (23.1)	159	89.0
Level 1 - Alert value	291 (47.1)	1677	343.3	96 (42.0)	467	262.7
Other OADs						
Number of subjects	1868			1290		
Exposure time (years)	1863			1196		
ADA 2018 classification	154 (7.9)	457	22.2	99 (7.6)	195	15.7
Level 3 - Severe	2 (0.1)	2	0.1	0		
Level 2 - Clinically significant	29 (1.4)	33	1.7	22 (1.6)	26	2.0
Level 1 - Alert value	140 (7.2)	422	20.4	88 (6.9)	169	13.6

Phase 3a pool: PIONEER 1-5 and 7-10. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. 'on-treatment without rescue medication': For hypoglycaemia the on-treatment without rescue medication period is defined as the period from date of first dose of trial product to date of last dose of trial product or initiation of rescue medication whichever comes first. N: number of subjects with at least one episode; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one episode (%) and rate per 100 patient-years of exposure (R); E: number of episodes; ADA: American Diabetes Association 'ADA 2018 classification': 'Severe': requiring assistance from another person for recovery; 'Clinically significant': plasma glucose <3.0 mmol/L (54 mg/dL); 'Alert value': plasma glucose <=3.9 mmol/L (70 mg/dL); SU: sulphonylurea; OAD: oral anti-diabetic drug.

Source: Table 2-73 ISS

As expected, the proportion of patients with any hypoglycemia was lower when semaglutide was added to no anti-diabetic background medication, and higher when administered on a background of insulin and/or sulfonylureas. The majority of severe hypoglycemic episodes are noted with semaglutide on a background of insulin, which is, again, expected based on the knowledge with other GLP-1 RAs.

Reference ID: 4494348

In the renal impairment study, semaglutide was associated with a higher incidence of clinically significant hypoglycemia (5.5% vs 3.1% with placebo). No severe hypoglycemia was reported from this study.

In conclusion, severe hypoglycemic events were more common with oral semaglutide vs comparator in all pools, particularly on a background of insulin and/or sulfonylureas. No clear dose dependence was seen for oral semaglutide regarding either clinically significant or severe hypoglycemia.

8.5.2. Diabetic Retinopathy

Diabetic retinopathy was identified as a safety issue during review of the subcutaneous semaglutide drug product. In SUSTAIN 6, the pre-market CVOT for subcutaneous semaglutide, a higher incidence of adjudicated diabetic retinopathy complications was seen with semaglutide vs standard of care. As a result, diabetic retinopathy was defined as a safety area of interest for the oral semaglutide program.

The risk of diabetic retinopathy with oral semaglutide was assessed via medDRA search, data collected on the diabetic retinopathy data collection forms, and eye examination results at baseline and end of treatment. Even for PIONEER 6, all diabetic retinopathy AEs were collected, not only SAEs.

The in-trial period was used for evaluation of diabetic retinopathy due to the potentially long latency between onset and diagnosis.

Additionally, proliferative retinopathy or maculopathy requiring acute treatment was an exclusion criterion for all PIONEER trials. Fundoscopy (with dilation) was performed at baseline and end of treatment/end of trial for all PIONEER trials.

<u>MedDRA search</u>

There were more AEs of diabetic retinopathy with semaglutide vs comparator in all pools, and PIONEER 6. Very few SAEs were reported, and no notable imbalances were seen between the treatment groups.

Reference ID: 4494748

Table 122 AEs of Diabetic Retinopathy and Related Complications- MedDRA search

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

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

Source: Table 2-76 ISS

In the phase 3a pool, MedDRA search identified 294 events of diabetic retinopathy (269 patients). The most frequently reported AEs were under the preferred terms diabetic retinopathy and retinopathy. Two patients on oral semaglutide (<0.1%), and 3 on comparator (0.2%) had SAEs of diabetic retinopathy. Only one event lead to premature trial product discontinuation, in a patient with AE of retinopathy proliferative in the oral semaglutide 14 mg group.

Reference ID: 4494748

Table 123 AEs of Diabetic Retinopathy and Related Complications – MedDRA Search – by PT – Phase 3a Pool – In-Trial

	Oral sema N (Adj.%)	E	Adj.R	Comparator N (Adj.%)	E	Adj.R
Number of subjects	4116			2236		
Observation time (years)	4719			2452		
All events	195 (4.2)	211	4.0	74 (3.8)	83	3.5
Diabetic retinopathy	154 (3.3)	155	2.9	59 (3.0)	60	2.6
Retinopathy	15 (0.3)	16	0.3	4 (0.2)	4	0.2
Retinal haemorrhage	9 (0.2)	9	0.2	3 (0.2)	3	0.1
Maculopathy	8 (0.2)	9	0.2	3 (0.2)	3	0.1
Diabetic retinal oedema	7 (0.2)	7	0.2	4 (0.2)	4	0.1
Macular oedema	6 (0.1)	6	<0.1	2 (0.1)	3	0.1
Retinal detachment	3 (<0.1)	3	<0.1	1 (<0.1)	1	<0.1
Vitreous detachment	2 (<0.1)	2	<0.1	3 (0.2)	3	0.2
Visual acuity reduced	1 (<0.1)	1	<0.1	0		
Retinal oedema	1 (<0.1)	1	<0.1	0		
Retinopathy proliferative	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Vitreous haemorrhage	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1

Phase 3a pool: PIONEER 1-5 and 7-10. Oral sema: data from all three oral semaglutide doses (3, 7 and 14 mg). Comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group. N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of observation (R); E: number of events.
Source: Table 2-77 ISS

In PIONEER 6, 240 events were identified in 214 patients via MedDRA search. As for the phase 3a pool, the most frequently reported AEs were diabetic retinopathy and retinopathy. It appears that the difference between the treatment arms is mostly due to the events reported with the preferred term diabetic retinopathy, which is not informative. Events of vitreous detachment, retinal hemorrhage, and retinal detachment were only reported with semaglutide. One event was an SAE (proliferative retinopathy on placebo), and one event led to premature discontinuation (maculopathy on placebo).

Table 124 AEs of Diabetic Retinopathy and Related Complications – MedDRA Search – by PT – PIONEER 6 – In-Trial

	Oral sema N (%)	E	R	Placebo N (%)	E	R
Number of subjects	1591			1592		
Observation time (years)	2101			2081		
Events	113 (7.1)	127	6	101 (6.3)	113	5
Diabetic retinopathy	93 (5.8)	97	5	76 (4.8)	81	4
Retinopathy	7 (0.4)	8	0	17 (1.1)	17	1
Maculopathy	5 (0.3)	6	0	3 (0.2)	3	0
Diabetic retinal oedema	4 (0.3)	4	0	1 (0.1)	1	0
Macular oedema	4 (0.3)	4	0	8 (0.5)	9	0
Vitreous detachment	4 (0.3)	4	0	0		
Retinal haemorrhage	2 (0.1)	2	0	0		
Retinal detachment	1 (0.1)	1	0	0		
Vitreous haemorrhage	1 (0.1)	1	0	1 (0.1)	1	0
Retinopathy proliferative	0			1 (0.1)	1	0

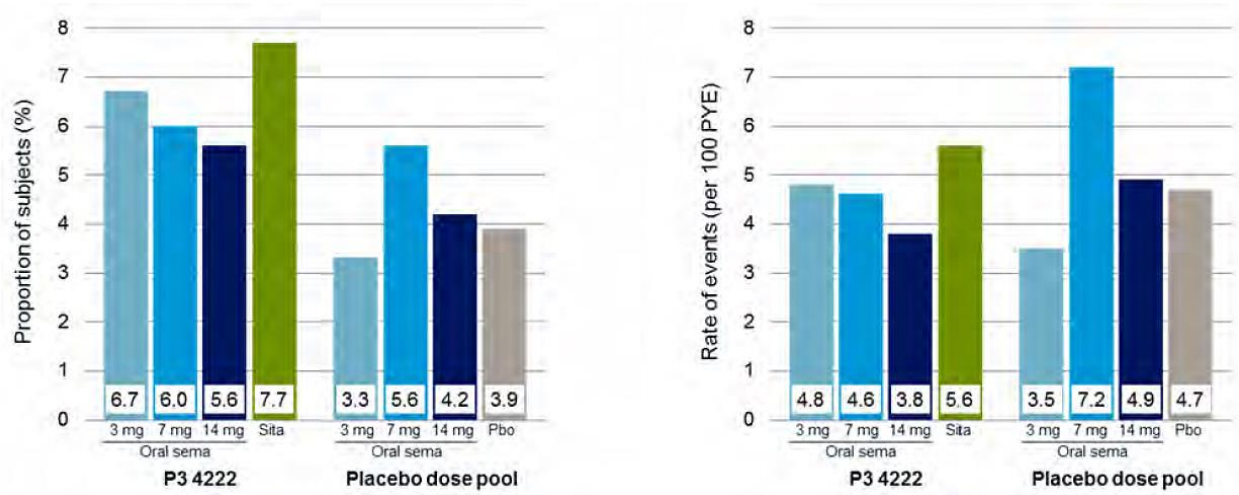
N: number of subjects with at least one event; %: proportion of subjects with at least one event; E: number of events; R: events per 100 years of observation.

Reference ID: 4497478

Source: Table 2-80 ISS

The increase in diabetic retinopathy AEs was not seen consistently in all PIONEER trials, and no dose dependence was seen for semaglutide in PIONEER 3 and the placebo dose pool, as shown below.

Figure 41 AEs of Diabetic Retinopathy by Semaglutide Dose, MedDRA Search – In-Trial



Source: Figure 2-32 ISS

<u>Additional data collected on diabetic retinopathy</u>

Additional data were collected for 268 of the 294 AEs of diabetic retinopathy and related complications in the phase 3a pool. Most events (>93%) were identified during routine examinations and not based on symptoms. More than 75% of events were non-proliferative diabetic retinopathy, and >85% did not require treatment. Overall the additional information collected is not very helpful in identifying the reason for the increased incidence of AEs related to diabetic retinopathy with oral semaglutide vs comparator, at least for the phase 3a pool.

Reference ID: 4494348

Table 125 Additional Data Collection on Diabetic Retinopathy – Phase 3a Pool – In-Trial

	Oral sema E (%)	Comparator E (%)
Number of events	192 (100)	76 (100)
Type of event		
Neovascular glaucoma	0	0
Traction retinal detachment [1]	2 (1.0)	1 (1.3)
Diabetic macular oedema	19 (9.9)	11 (14.5)
Proliferative diabetic retinopathy	6 (3.1)	4 (5.3)
Non-proliferative diabetic retinopathy	150 (78.1)	57 (75.0)
Other significant eye disease	15 (7.8)	3 (3.9)
Event identified by		
Symptoms	10 (5.2)	5 (6.6)
Routine examination	182 (94.8)	71 (93.4)
Treatment given		
Treatment [2]	26 (13.5)	11 (14.5)
Observation	166 (86.5)	65 (85.5)

Phase 3a pool: PIONEER 1-5 and 7-10. Oral sema: data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin,empagliflozin, liraglutide, dulaglutide and placebo.
The additional data was collected by eye (left and right), but the event only counted in the most severe category for any eye. For type of event, the following ranking was applied: neovascular glaucoma, retinal detachment, macular oedema, proliferative retinopathy, non-proliferative retinopathy, other significant eye disease. [1]: traction retinal detachment secondary to diabetic retinopathy; [2]: treatment includes: Focal laser treatment/photocoagulation for macular oedema; scatter laser treatment/panretinal photocoagulation (PRP) for proliferative diabetic retinopathy; intraviteral agents; vitrectomy for diabetic retinopathy; or other treatment.

Source: Table 2-78 ISS

For PIONEER 6, additional data were collected for 230 of the 240 AEs of diabetic retinopathy.

Reference ID: 4494748

Table 126 Additional Data Collected on Diabetic Retinopathy – PIONEER 6 – In-Trial

	Oral sema E (%)	Placebo E (%)
Number of events	120 (100)	110 (100)
Type of event		
Neovascular glaucoma	0	0
Traction retinal detachment [1]	1 (0.8)	0
Diabetic macular oedema	17 (14.2)	17 (15.5)
Proliferative diabetic retinopathy	10 (8.3)	13 (11.8)
Non-proliferative diabetic retinopathy	78 (65.0)	74 (67.3)
Other significant eye disease	14 (11.7)	6 (5.5)
Event identified by		
Symptoms	9 (7.5)	16 (14.5)
Routine examination	111 (92.5)	94 (85.5)
Treatment given		
Treatment [2]	27 (22.5)	29 (26.4)
Observation	93 (77.5)	81 (73.6)

The additional data were collected by eye (left and right), but the event only counted in the most severe category for any eye. For type of event, the following ranking was applied: neovascular glaucoma, retinal detachment, macular oedema, proliferative retinopathy, non-proliferative retinopathy, other significant eye disease. [1]: traction retinal detachment secondary to diabetic retinopathy; [2]: treatment includes: Focal laser treatment/photocoagulation for macular oedema; scatter laser treatment/panretinal photocoagulation (PRP) for proliferative diabetic retinopathy; intraviteral agents; vitrectomy for diabetic retinopathy; or other treatment.

Source: Table 2-81 ISS

Overall, for the phase 3 a pool and PIONEER 6, the patients with diabetic retinopathy events had longer diabetes duration, and a larger proportion of patients had diabetic retinopathy at baseline when compared to patients without diabetic retinopathy events. Additionally, in both treatment groups, patients with diabetic retinopathy events were more likely to be on insulin compared with patients without event. All this is consistent with the known pathophysiology of diabetic retinopathy, as they are all indicators of a more advanced diabetes stage which is associated with more diabetes complications in general. However, it does not clarify why the incidence of events was higher with semaglutide. Most events were identified via routine eye examination, and only about a quarter of events required intervention.

<u>Eye examination results</u>

In addition to baseline and end of treatment, eye examinations were performed approximately 1 year into the trials for PIONEER 3 and 6.

No differences were seen between semaglutide and comparator with regard to the eye examination results, or shifts from baseline to end of treatment, in any of the pools, or PIONEER 6.

Reviewer comment: The interpretation of the retinopathy data is limited by the way it was assessed, the duration of the studies, and the relatively low risk population. While overall the

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proportion of patients on oral semaglutide were reported more frequently with PTs suggestive of diabetic retinopathy, the differences were small in all pools and PIONEER 6, not reaching the level of significance observed with subcutaneous semaglutide. Overall, the clinical program for oral semaglutide does not provide any clarity over what was seen with subcutaneous semaglutide, but it also does not appear to introduce any additional risk.

8.5.3. Lactic acidosis

In animals, mortality was observed in all toxicology species when SNAC was administered at high doses (≥200 mg/kg depending on the species). The mortality is considered to be due to inhibition of cellular respiration, mainly via an inhibition of complex I in the electron transport chain, and is associated with high exposure, particularly high initial plasma concentration levels in individual animals.

The expected clinical expression of a significant inhibition of complex I in humans would be an event of lactic acidosis. In line with this, literature supports the use of lactate levels as a marker of potential drug-induced mitochondrial complex I inhibition in humans in addition to a clinical evaluation. Lactic acidosis is therefore included as a safety focus area in all phase 3a trials.

The risk of lactic acidosis has been evaluated based on investigator reported AEs using a predefined MedDRA search to capture all events and the outcome of the adjudication of suspected cases of lactic acidosis. Adjudication was done to increase the validity of the diagnosis and an event was confirmed if lactate concentration ≥5.0 mmol/L and pH <7.35 at the time of the event. As a potential drug-induced lactic acidosis would be the result of an acute effect of the drug, the on-treatment observation period has been used for this evaluation. Due to selective safety reporting requirements in PIONEER 6, the MedDRA search is performed among SAEs only for this trial.

Venous lactate levels were measured pre-dose and at two post-dose time points around the expected peak concentrations of SNAC (25 and 40 minutes post-dose) in PIONEER 1 and 2. This sampling schedule was applied after 4 and 26 weeks of treatment in both trials and also, after 52 weeks in the PIONEER 2 trial. SNAC exposure levels were measured concurrently to investigate the potential correlation between exposure and lactate levels.

A clinical pharmacology trial 4247 investigated the effect of supra-therapeutic doses of SNAC (doses up to 3.6 g - 12 times the clinical SNAC dose in the oral semaglutide tablet) on arterial lactate and other blood gas parameters. In part A of this trial, patients were dosed with a single supra-therapeutic dose of SNAC or placebo and the SNAC doses administered were 1.2, 2.4, or 3.6 g. Arterial blood samples (for lactate assessments and other blood gas parameters) were drawn by an intra-arterial catheter pre-dose and at 30 minutes, 60 minutes, 2 hours and 4 hours after dosing. The results of this study are discussed later in this section.

Reference ID: 4494748

MedDRA search

Few events of lactic acidosis were identified via MedDRA search as evidenced in the table below. This is not unexpected as lactic acidosis is a very rare event. No events were observed in the placebo pool.

Table 127 Lactic Acidosis – MedDRA Search

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Observation time (years)	4379				2335			
AEs	3	(<0.1)	3	<0.1	1	(<0.1)	1	<0.1
SAEs	0				1	(<0.1)	1	<0.1
Placebo pool								
Number of subjects	1519				665			
Observation time (years)	1197				523			
AEs	0				0			
SAEs	0				0			
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
SAEs	3	(0.2)	3	0	2	(0.1)	2	0

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

Source: Table 2-86 ISS

In the phase 3a pool, there were 3 AEs of lactic acidosis with semaglutide, and 1 with comparator. Only one SAE was reported in the phase 3a pool, with comparator. In PIONEER 6, 3 SAEs were reported with oral semaglutide vs 2 with placebo. The events were reported with preferred term lactic acidosis, and lactic acid increased as seen below.

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Table 128 Lactic Acidosis – AEs by SOC and PT – MedDRA Search – Phase 3a Pool and PIONEER 6 – On-Treatment

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	3	(<0.1)	3	<0.1	1	(<0.1)	1	<0.1
Investigations	2	(<0.1)	2	<0.1	0			
Blood lactic acid increased	2	(<0.1)	2	<0.1	0			
Metabolism and nutrition disorders	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Lactic acidosis	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
SAEs	3	(0.2)	3	0	2	(0.1)	2	0
Metabolism and nutrition disorders	3	(0.2)	3	0	2	(0.1)	2	0
Lactic acidosis	3	(0.2)	3	0	2	(0.1)	2	0

Phase 3a pool: PIONEER 1-5 and 7-10, comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. Oral sema: data from all three oral semaglutide doses (3, 7 and 14 mg).
PIONEER 6 comparator: placebo
Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R); E: number of events.
Source: Table 2-87 ISS

Six events were sent for adjudication from the phase 3a pool (in 5 patients), all from studies 4222 (5 events/4 patients) and 4223 (1 event/1 patient). Notably, one event of blood lactic acid increased was not even sent for adjudication, as the EAC chair or delegate rejected it during pre-evaluation. The event occurred in a 42 year old male on semaglutide (patient no (b) (6)/study 4223). None of the events of lactic acidosis from the phase 3a pool was confirmed by the EAC for the on-treatment period, but one event was confirmed for the in-trial period. Details regarding the events sent for adjudication are outlined below:

Confirmed:

- Patient no (b) (6): 64 year old male on semaglutide in study 4222, admitted with encephalitis, respiratory failure, and septic shock, 89 days after receiving the last dose of trial drug. Lactic acid was reported as 17.6 mmol/L, pH 6.95.

Not confirmed

- Patient no (b) (6): 64 year old female from study 4223 on empagliflozin, was reported with lactic acidosis during hospitalization for septic shock due to acute cholecystitis. The narrative reports that the initial lactic acid level was 5.5 mmol/L, but blood pH was not reported that day. The pH was reported as normal 2 days later.

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- Patient no (b) (6): 71 year old female treated with semaglutide from study 4222 was admitted with syncopal episode in the context of community acquired pneumonia.
- Patient no (b) (6): 27 year old male treated with semaglutide from study 4222 was admitted with right leg cellulitis and lactic acid was found to be elevated.
- Patient no (b) (6): 76 year old male treated with semaglutide from study 4222 was admitted with pneumonia and sepsis, lactic acid level was found to be elevated.

In PIONEER 6, 8 potential events (in 6 patients) were sent for adjudication, and the applicant states that all events were investigator reported. Only 2 events of lactic acidosis were confirmed by the EAC, one in each treatment group. All events sent for adjudication had confounders as they were reported in patients with sepsis, renal failure, etc. and lactic acid is likely to be elevated during such events. Details regarding the events sent for adjudication are presented below for clarity. Note that the upper limit of normal for lactic acid is about 2 mmol/L.

Confirmed by EAC:

- Patient no (b) (6): 54 year old female on oral semaglutide was diagnosed with lactic acidosis upon hospital admission for pyelonephritis/sepsis/acute renal failure. The event happened 11 months after the initiation of the trial drug. Lactic acid was 8.9 mmol/L, and pH was 7.28. The patient was also taking metformin 1000 mg BID prior to the event. Semaglutide was discontinued as a result of this event
- Patient no (b) (6): 70 year old female on placebo, was diagnosed with urosepsis, acute kidney injury and lactic acidosis about 6 months after the initiation of the study drug. There is no report of the patient taking metformin. Lactic acid was 8.9 mmol/L, and pH was 7.21.

Not confirmed by EAC:

- Patient no (b) (6): 64 year old male on semaglutide was reported with lactic acidosis when he presented to the hospital with syncopal episode and dehydration following a day of limited oral intake while consuming a large amount of alcohol at a family reunion. Lactate level on admission was 4.9 mmol/L. The patient was also taking metformin 500 mg BID.
- Patient no (b) (6): 73 year old male on placebo was reported with lactic acidosis when he was admitted with sepsis. At the time, lactate level was elevated at 3.3 mmol/L. The patient was also taking metformin 500 mg BID.
- Patient no (b) (6): 70 year old female on placebo reported with 3 events, one with PT urosepsis, and one with PT lactic acidosis, reported on the same day, and one with PT hyperosmolar hyperglycemic acidosis one day after (this one was positively adjudicated).
- Patient no (b) (6): 74 year old male on semaglutide was reported with lactic acidosis when admitted for hypotension and acute kidney injury, due to poor po intake, GI losses, and iatrogenic due to antihypertensive medications. Lactic acid level was 3.7 mmol/L.

Reference ID: 4494748

- Patient no (b) (6): 76 year old female on oral semaglutide was reported with lactic acidosis when admitted for hypoxia, acute kidney injury, poor oral intake. Lactic acid was 3.1 mmol/L, and pH was 7.28.

Reviewer comment: As expected, the number of events of lactic acidosis was exceedingly small. While more patients on semaglutide experienced events that were sent for adjudication, although they did not meet criteria for adjudication, vs comparators, evaluation of the narratives and adjudication packages suggest an alternative etiology for the lactic acid elevation in all of these cases. There is no evidence of increase lactic acidosis clinical events due to oral semaglutide based on the available clinical data.

<u>Lactate measurements</u>

Lactate data in patients with diabetes from Phase 3 trials:

Lactate was measured at selected visits and time points in PIONEER 1 and 2. In both trials, dosing with oral semaglutide did not increase mean or individual lactate levels and there was no difference in lactate levels between oral semaglutide and comparators (placebo/empagliflozin). There was also no correlation between SNAC exposure and concurrent lactate level.

In PIONEER 1, there were 2 patients with high lactate levels post dose, observed at week 26.

- Patient no (b) (6) on semaglutide 14 mg with pre-dose lactate level of 1.38 mmol/L, 25 minutes post-dose 8.44 mmol/L, and 40 minutes post-dose 1.63 mmol/L
- Patient no (b) (6) on semaglutide 3 mg, pre-dose 1.92 mmol/L, 25 minutes post-dose >upper limit of quantification (>13.32 mmol/L), and 40 minutes post-dose 0.9 mmol/L

No outliers were reported from PIONEER 2.

Lactate data in healthy volunteers – clinical pharmacology trial 4247:

There were no apparent changes over the measured time period, or differences between treatments in arterial lactate levels.

8.5.4. Immunogenicity

Since semaglutide is a protein-based drug, localized or generalized immune and allergic reactions are possible. Immunogenicity was assessed via MedDRA search, and development of anti-semaglutide antibodies. For PIONEER 6 the MedDRA search was performed to identify immunogenicity-related SAEs only. In selected trials, PIONEER 1–5 and 9, antibody assessments were performed at selected site visits throughout the treatment period. In the remaining trials

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including PIONEER 6, antibodies were only assessed in case of suspicion of severe hypersensitivity reactions possibly related to trial product.

Immunogenicity-related AEs

The MedDRA search included the following SMQs: anaphylactic reaction, angioedema, severe cutaneous adverse reaction, anaphylactic/anaphylactoid shock conditions, and hypersensitivity. There was no imbalance in immunogenicity AEs not favoring semaglutide in either pool or PIONEER 6.

Table 129 Total Immunogenicity-Related AEs – MedDRA Search – Phase 3a Pool, Placebo Pool and PIONEER 6 – On-Treatment

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	129	(2.9)	139	2.9	98	(4.6)	118	5.5
SAEs	3	(<0.1)	3	<0.1	2	(0.1)	2	0.2
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	31	(1.8)	32	2.2	23	(3.5)	28	6.2
SAEs	0				2	(0.3)	2	0.5
	N	(%)	E	R	N	(%)	E	R
PIONEER 6								
Number of subjects	1591				1592			
Exposure time (years)	1932				1987			
SAEs	1	(0.1)	1	0	3	(0.2)	3	0

Phase 3a pool: PIONEER 1-5 and 7-10, comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide, placebo. Placebo pool and PIONEER 6 comparator: Placebo
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). Placebo pool: PIONEER 1, 4 and 8. For the pools, the % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R), whereas for the trials, the % and R are unadjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure (R). N: number of subjects with at least one event; PYE: patient-years of exposure; E: number of events; 'Relationship to trial product': as judged by the investigator; seq.: sequelae.

Source: Table 2-90 ISS

Commonly reported PTs in the phase 3a pool were rash, eczema, dermatitis, and urticaria, and they were reported less with semaglutide vs comparator. Notably angioedema was reported more commonly with semaglutide (6 patients, 0.2% vs 1 patient with comparator, <0.1%), and there was one patient reported with anaphylactic reaction in the semaglutide arm vs none in comparator.

SAEs

- Patient no (b) (6): 62 year old female from study 4222 on semaglutide reported angioedema (swelling of lips, tongue, and difficulty breathing) 150 days after starting

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trial drug. The sponsor stated that the patient's history of pollinosis was a confounding factor. Regardless, semaglutide was not discontinued due to this adverse event.

- Patient no (b) (6): 63 year old female from study 4282 on semaglutide presented with hypotension diagnosed as drug-induced shock on trial day 314, which was likely caused by levofloxacin. The patient started taking levofloxacin 2 days prior to the event because of fevers. Semaglutide was temporarily discontinued due to this event which involved prolonged hospitalization.
- Patient no (b) (6): 56 year old female from study 4223 on semaglutide developed anaphylactic reaction due to exposure to pine needles 6-7 weeks after the initiation of the study drug. The event was an SAE. The patient had a previous similar reaction to pine needle exposure.
- Patient no (b) (6): 47 year old female from study 4233 on placebo with SAE allergic dermatitis about 1 month after starting treatment with the study drug. The patent is reported to have had a generalized pruritic rash, but no cardiovascular or respiratory reaction. The trial drug was discontinued.
- Patient no (b) (6): 62 year old male from study 4233 on placebo with SAE of circulatory shock due to pulmonary embolism. The symptoms started with a near-syncope 3 days after inception of the study drug, followed by pulmonary embolism and circulatory shock diagnosis 5 days after trial drug start. The trial product was discontinued due to this event.

AEs:

- Patient no (b) (6): 42 year old male on semaglutide from study 4233 with PT angioedema 79 days after trial drug started, likely due to citrus fruit exposure, not reported as SAE and not leading to discontinuation
- Patient (b) (6): 64 year old female from study 4222 on semaglutide with event of angioedema on day 6 after starting the trial drug. No confounding factors were noted, and the trial drug was discontinued
- Patient (b) (6): 51 year old male from study 4222 on semaglutide with lip swelling documented with PT angioedema on the day of the trial drug start, was considered to be due to ARB or HCTZ or NSAIDS and resolved with antihistamines. The study drug was continued.
- Patient no (b) (6): 53 year old male from study 4223 on semaglutide with lip swelling on trial day 16 coded as angioedema, thought to be due to benazepril which was discontinued. Semaglutide was not discontinued due to this event.
- Patient (b) (6): 68 year old female from study 4257 on semaglutide with swelling of lips and mouth coded with PT angioedema on trial day 368. Semaglutide was not discontinued due to this event.
- Patient (b) (6): on liraglutide from study 4224 with right face angioedema coded with PT angioedema on trial day 22. Liraglutide was not discontinued due to this event.

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It is not clear that there was an increase in angioedema with semaglutide, as AEs of eye edema, facial and lip swelling were reported more with comparator vs semaglutide with events reported in 7 patients on comparator vs 2 with semaglutide. From review of the information available on the angioedema reported with semaglutide, it appears that the events were reported as swelling of various parts of the face but coded as angioedema, and therefore were similar to the events reported with comparator.

Additionally, the data from PIONEER 6 does not support an increase in serious allergic reactions with semaglutide. In PIONEER 6, the MedDRA search for immunogenicity-related events identified a total of 4 SAEs (1 with oral semaglutide and 3 with placebo) with onset during the on-treatment period.

- Patient no (b) (6): 73 year old male on semaglutide was reported with SAE of pharyngeal edema on trial day 173. The patient was hospitalized with neck pain which was thought to be bacterial, and MRI showed retropharyngeal edema. The event led to temporary study drug discontinuation.
- Patient (b) (6): 61 year old female on placebo reported with bronchospasm in the context of left ventricular failure and myocardial infarction on trial day 19. The trial drug was not discontinued due to the event.
- Patient no (b) (6): 72 year old female on placebo reported with anaphylactic reaction after consumption of apple pie approximately 11 months after inception of the study drug. The event led to temporary study drug discontinuation.
- Patient no (b) (6): 70 year old male on placebo reported with angioedema on trial day 101. The patient also had the following as confounders: left submandibular adenitis, allergy to penicillin, and was on perindopril for hypertension. The study drug was discontinued due to the event.

<u>Anti-semaglutide antibodies</u>

In PIONEER 1–5 and 9, anti-semaglutide antibody formation was low; a total of 14 patients (corresponding to 0.5% of patients with antibody assessment in PIONEER 1–5 and 9) tested positive for anti-semaglutide antibodies at any time point post-baseline

Out of the 14 patients, 4 patients were positive at more than one visit post-baseline

- 2 patients with treatment induced anti-semaglutide antibodies tested positive for anti-semaglutide antibodies at 2 or 3 additional visits post baseline but not at the follow-up visit. In both patients the antibody response was transient and disappeared after 14 weeks of treatment.
- 2 patients with pre-existing (before start of dosing) antibodies tested positive, at additional 1 or 2 visits during the treatment period (week 4, and weeks 4 and 8, respectively) and at the follow-up visit. The level of anti-semaglutide antibodies in the two patients were highest at baseline, decreased during treatment and were at the lowest level at follow-up.

Reference ID: 4494748

Six patients on oral semaglutide had a sample collected due to suspicion of severe acute hypersensitivity. All samples collected were tested negative for anti-semaglutide IgE antibodies and anti-semaglutide binding antibodies.

Reviewer comment: There is no evidence that semaglutide causes immunogenicity related AEs, and the anti-semaglutide antibody formation was low.

8.5.5. Creatine Kinase

In the phase 2 dose-finding trial, several patients had CK levels >ULN, including 2 patients treated with oral semaglutide with CK >10xULN (one of whom co-reported an SAE of rhabdomyolysis).

Increases in CK were evaluated, and if levels were >10X ULN, this was to be reported as an AE, and required additional data collection.

In the phase 3a pool, ratio to baseline levels of CK were stable over time and similar with oral semaglutide (0.97) and comparator (1.00) at the end of treatment.

Table 130 Creatine Kinase (U/L) – Categorical Summary of Maximum Post-Baseline Values – Phase 3a Pool and Placebo Pool – On-Treatment

	Oral sema N (Adj.%)	Comparator or Placebo N (Adj.%)
Phase 3a pool		
Number of subjects	4116	2236
N	4028	2186
Low (<LLN)	11 (0.3)	5 (0.2)
Normal	2797 (70.6)	1504 (68.4)
High (>ULN)	1220 (29.1)	677 (31.5)
>2x ULN	306 (7.1)	154 (7.1)
>3x ULN	112 (2.7)	61 (2.8)
>5x ULN	32 (0.8)	21 (1.0)
>10x ULN	7 (0.2)	7 (0.4)
Placebo pool		
Number of subjects	1519	665
N	1484	650
Low (<LLN)	4 (0.3)	1 (0.2)
Normal	1032 (70.4)	435 (66.8)
High (>ULN)	448 (29.3)	214 (33.1)
>2x ULN	106 (6.7)	47 (7.2)
>3x ULN	42 (2.7)	17 (2.6)
>5x ULN	11 (0.7)	8 (1.2)
>10x ULN	3 (0.2)	2 (0.3)

Phase 3a pool: PIONEER 1-5 and 7-10, Comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide, placebo. Comparator for Placebo pool: Placebo. Placebo pool: PIONEER 1, 4 and 8.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). The maximum value from all post-baseline observations in the observation period was used.
N: number of subjects contributing to the summary statistic; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects; LLN: lower limit of the normal; ULN: upper limit of the

Reference ID: 4494348

Source: Table 2-93 ISS

There was no dose-response of oral semaglutide for the proportion of patients with maximum postbaseline CK levels >ULN, or in the number of patients with maximum post-baseline CK levels of >10xULN in PIONEER 3 or the placebo dose pool.

In PIONEER 6, mean CK levels were stable over time and similar across treatment groups. The proportions of patients with CK levels above the normal range at the end of trial were similar for oral semaglutide and placebo. A total of 6 patients in the oral semaglutide group and 4 patients in the placebo group had transient increases in CK to values >10xULN.

Across PIONEER 1−10, 3 SAEs of rhabdomyolysis (PT) were reported in 3 patients (2 with oral semaglutide and 1 with placebo). The proportion of patients with AEs of blood creatine phosphokinase increased was similar with oral semaglutide (1.5%) vs comparator (1.4%) in the phase 3a pool. In the placebo pool, an imbalance was seen with oral semaglutide vs placebo (1.3% vs 0.6%).

In PIONEER 6, 2 non-serious AEs leading to premature trial product discontinuation were reported as blood creatine phosphokinase increased (PT), 1 with oral semaglutide and 1 with placebo.

In conclusion, despite some numeric imbalance, the totality of data from the phase 3 trials with oral semaglutide does not appear to suggest any increased risk of increased CK or rhabdomyolysis with semaglutide.

8.5.6. Hypovolemia

Hypovolemia may be a safety issue due to the GI AEs associated with all GLP-1 RAs. The addition of SGLT2i to GLP-1 RAs can further increase the risk of hypovolemia.

In the phase 3a pool, events of potential hypovolemia were marginally more common with semaglutide vs comparator. The preferred terms are presented in the table below.

Table 131 Hypovolemia MedDRA Search Phase 3a Pool, On-Treatment

Preferred term	Semaglutide	Comparator
	N=4116	N=2236
Fall	41 (1%)	20 (0.9%)
Syncope	11 (0.3%)	1 (<0.1%)
Hypotension	13 (0.3%)	7 (0.3%)
Shock	1 (<0.1%)	1 (<0.1%)

Source: Reviewer generated using JReview, ISS datasets ADAE and ADSL

Reference ID: 4494748

In the phase 3a pool, 160 patients were on a combination of GLP1RA and SGLT2i. In this subpopulation, only one event of hypovolemia was identified, in a patient on semaglutide 14 mg.

The SAEs of potential hypovolemia were balanced in PIONEER 6, as seen below. 165 patients (10.4%) were on both oral semaglutide and SGLT-2i's at baseline and an additional 71 patients (4.5%) on oral semaglutide initiated SGLT-2i treatment during the in-trial period. Amongst these 236 patients, one patient reported an SAE of hypovolemia while using an SGLT-2i in combination with oral semaglutide (syncope).

Table 132 Hypovolemia MedDRA Search SAEs PIONEER 6, On-Treatment

Preferred term	Semaglutide	Comparator
Fall	6	11
Syncope	7	4
Hypotension	5	4

Source: Reviewer generated using JReview, ISS datasets ADAE and ADSL

8.6.4 Month Safety Update

This safety update includes new or updated safety data reported by May 3, 2019:

- Completed trials: New or updated deaths, SAEs and pregnancies reported between February 18, 2019 and May 3, 2019 were included from the 10 completed phase 3a trials.
- Ongoing trials: All deaths, SAEs and pregnancies from the 3 ongoing trials (2 clinical pharmacology trials and PIONEER 7 extension trial) were included from FPFV to May 3, 2019.
- Nonclinical studies: No new nonclinical data since the original ISS cut-off date (November 2, 2018)

No deaths or pregnancies have been reported in this safety update.

<u>SAEs</u>

Completed trials

- One new SAE was reported which originated from the main phase of PIONEER 7 (osteoarthritis).
- One SAE (a neoplasm) was updated from not recovered to recovering (PIONEER 6).

Both SAEs were reported for patients on oral semaglutide 3 mg.

Ongoing trials

Reference ID: 4494748

A total of 48 SAEs were reported by 32 patients in the 3 trials that were ongoing from FPFV to May 3, 2019. The majority of the SAEs (46 of 48) were reported by 30 patients in the PIONEER 7 extension trial.

Table 133 Overview of Blinded SAEs – Trials 4248, 4427 and P7 4257 Ext – SAS

	4248				4427				P7 4257 ext			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	15				105				381			
Exposure time (years)	10				13				418			
Total number of events	1	(6.7)	1	10	1	(1.0)	1	8	30	(7.9)	46	11
Severity												
Severe	1	(6.7)	1	10					10	(2.6)	13	3
Moderate					1	(1.0)	1	8	19	(5.0)	20	5
Mild									8	(2.1)	13	3
Outcome												
Not recovered									4	(1.0)	6	1
Recovered with seq.	1	(6.7)	1	10								
Recovering					1	(1.0)	1	8	2	(5)	3	1
Recovered									27	(7.1)	37	9
Action to trial product												
Drug withdrawn	1	(6.7)	1	10								
Not Applicable					1	(1.0)	1	8				
Missing									30	(7.9)	46	11
Relatedness												
Possible	1	(6.7)	1	10					2	(5)	3	1
Unlikely					1	(1.0)	1	8	28	(7.3)	43	10

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 exposure (trials 4248 and 4427) and events per 100 years of observation (trial 4257-EXT)
4257-Ext: In-trial period calculated for extension part only, including subjects in the sustainability part of the trial. 4248, 4427: on-treatment period
Subcategories with no events are not included in the table.
Source: Table 2-1 4MSU

The rate of SAEs was similar to that reported with oral semaglutide in the T2DM NDA, and each SAE preferred term was reported by few patients. Cardiac disorders were the most frequently reported SAEs by SOC in the 3 ongoing trials and this was consistent with what was reported with both oral semaglutide and comparators in the phase 3a pool and with oral semaglutide and placebo in PIONEER 6 of the oral semaglutide T2DM NDA.

8.7. Safety Analyses by Demographic Subgroups

The potential impact of various factors (demographic parameters) on the safety profile of semaglutide) was investigated based on the phase 3a pool. These factors included sex, baseline age, race, ethnicity, baseline CV history, baseline renal function (eGFR), geographic region, and

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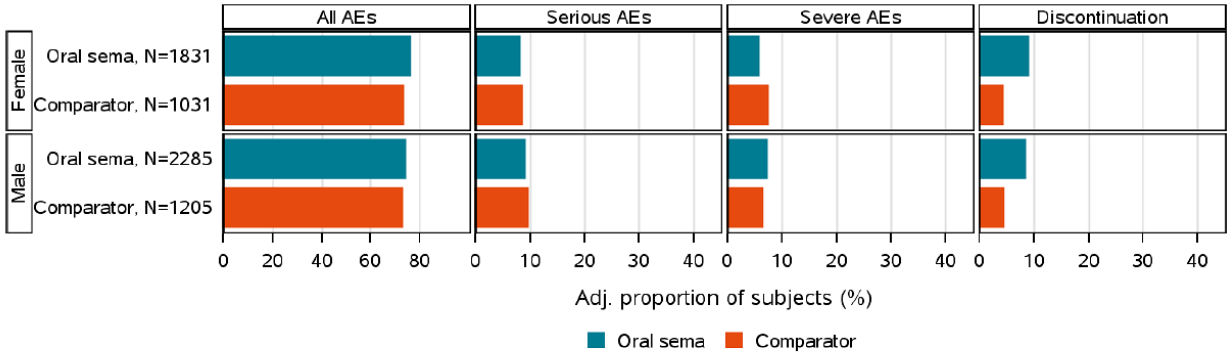
antidiabetic background medication.

8.7.1. Sex

The exposure by sex was balanced in the phase 3a pool for both treatment groups. The proportion of female vs male patents with AEs, and SAEs were comparable for both treatment groups.

Figure 42 AE Overview by Sex – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-1 ISS

When looking at preferred terms reported in >5% of patients for either sex, it appears that gastrointestinal AEs (nausea, diarrhea, constipation, vomiting, dyspepsia, abdominal pain) were more common in women vs men when treated with semaglutide. This may be due to higher exposure due to the potential lower body weight in women.

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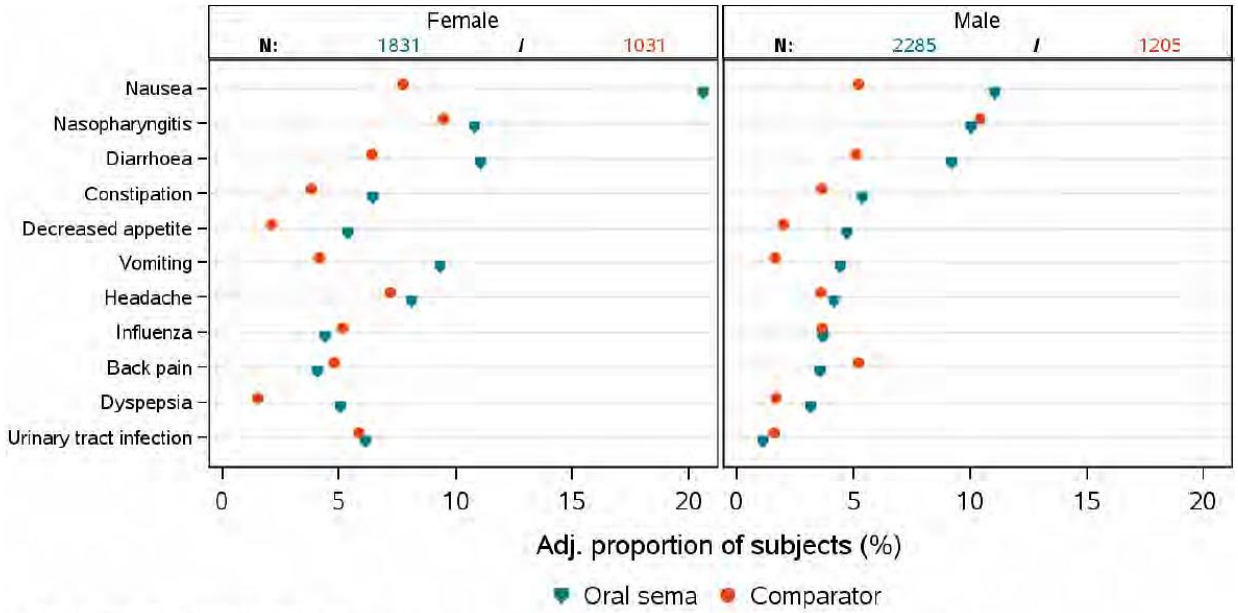
Figure 43 AEs by Sex and PT – Most Frequent (>=5%) – Dot Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
Sorted in descending order by preferred term based on the proportion of subjects with at least one event in the oral semaglutide group within the category with the highest number of subjects in the oral semaglutide group.
N: number of subjects; Adj. The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-2 ISS

8.7.2. Age

The trial population was evaluated based on baseline age as follows:

- Age <65 years
- Age ≥65 years
- Age ≥75 years

Exposure by age and treatment group is outlined below. Most patients were between ages of 18 and 65.

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Table 134 Number of Patients by Age Groups – Phase 3a Pool – On-Treatment

	Oral sema		Comparator	
Subjects and exposure	N	PYE	N	PYE
18 <= years < 65	2887	3136	1564	1670
65 <= years	1229	1243	672	664
75 <= years	199	175	120	102

Phase 3a pool: PIONEER 1-5 and 7-10. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. N: number of subjects; PYE: patient-years of exposure

Source: Table 5-2 ISS

In the phase 3a pool, the proportion of patients with AEs and SAEs were overall comparable across the three age groups with oral semaglutide vs comparator. The proportion of elderly patients ≥75 years with SAEs was slightly higher with oral semaglutide vs comparator, whereas the proportion of elderly patients ≥75 years with severe AEs was lower with oral semaglutide vs comparator.

The proportion of patients with oral semaglutide who had AEs leading to premature trial product discontinuation increased with age, and while a similar tendency was seen with comparator, the differences between age groups were larger with oral semaglutide than with comparator.

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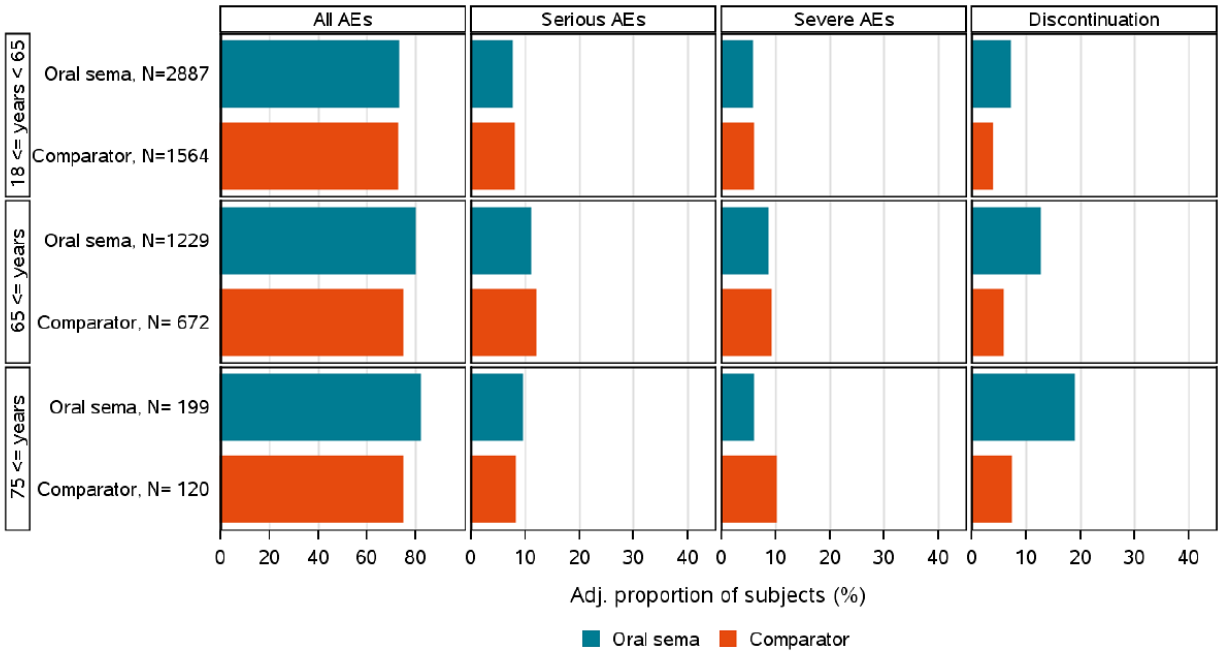
Figure 44 AE Overview by Age Groups – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-3 ISS

The most frequent preferred terms (≥5%) are shown below by age group. It does appear that older patients have an increase incidence of gastrointestinal AEs on semaglutide when compared to younger patients.

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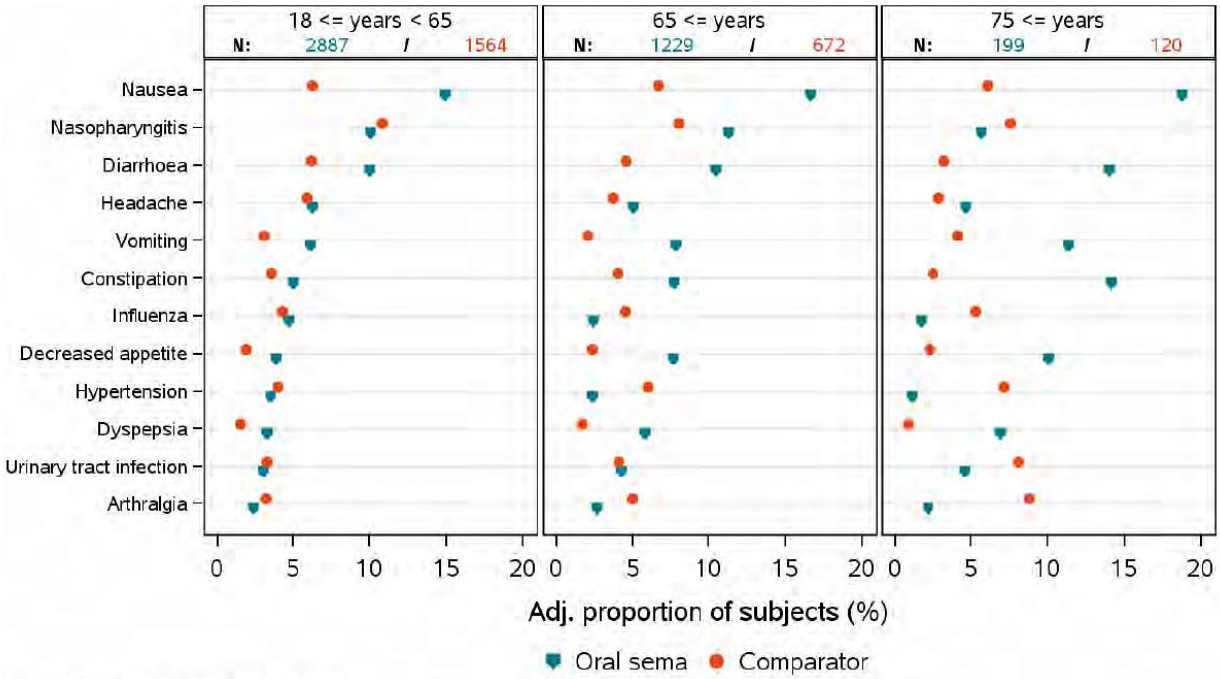
Figure 45 AEs by Age Groups and PT – Most Frequent (>=5%) – Dot Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
Sorted in descending order by preferred term based on the proportion of subjects with at least one event in the oral semaglutide group within the category with the highest number of subjects in the oral semaglutide group.
N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-4 ISS

Although not represented above, weight decrease and falls were more common in semaglutide in patients over the age of 65 compared to patients below the age of 65, although the event numbers are small. Evaluation of the information available for the fall events in patients above the age of 75 does not suggest hypoglycemia as a cause, although it is notable that the patients above the age of 75 were mainly from trials where insulin and/or sulfonylureas were allowed as background medications (PIONEER 3, 5, and 8).

Table 135 Weight Decrease and Fall Preferred Terms by Age Group and Treatment Arm, Phase 3a Pool

	Oral semaglutide N (Adjusted %)	**Comparator N (Adjusted %)**
Weight decrease		
18 to <65	19 (0.7)	2 (0.1)
>65	18 (1.3)	2 (0.2)
>75	4 (1.6)	0

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Fall		
18 to <65	14 (0.5)	10 (0.6)
>65	27 (2.4)	10 (1.4)
>75	7 (3.5)	1 (1.2)

Source: Excerpted from Table 7.7.10 ISS

8.7.3. Race

The trial population was divided into subgroups by race as follows:

- White
- Asian
- Black/African-American
- Other (American Indian, Alaska Native, Native Hawaiian, Pacific Islander)
- Not applicable

As most patients were white for the key efficacy trials, the data on other racial subgroups should be interpreted with caution. Exposure by race is presented in the table below.

Table 136 Number of Patients by Race – Overview – Phase 3a Pool – On-Treatment

	Oral sema		Comparator	
Subjects and exposure	N	PYE	N	PYE
White	2579	2724	1562	1608
Black or African American	248	271	146	150
Asian	1115	1183	431	464
Other	81	93	42	50
Not applicable	93	107	55	63

Phase 3a pool: PIONEER 1-5 and 7-10. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. N: number of subjects; PYE: patient-years of exposure

Source: Table 5-3 ISS

No major differences were observed regarding AEs, SAEs, and AEs leading to discontinuation between the racial subgroups in the phase 3a pool.

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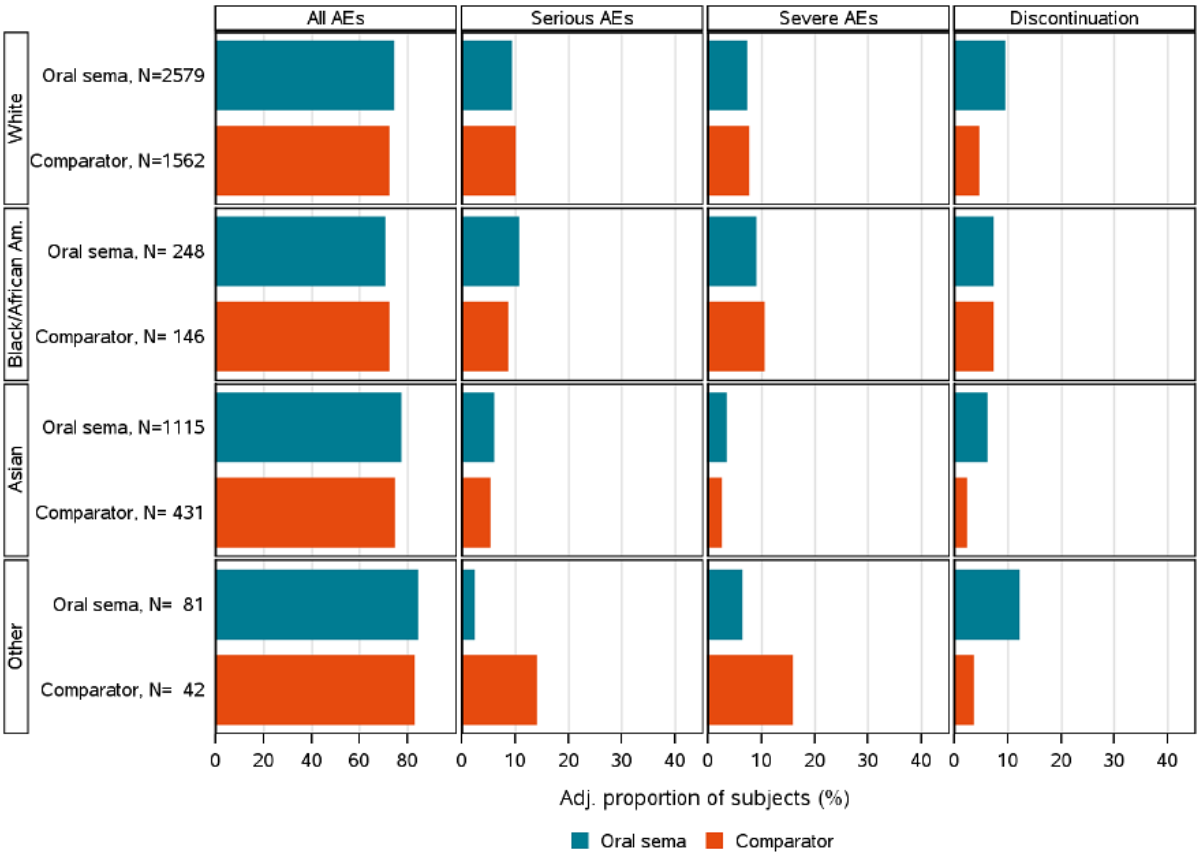
Figure 46 AE Overview by Race – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Am.: American;
Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-5 ISS

The applicant noted that

- For blood creatine phosphokinase increased (PT), a treatment difference was observed with oral semaglutide vs comparator (1.3% vs 0.5%) only in the Asian subgroup
- For weight decreased (PT), the treatment difference was most pronounced in the Asian subgroup

In conclusion, semaglutide safety does not appear to be affected by the racial subgroup based on the available data, with the caveat that the great majority of patients in clinical trials were white.

8.7.4. Ethnicity

The trial population was divided into subgroups by ethnicity as follows:

- Not Hispanic/Latino

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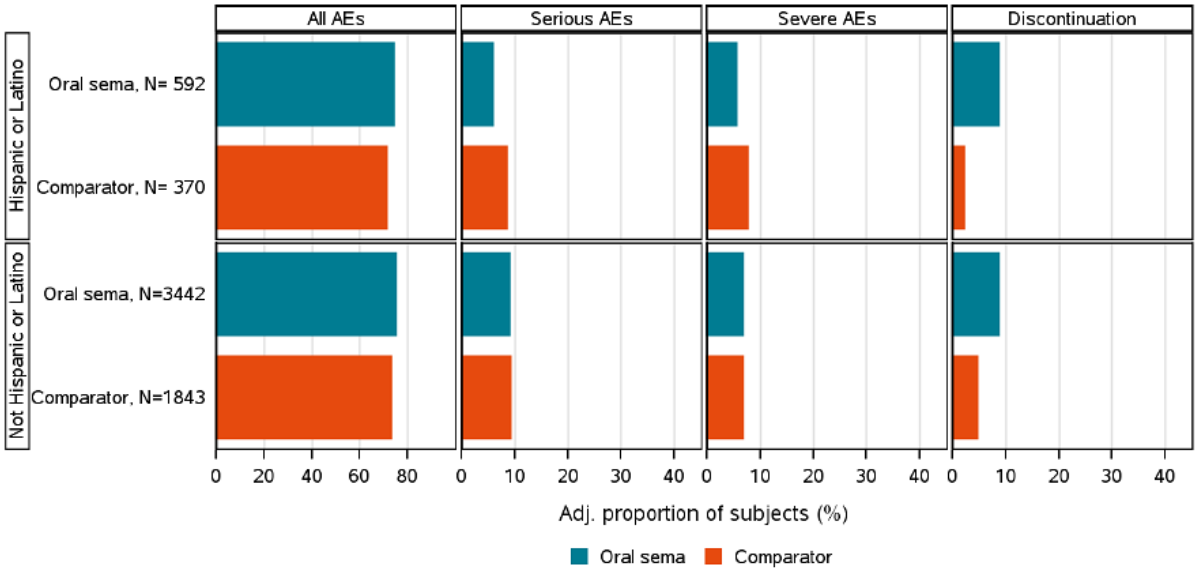
- Hispanic/Latino

Most patients in the phase 3a pool were non-Hispanic/Latino.

Figure 47 AE Overview by Ethnicity – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-7 ISS

For the following SOCs and/or PTs, treatment differences for oral semaglutide vs comparator were more pronounced among patients of Hispanic/Latino vs non-Hispanic/Latino ethnicity

- Diarrhea (PT): The treatment difference was more pronounced among the patients of Hispanic/Latino than non-Hispanic/Latino ethnicity
- Diabetic retinopathy (PT): A small treatment difference was present among the patients of Hispanic/Latino ethnicity (4.1% vs 1.9%), but not among the non-Hispanic/Latino patients (2.9% vs 3.1%)

8.7.5. Weight

The trial population was divided by the applicant into subgroups by baseline body weight as follows:

- <70 kg
- 70–<90 kg
- 90–<110 kg
- >110 kg

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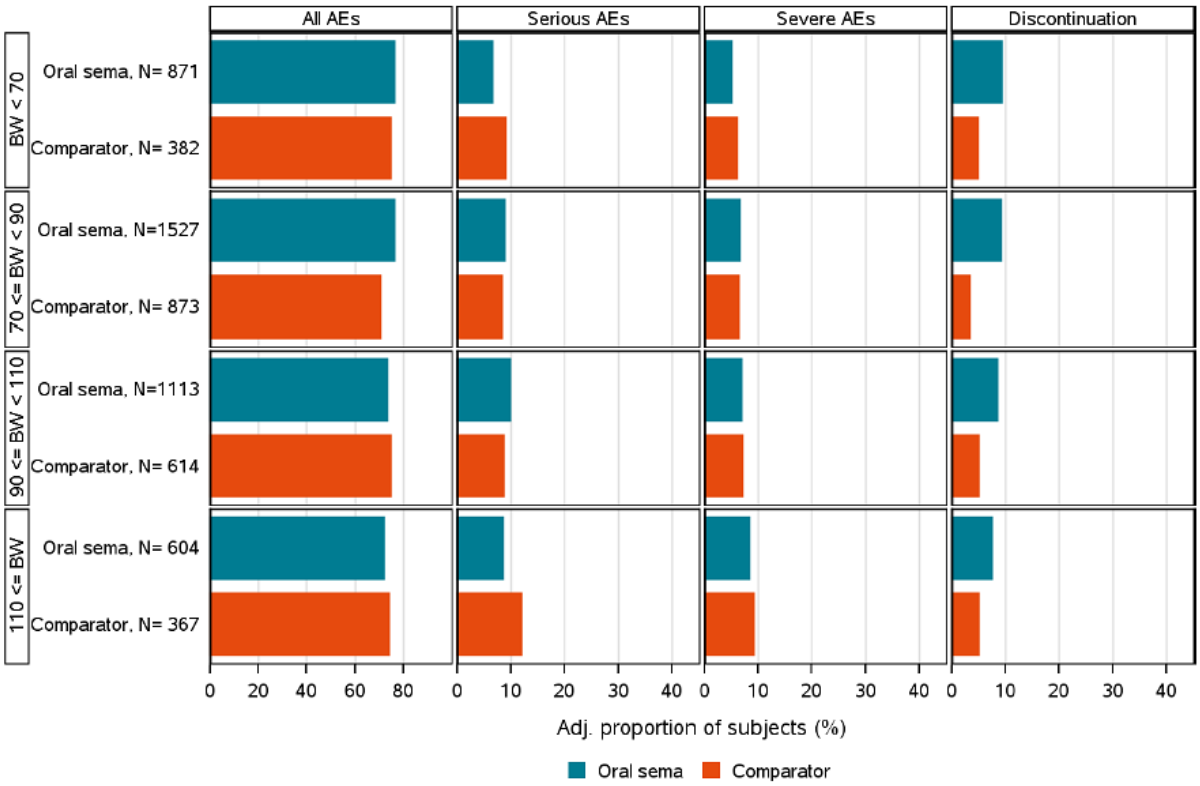
Figure 48 AE Overview by Body Weight Groups – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
BW: body weight; 'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-9 ISS

While overall there were no major differences between the weight subgroups, the applicant noted the following:

- Gastrointestinal disorders SOC: treatment difference (oral semaglutide vs comparator) was generally most pronounced in the <70 kg and 70–<90 kg subgroups (driven by PTs vomiting, constipation, abdominal discomfort).
- Decreased appetite (PT): An inverse correlation to body weight was observed with oral semaglutide, but not with comparators.
- Weight decreased (PT): An inverse correlation to body weight was observed with oral semaglutide, but not with comparators.

These differences may be due to higher exposure in patients with lower weight.

8.7.6. Baseline renal function

The trial population was divided into subgroups by baseline renal function (based on estimated eGFR clearance according to the MDRD equation) as follows:

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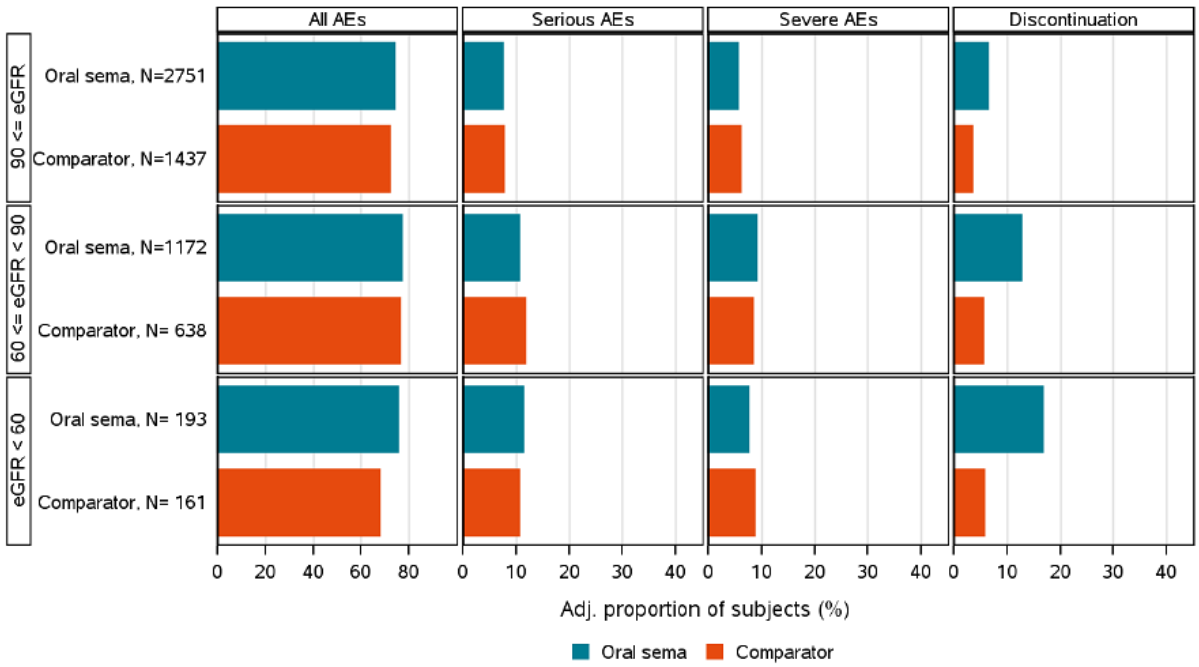
- Normal renal function [≥90 mL/min per 1.73 m2]
- Mild renal impairment [60−89 mL/min per 1.73 m2]
- Moderate renal impairment [<60 mL/min per 1.73 m2]

Patients with severe renal impairment (15−30 mL/min per 1.73 m2) or end-stage renal disease (<15 mL/min per 1.73 m2) were excluded from all trials.

Figure 49 AE Overview by Renal Function – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
The renal function categories are based on the eGFR as per CKD-EPI. eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-13 ISS

For the following SOCs and/or PTs, oral semaglutide-related treatment differences were more pronounced in patients with renal impairment than in patients with normal renal function:

- Gastrointestinal disorders SOC (driven in part by PTs nausea, vomiting, dyspepsia)
- Decreased appetite (PT)
- Investigations SOC (driven in part by PTs weight decreased, pancreatic enzymes increased)
- Renal and urinary disorders SOC

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Additionally, PIONEER 5 was a dedicated trial comparing oral semaglutide 14 mg to placebo in patients with moderate renal impairment. In this trial, 324 patients with moderate renal impairment were randomized to receive either oral semaglutide (163 patients) or placebo (161 patients). Overall, oral semaglutide was safe and well tolerated in patients with moderate renal impairment. A greater proportion of patients treated with oral semaglutide vs placebo had AEs (73.6% vs 65.2%), but there was no difference in the proportions of patients with SAEs (10.4% vs 10.6%). AEs leading to premature trial product discontinuation were reported in a higher proportion of patients with oral semaglutide vs placebo (14.7% vs 5.0%). This was mainly due to GI AEs, which were reported by a larger proportion of patients with oral semaglutide than placebo (44.8% vs 16.8%)

8.7.7. Geographic region

The trial population was divided to subgroups by region as follows:

- Europe
- North America (United States, Canada)
- South America
- Asia
- Africa

Most patients were from Europe, North America, and Asia, with few patients from South America and Africa.

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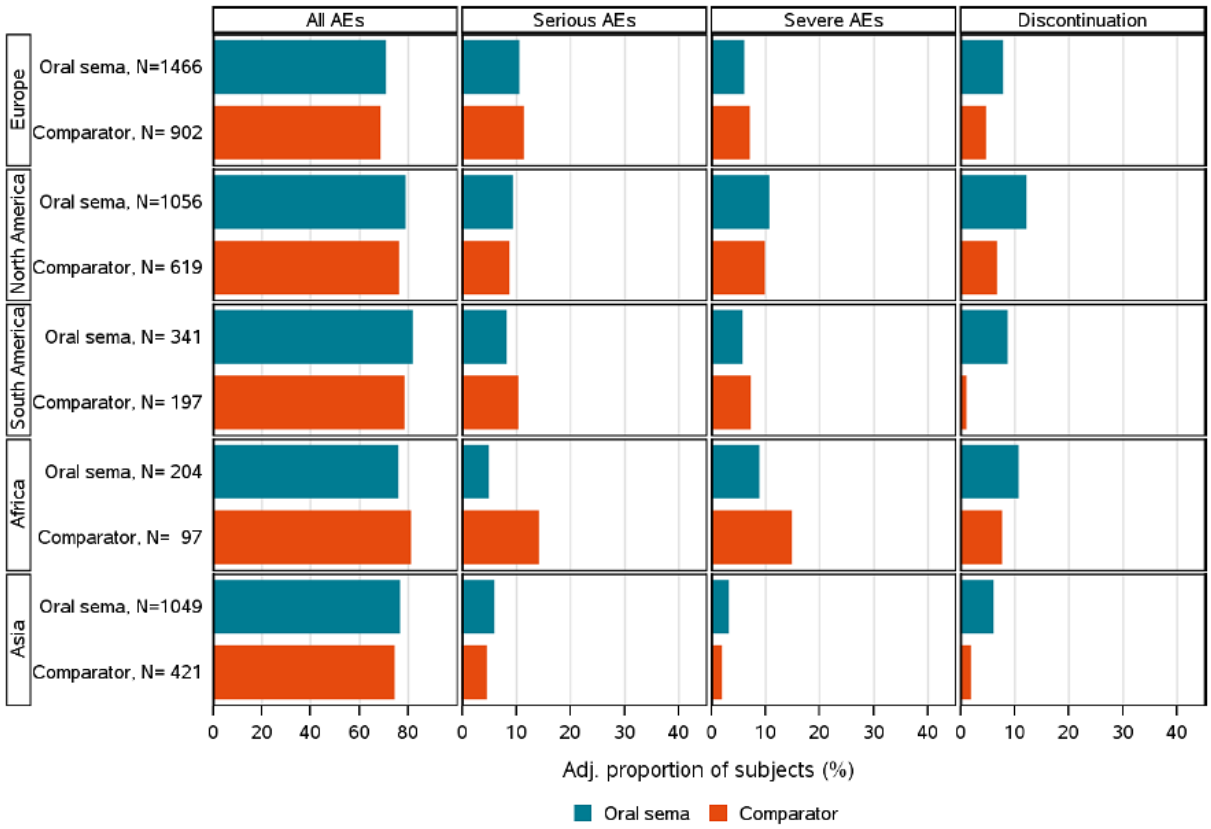
Figure 50 AE Overview by Region – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

Source: Figure 5-19 ISS

The following SOCs and PTs were associated with differences between the regional subgroups:

- Gastrointestinal disorders SOC: the overall treatment difference was most pronounced in North America and South America, driven by PTs nausea, diarrhea, constipation and gastroesophageal reflux disease
- Headache (PT): a treatment difference was observed with oral semaglutide vs comparator only in Africa

In conclusion, while the treatment difference for specific PTs was more pronounced in specific subgroups, the differences were small and do not necessarily impact the overall safety profile of semaglutide.

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8.7.8. Antidiabetic background medication

The trial population was divided into subgroups by antidiabetic background medication as follows:

- None
- Metformin only
- SU±metformin
- SGLT-2 inhibitors±metformin
- Insulin±OADs
- Other

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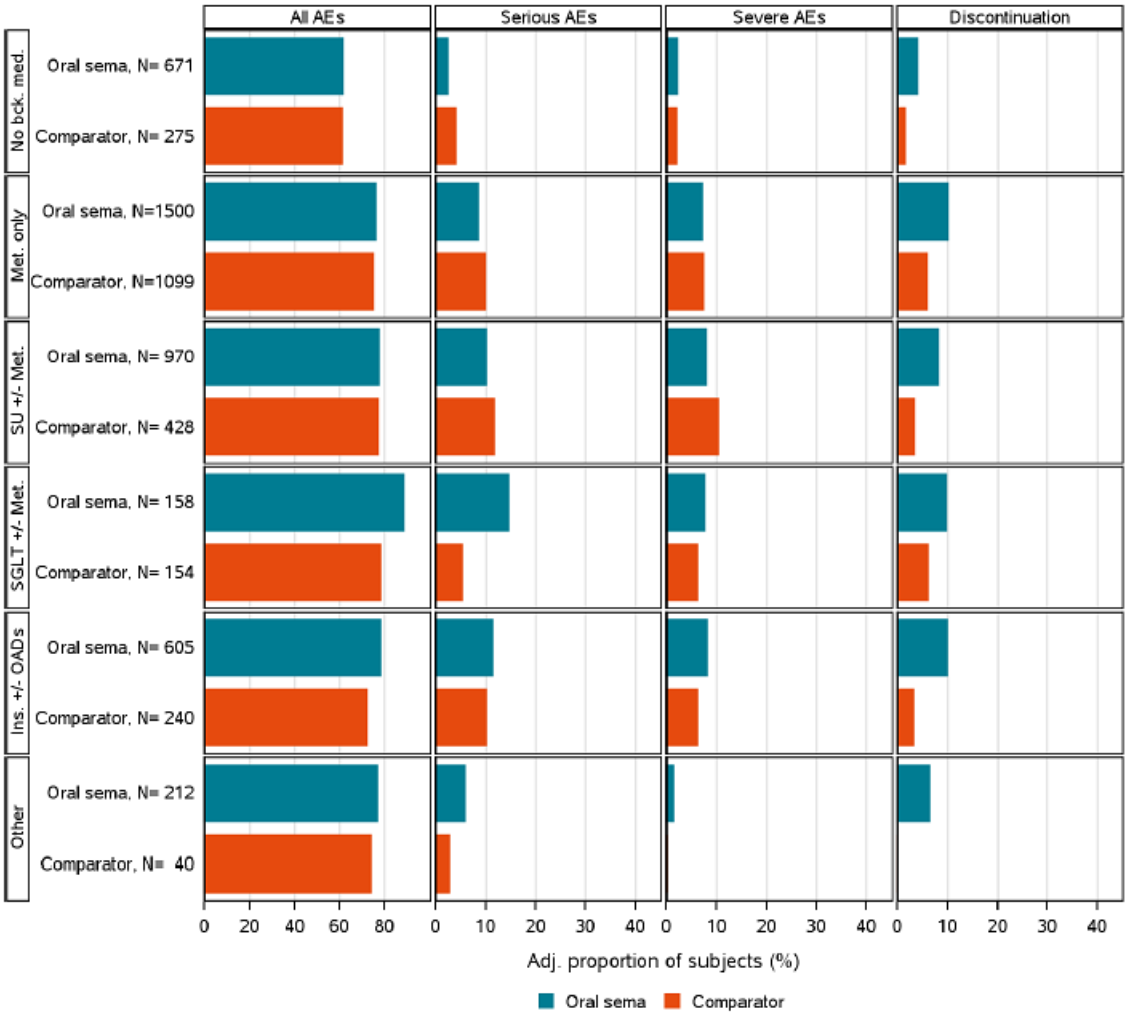
Figure 51 AE Overview by Anti-Diabetic Background Medication – Bar Plot – Phase 3a Pool – On-Treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%); Met.: Metformin; SU: sulphonylurea; SGLT: sodium-glucose cotransporter-2 inhibitor; Ins.: insulin; OAD: oral antidiabetic drug.

Source: Figure 5-21 ISS

The following SOCs and PTs were associated with differences across the anti-diabetic background medication subgroups:

- Gastrointestinal disorders SOC: There was a treatment difference in all subgroups; it was most pronounced in the insulin±OADs subgroup, driven by PTs nausea, diarrhea, vomiting and constipation
- Nervous system disorders SOC: A treatment difference was present in the SGLT-2i±metformin subgroup, driven by headache (PT)

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- Decreased appetite (PT): A treatment difference was most pronounced in the subgroup taking insulin±OADs as anti-diabetic background medication
- Investigations SOC: A treatment difference was mainly present in the insulin±OADs subgroup, driven by lipase increased (PT)
- Renal and urinary disorders SOC: A more pronounced treatment difference was present in the SGLT-2i±metformin subgroup compared to the other subgroups
- Hepatobiliary disorders SOC: A small treatment difference was present in the SGLT-2i±metformin and insulin±OADs subgroups

The applicant concludes that, although minor differences were observed between the subgroups, the overall safety profile of semaglutide was not substantially affected by different antidiabetic background medications. While I generally agree with the applicant assessment, some differences were seen in the evaluation of hypoglycemia, however, this is discussed separately in section 8.4.4.

8.8. Specific Safety Studies/Clinical Trials

PIONEER 6 is a CVOT of short duration which was conducted to rule out unacceptable increase in CV risk with semaglutide pre-marketing. No increase in CV risk with semaglutide was observed pre-marketing.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

As noted in the Pharmacology and Toxicology review, the administration of semaglutide once daily by subcutaneous injection to mice and rats for two years resulted in an increased incidence of thyroid C-cell adenoma and combined C-cell adenoma and carcinomas in all treated groups. Thyroid neoplasms occurred at the clinical exposure in rats, and at slightly higher than the clinical exposure in mice (2X and 5X in female and males, respectively). The incidence of C-cell carcinomas was statistically significant increased in male rats at ≥0.01 mg/kg/day (0.4X the clinical exposure). A numerical increase in C-cell carcinoma was noted in mice. Proliferative C-cell changes in rodents are a known class effect of long-acting GLP-1R agonists and have been reported in rodent carcinogenicity studies with liraglutide, exenatide, lixisenatide, and dulaglutide. Based on the mechanistic data available for semaglutide and other GLP-1R agonists, the absence of GLP-1Rs on normal monkey or human thyroid C-cells, and the absence of changes in calcitonin levels or proliferative lesions in chronic monkey studies, the applicant believes that the human relevance of rodent C-cell tumors is low. However, it is currently unclear whether a lack of calcitonin secretion in non-human primates and humans is a valid indicator that a mitogenic signal is not being initiated in these non-rodent species. Therefore, the human relevance of C-cell tumors is unknown. Regardless, the potential risk of C-cell tumors is captured in the prescribing information for all GLP-1Ras.

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Information regarding SNAC from the Pharmacology and Toxicology review by Dr Elena Braithwhite is outlined below:

- In a 2-year carcinogenicity study in Sprague Dawley rats, oral doses of 75, 200 or 500 mg/kg/day (males: 1-, 3-, or 10-fold the clinical AUC0-24h, females: 0.2-, 0.6-, or 7-fold the clinical AUCmax) did not result in neoplastic findings that were related to oral SNAC exposure.
- Increased mortality was observed in female rats receiving 200 or 500 mg/kg/day starting at ~ Week 80 and SNAC dosing was stopped for the remainder of the study at Week 103 for the 200 mg/kg/day group and at Week 99 for the 500 mg/kg/day group. No consistent cause of death was identified at the histopathological examination. Although the typical clinical signs associated with SNAC toxicity were not noted, relationship of mortality to SNAC exposure cannot be excluded.
- In a 26-week carcinogenicity study in rasH2 mice, oral doses of 0, 30, 100, or 300 (males: 0.01-, 0.06-, or 0.3-fold the clinical AUC0-24h, females: 0.04-, 0.1-, or 0.7-fold the clinical AUC0-24h) did not result in neoplastic findings that were related to oral SNAC exposure.

Please see Pharmacology and Toxicology review by Dr Elena Braithwhite for details.

8.9.2. Human Reproduction and Pregnancy

A total of 8 pregnancies were reported in six trials of the oral semaglutide clinical development program; 7 in women treated with oral semaglutide and 1 in a woman treated with sitagliptin.

In all cases, the fetuses were exposed to oral semaglutide for a short time during the first trimester, until the pregnancy was discovered and trial product discontinued. No congenital anomalies were reported in children of women treated with oral semaglutide. For one patient treated with oral semaglutide an SAE (PT: umbilical cord compression) and 2 non-serious AEs (PTs: premature baby, jaundice neonatal) related to the baby were reported.

Table 137 All Pregnancies Reported in the Oral Semaglutide Clinical Development Program

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Actual treatment	Subject ID	Baseline age/BMI	Exposure of foetus (approx. weeks+day)[a]	Outcome of pregnancy
Oral semaglutide				
Oral semaglutide 3 mg	(b) (6)	32/35.7	8+2	Unknown (lost to follow up)
Oral semaglutide 7 mg		41/44.4	9+6	Healthy child
Oral semaglutide 7 mg		26/46.6	11+0	Elective abortion not related to AEs in the foetus
Oral semaglutide 14 mg		31/29.4	7+4	Healthy child
Oral semaglutide 14 mg		37/22.2	3+3	Healthy child
Oral semaglutide 14 mg		33/52.6	4+3	Healthy child
Oral semaglutide 40 mg		29/35.6	8+6	Healthy child
Comparators				
Sitagliptin 100 mg	(b) (6)	25/36.3	8+3	Child with 2 congenital anomalies (PTs: dacryostenosis congenital; chordee)

Notes: a: Approximate period of exposure includes a washout period of five weeks for subjects treated with oral semaglutide.
Source: Table 5-12 ISS

8.9.3. Pediatrics and Assessment of Effects on Growth

Not applicable. There is no data on semaglutide in pediatric patients.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Limited data are available regarding overdoses of semaglutide. Expected adverse events in connection with an overdose of semaglutide are GI AEs and hypoglycemia (especially if combined with SU and insulin).

In the phase 3a pool, AEs of overdose (preferred term: overdose, accidental overdose) occurred in ≤0.7% of patients, with no differences between the treatment groups. Only one was an SAE, with placebo, and it was an accidental overdose of combination crack/cocaine and alcohol. No events of hypoglycemia were reported within 7 days of any semaglutide overdose.

One SAE of accidental overdose was identified from PIONEER 6, where one patient took 75 units of Humalog insulin instead of Tresiba.

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8.9.5. Safety Concerns Identified Through Postmarket Experience

Not applicable. There is no postmarketing experience with oral semaglutide. Subcutaneous semaglutide was approved in 2018. No new safety concerns have been identified in the postmarketing experience to date.

8.9.6. Expectations on Safety in the Postmarket Setting

Semaglutide is intended to be prescribed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. No new safety concerns have been identified from review of the clinical data, in addition to the safety concerns with the subcutaneous semaglutide and the GLP-1 RA class of drugs.

8.9.7. Additional Safety Issues From Other Disciplines

Because of issues pertaining of potential SNAC concentration in breast milk (observed in animal models, unknown in humans), a postmarketing lactation study was recommended by the Division of Pediatrics and Maternal Health (DPMH) for further evaluation.

8.10. Integrated Assessment of Safety

The safety of oral semaglutide has been studied in 10 phase 3 trials, with over 5000 semaglutide-treated patients, including patients across the T2DM spectrum, from drug-naïve to patients using a variety of background antidiabetics, including metformin, SU, and insulin. The clinical program included a study in patients with renal impairment, and a pre-market cardiovascular outcomes trial which enrolled patients with high CV risk and other diabetes comorbidities.

Overall, the semaglutide safety profile was consistent across the phase 3 studies, and with the known safety profile for GLP1 RAs.

A number of medical events of special interest were pre-defined and captured across all phase 3 trials (based on the information already known with other GLP1 RAs), and some of these events were adjudicated. Additional events based on safety from the development program for oral semaglutide (lactic acidosis, CK elevations) were added to the list of adverse events of interest.

Semaglutide treatment appears to result in treatment discontinuation more frequently vs all comparators, and particularly when compared to placebo. This is mostly due to GI AEs (nausea, vomiting, diarrhea, and preferred terms related to abdominal pain), and it was dose dependent in studies where more than one dose of semaglutide was evaluated.

Deaths and SAEs were balanced with semaglutide vs comparator/placebo in the phase 3a and placebo pools. Cardiac disorders were the most frequently reported SAEs with both oral

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semaglutide and comparators.

As expected with the drug class, GI AEs (nausea, vomiting, diarrhea), reduced appetite and weight decrease and hypoglycemia (when combined with insulin or SU) were adverse drug reactions most commonly reported with semaglutide. GI AEs were mostly reported as mild or moderate, with few events reported as SAEs. Additionally, most of the GI AEs were reported during the uptitration period for oral semaglutide, and the GI AEs with semaglutide did appear to be dose-dependent. While the GI AEs could lead to dehydration and renal impairment, no increase in acute renal events was apparent in the development program. However, this is an issue that will require monitoring in post-marketing setting.

The data do not suggest an increased risk for major adverse cardiovascular events with semaglutide. Deaths were balanced in the phase 3a and placebo pools. Overall MACE events were less frequent with oral semaglutide vs placebo, although superiority was not demonstrated statistically. Events of hospitalization for heart failure were balanced between treatment groups in PIONEER 6.

Renal disorders were reported more frequently with semaglutide vs comparator in the phase 3a pool, but not in PIONEER 6. Acute kidney injury was an adjudicated event in the oral semaglutide clinical program, and events that were confirmed were further categorized as stage 1, 2 or 3. In the phase 3a pool, a marginally higher proportion of patients on semaglutide experienced such events, while the reverse was observed in PIONEER 6, the cardiovascular outcomes trial. Most of the events in the phase 3a pool were reported from PIONEER 5 which was a study in patients with moderate renal impairment. The totality of the evidence does not suggest an increase in renal events with oral semaglutide. Renal function tests were generally stable over the course of the trials, both with semaglutide and with comparator, and no imbalance was seen in renal function outliers. In PIONEER 5, the renal impairment trial, renal function parameters were also stable over time with semaglutide 14 mg and placebo. A higher number of patients on semaglutide had an eGFR value <30 mL/min/1.73m2 with semaglutide (9) vs 5 with placebo, however it is not clear whether this numerical imbalance is due to chance.

As for other GLP-1 RAs, MTC was assessed to be an important potential risk for semaglutide, based on nonclinical data and due to the potential serious clinical consequences and impact on the individual patient as well as on public health. Only one event of medullary microcarcinoma was reported in the clinical development program, and it appears that the pathology was preceding the initiation of semaglutide treatment. Calcitonin levels were monitored during the trials and few patients had elevated calcitonin levels >50 or >100 ng/L.

Cholelithiasis was more frequently seen with semaglutide vs placebo in the placebo pool, but this was not observed in the phase 3a pool or PIONEER 6 where events were balanced between treatment groups. No dose response was observed for semaglutide. Cholecystitis was rare but

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was reported by a larger proportion of patients in the semaglutide arm vs placebo in the placebo pool (4 events with semaglutide vs 0 with placebo). This is in line with safety information reported with other members of the class.

Events of pancreatitis were also adjudicated in the oral semaglutide clinical program. The MedDRA search, and the adjudication, did not identify an imbalance between semaglutide and comparator regarding pancreatitis events. However, a larger number of pancreatitis events on semaglutide were sent for adjudication but not positively adjudicated for reasons that are not entirely clear. Regardless, the number of events is low and could represent, at most, a small numerical imbalance. The risk of pancreatitis is already outlined in the prescribing information for GLP-1RAs. Mean serum amylase and lipase did increase over time with semaglutide, as seen with other members of the drug class, but the outliers were balanced between the treatment groups.

A numerical imbalance in certain malignancies was observed in the phase 3a pool, however these imbalances were not observed in PIONEER 6. Skin, prostate, lung, colorectal, and thyroid cancers were more common with semaglutide vs comparator in the phase 3a pool. It is not clear how such malignancies would be the result of semaglutide treatment over such a short period of time and is therefore likely that these imbalances were due to chance. Most patients had confounding factors, and the number of events was small. Pancreatic cancer events were balanced between the treatment groups in the phase 3a pool and PIONEER 6.

Liver events were balanced between the treatment groups in all pools, and only 2 SAEs of potential drug induced lived injury were identified, one on semaglutide and one on placebo, all with potential confounders. Most liver events were reported with preferred term hepatic steatosis, balanced between treatment groups. Few liver disease SAEs were reported from the entire phase 3 program, and they were generally balanced between the treatment groups except in the placebo pool where 2 SAEs were reported with semaglutide vs none with placebo. Mean levels of liver function parameters were stable over the course of the trials, and outliers were balanced between the treatment groups. Two cases of Hy's law were noted, both in PIONEER 6, one on semaglutide and one on placebo. Again, both had alternative etiologies as explanation for the liver function abnormality. Overall there is no information to suggest a liver safety signal for oral semaglutide.

Severe hypoglycemia, as expected, was rare. Hypoglycemia was balanced between treatment groups in the phase 3a pool, but it occurred at a higher rate with semaglutide vs placebo in the placebo pool, and in the renal impairment trial PIONEER 5. Hypoglycemia with semaglutide occurred more on a background of insulin and/or insulin secretagogues as expected with this drug class. No dose-response was observed for hypoglycemia, likely due to the small number of events.

Semaglutide treatment was associated with an increase in pulse rate which was expected with

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this drug class. Despite some small differences in pulse rate AEs, the body of data does not support an increase in clinical events related to increase in heart rate.

Semaglutide treatment did not have any impact on creatine kinase levels, and the proportion of patients with transient CK elevations was similar between semaglutide and comparator in the phase 3a pool and PIONEER 6.

There were no indications of an immunogenic response against semaglutide as witnessed by low frequencies of anti-semaglutide antibodies (0.5%), with no neutralizing antibodies as well as no IgE's. Furthermore, immunogenicity-related AEs were balanced between treatment groups.

The risk of retinopathy with oral semaglutide was evaluated in light of the increased risk observed with subcutaneous semaglutide. Eye examinations were performed at screening and at the end of treatment for all trials. While marginally more events were identified via MedDRA search with semaglutide vs comparators, the results of the eye examinations did not suggest any difference between semaglutide and comparator. The significance of these findings in such short-term trials is not clear.

Because of the SNAC component of oral semaglutide, and its potential inhibition of electron chain transport, clinical events of lactic acidosis were collected during the trials and adjudicated, and lactic acid levels were monitored in selected trials. Few events of lactic acidosis were confirmed in the phase 3 program, none with placebo, but otherwise generally balanced between semaglutide and comparator. While some events reported with preferred term of lactic acidosis were not confirmed by the EAC, all lactic acidosis events had confounders such as metformin use, infection and renal failure. Semaglutide did not appear to impact lactic acid levels.

In conclusion, no unexpected safety findings were seen with oral semaglutide vs comparator/placebo. The safety profile was generally consistent across sub-groups of sex, age, race, ethnicity, CV history, renal function, region, anti-glycemic background medication.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

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10.1. Prescription Drug Labeling

Labeling is not yet finalized at the time of this review. I will discuss my opinion regarding some information from the prescribing information below.

Section 1 Proposed indication:
TRADENAME is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Reviewer comment: The indication is supported by the efficacy findings

Section 2 Dosage and administration
2.1 Important Administration Instructions

- Instruct patients to take TRADENAME at least 30 minutes before the first food, beverage, or medication of the day with no more than 4 ounces of plain water only [see Clinical Pharmacology (12.3)]. (b) (4) Waiting less than 30 minutes, or taking TRADENAME with food, beverages (other than plain water) or other medications will lessen the effect of TRADENAME by decreasing its absorption. (b) (4)
- Swallow TRADENAME whole. Do not split, crush or chew tablets.

2.2 Recommended Dosage

- Start TRADENAME with 3 mg once daily for 30 days then increase the dose to 7 mg once daily.
- Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose.
- Taking two 7 mg TRADENAME tablets to achieve a 14 mg dose is not recommended.
- If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

Reviewer comment: This is generally reasonable. The details in administration are necessary as the absorption of semaglutide and/or SNAC is highly variable.

Section 5 Warnings and Precautions
Similar to subcutaneous semaglutide.

Reviewer comment: The overall presentation is reasonable. Certain details regarding data presentation with oral semaglutide particularly for events of pancreatitis are under discussion with the applicant.

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Section 6 Adverse reactions
Generally presented as for other members of the class.

Section 8 Use in specific populations – Pregnancy and Lactation
DPMH was consulted to provide input regarding the pregnancy and lactation section in the prescribing information. Based on the currently available clinical and non-clinical data (SNAC present in breast milk in animal studies), DPMH recommended the following language for the highlights of the prescribing information:

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
• Pregnancy: May cause fetal harm (8.1).
• Lactation: Breastfeeding not recommended (8.2).
• Females and Males of Reproductive Potential: Discontinue TRADENAME in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

Please see DPMH review by Dr Jane Liedtka for recommendations for the full prescribing information.

Section 14 Clinical Studies
The applicant proposes to include efficacy data from studies PIONEER 1-5, and 7, 8, including HbA1c, FPG, and weight loss data. Additionally, selected information from PIONEER 6 is to be included in support of no increased CV risk with oral semaglutide.

Reviewer comment: The overall information proposed for inclusion in section 14 of the PI is reasonable. Will ask the applicant to make changes to align the label with other members of the class, such as presentation of weight data in text format, and presenting only data from the main study phase, and not open label study extensions. One major difference from other member of the class pertains to the lactation recommendation (do not breastfeed) and it is due to the uncertainties related to the SNAC component of oral semaglutide. A postmarketing study will be required for clarification.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was deemed to be necessary for semaglutide.

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12. Postmarketing Requirements and Commitments

The review team is recommending the following Post Marketing Requirements:

1) Conduct a 26-week, randomized, double-blind, placebo-controlled parallel group study of the safety and efficacy of Rybelsus (semaglutide) tablets for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 26-week open-label, controlled extension. Background therapy will consist of either metformin, insulin, or metformin plus insulin.
2) Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Rybelsus (semaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Rybelsus (semaglutide).
3) Conduct a milk-only lactation study in lactating women who have received Rybelsus (semaglutide) tablets semaglutide oral tablet therapeutically to assess concentrations of semaglutide and salcaprozate sodium (SNAC) in breast milk using a validated assay.

The following Post marketing Commitments are recommended as well:

4) The assay used to monitor neutralizing activity of anti-drug antibodies is not sensitive. Develop a sensitive assay to assess the neutralizing activity of anti-semaglutide antibodies and its cross-neutralizing effect on native GLP-1.
5) Assess the incidence of neutralizing antibodies to semaglutide and GLP-1 in subjects treated with semaglutide. The samples can be derived from pre-existing clinical studies, but a plan to select the samples should be agreed upon with the Agency.

13. Appendices

13.1. References

NA

13.2. MedDRA Queries used for the safety analyses

MedDRA version 20.1– list of terms within safety focus areas

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HLGT: higher level group term, HLT: higher level term, NEC: not elsewhere classified, NNMQ: Novo Nordisk MedDRA queries, PT: preferred term, SMQ: standard MedDRA queries, SOC: system organ class

1. Gastrointestinal disorders
SOC gastrointestinal disorders, primary events

2. Renal disorders
'SMQ Acute Renal Failure', narrow scope only

3. Hypovolemia
'SMQ: Hypovolemic shock conditions' (narrow scope) + two additional PTs: Hypotension and Syncope'.
Note: this area of interest should only be included for trials having SGLT-2 inhibitors as background.

4. Hepatic disorders
'SMQ Drug related hepatic disorders – comprehensive search', excluding the two sub-SMQs Liver neoplasms, benign (incl cysts and polyps) (SMQ) and Liver neoplasms, malignant and unspecified (SMQ))

5. Gallbladder-related disorders
SMQ: Biliary tract disorders
SMQ: Biliary system related investigations, signs and symptoms
SMQ: Gallbladder related disorders
SMQ: Gallstone related disorders
SMQ: Infectious biliary disorders
Narrow scope for all SMQs.

6. Cardiovascular disorders
Narrow scope only for the following SMQs
1. Central nervous system vascular disorders (SMQ);
2. Ischemic heart disease (SMQ);
3. Cardiac arrhythmias (SMQ);
4. Cardiac failure (SMQ);
5. Cardiomyopathy (SMQ);
6. Embolic and thrombotic events (SMQ) (contains sub-SMQs);
7. Shock (SMQ) (contains sub-SMQs);
8. Torsade de pointes/QT prolongation (SMQ)

7. Pancreatitis
SMQ acute pancreatitis, narrow scope.

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HLT acute and chronic pancreatitis (including primary and secondary terms)

8. Neoplasms
SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) (primary and secondary terms)
SMQ Biliary neoplasms
SMQ Breast neoplasms, malignant and unspecified
SMQ Liver neoplasms, benign (incl cysts and polyps)
SMQ Liver neoplasms, malignant and unspecified
SMQ Malignancies
SMQ Malignant lymphomas
SMQ Oropharyngeal neoplasms
SMQ Ovarian neoplasms, malignant and unspecified
SMQ Premalignant disorders
SMQ Prostate neoplasms, malignant and unspecified
SMQ Skin neoplasms, malignant and unspecified
SMQ Uterine and fallopian tube neoplasms, malignant and unspecified
Broad scope for all the SMQs as well as all PTs in the SOC which have not been included in the SMQs.

9. Malignant neoplasms
SMQ malignant tumors

10. Diabetic retinopathy and related complications includes the following PTs:
Amaurosis
Cystoid macular edema
Diabetic blindness
Diabetic eye disease
Diabetic glaucoma
Diabetic retinal edema
Diabetic retinopathy
Diabetic uveitis
Exudative retinopathy
Macular ischemia
Macular edema
Macular opacity
Macular pseudohole
Maculopathy
Night blindness
Papilledema
Papillophlebitis
Retinal deposits

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Retinal detachment
Retinal exudates
Retinal hemorrhage
Retinal ischemia
Retinal neovascularization
Retinal edema
Retinal pallor
Retinal vascular occlusion
Retinopathy
Retinopathy proliferative
Sudden visual loss
Visual acuity reduced
Visual acuity reduced transiently
Vitreal cells
Vitreous detachment
Vitreous hemorrhage
Vitreous opacities

11. Lactic acidosis
SMQ 'Lactic acidosis' (broad and narrow scope) excluding the PTs 'blood bicarbonate decreased' and 'blood bicarbonate abnormal')

12. Immunogenicity
Anaphylactic reaction (SMQ)
Angioedema (SMQ)
Severe cutaneous adverse reactions (SMQ)
Anaphylactic/anaphylactoid shock conditions (SMQ)
Hypersensitivity (SMQ)
Narrow scope for all SMQs .

13. Rare events
SMQ: Acute renal failure (SMQ), narrow terms only
SMQ: Agranulocytosis (SMQ) narrow terms only
SMQ: Anaphylactic reaction (SMQ) narrow terms only
SMQ: Cardiac arrhythmias (SMQ), broad and narrow
SMQ: Cholestasis and jaundice of hepatic origin (SMQ), broad and narrow terms
SMQ: Guillain-Barre syndrome (SMQ), narrow terms only
SMQ: Hematopoietic cytopenias affecting more than one type of blood cell (SMQ), broad and narrow
SMQ: Hematopoietic leukopenia (SMQ), broad and narrow terms
SMQ: Hematopoietic thrombocytopenia (SMQ), narrow terms only
SMQ: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ),

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narrow terms only
SMQ: Hepatitis, non-infectious (SMQ), broad and narrow terms
SMQ: Severe cutaneous adverse reactions (SMQ), narrow terms only
SMQ: Interstitial lung disease (SMQ) narrow terms only
SMQ: Neuroleptic malignant syndrome (SMQ), narrow terms only
SMQ: Pseudomembranous colitis (SMQ), narrow terms only
SMQ: Retroperitoneal fibrosis (SMQ), narrow terms only
SMQ: Acute Pancreatitis, narrow (A) terms only
SOC: Congenital, familial and genetic disorders (SOC), (primary and secondary routed PTs)
HLT: Acute and chronic pancreatitis (primary and secondary routed PTs)
HLT: Angioedemas (primary and secondary routed PTs)
HLT: Glomerulonephritis and nephrotic syndrome (primary and secondary routed PTs)
HLT: Nephritis NEC (primary and secondary routed PTs)
PT: disseminated intravascular coagulation
PT: Multi-organ failure
Note: It is only PTs that have not been covered by other search areas, which have been included in
the CTRs. In the safety summary the searches heart rate increased and ability to drive overlap with
the rare search.

14. Overdose
HLT 'Overdoses NEC'.
In addition, the following PTs are also included:
- Accidental overdose,
- Completed suicide,
- Suicide attempt

15. Medication errors
‘SMQ Medication error’, broad and narrow scope terms.

16. Abuse and Misuse
Drug abuse and dependence (SMQ): all narrow terms,
From the SMQ Suicide/self-injury, the following selected PTs: Complete suicide, Intentional self injury,
Poisoning deliberate, Suicide attempt, and Assisted suicide.
From the HLT Intentional Product Misuses the PTs: Intentional device misuse and Intentional Product misuse
From the HLT Intentional product uses issues the PTs: Intentional dose omission and Performance
enhancing product use

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17. Suspected transmission of an infectious agent
HLT: Infectious disorders carrier (only primary terms)
HLT: Infectious transmissions (only primary terms)

18. Heart rate increased
Search criteria: the following PTs:
Tachycardia
Sinus tachycardia
Heart rate increased

13.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): 4221

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1025		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 16		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 15 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)

Reference ID: 4494348

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4222

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1055		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 261		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4223

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 472		
Number of investigators who are Sponsor employees (including both full-time and part-time		

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employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)1		
Is an attachment provided with the reason:	Yes ☒ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4224

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 381		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

Reference ID: 4494348

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 8 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4233

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 529		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 9		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S		

Reference ID: 4494348

Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4234

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 538		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Reference ID: 4494348

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4257

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 411		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4280

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Reference ID: 4494348

Total number of investigators identified: 615		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4281

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 139		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

Reference ID: 4494748

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 4282

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 205		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		

Reference ID: 4494348

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Reference ID: 4497478

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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