Risk Management Plan

Semaglutide s.c. and oral semaglutide

Active substance(s)	Semaglutide
RMP version number	9.1
Data lock point for this RMP	05 Mar 2024
Date of final sign off	See signature page
Rationale for submitting an updated RMP	Submission to EMA in connection with the results from study NN9924-4669, investigating semaglutide and SNAC concentrations in breastmilk following the administration of oral semaglutide in healthy, lactating females. Lactation is proposed to be removed from the missing information for oral semaglutide for T2D (Rybelsus®).
Summary of significant changes in this RMP	Data pertaining to oral semaglutide for T2D in healthy lactating females have been included in the relevant sections throughout the RMP, based on finalisation of the clinical study NN9924-4669. Throughout the relevant sections of the RMP, the following has been included: • Data from lactation study NN9924-4669. • Exposure to Wegovy® in the CVOT study SELECT (EX9536-4388). • New high doses of Rybelsus® (25mg and 50 mg). • New formulation D of Rybelsus® (1.5 mg, 4mg and 9 mg). • Non-project specific updates. Post-authorisation exposure for Ozempic®, Rybelsus® and Wegovy® has been updated as of the DLP. Furthermore, the section on additional PV activity has been updated to reflect the updated milestones for the protocol and final study report submissions for study MTC-22341 for semaglutide s.c. for T2D and for weight management.
Other RMP versions under evaluation	None
Details of the currently approved RMP	Version number: 8.1 Approved with procedure: EMEA/H/C/005422/II/0009 (Wegovy®), EMEA/H/C/xxxx/IB/WS/2541 (Ozempic® and Rybelsus®) Date of approval (CHMP opinion): 31 August 2023
QPPV	Karsten Lollike
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Abbreviations

ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVOT	cardiovascular outcomes trial
DLP	data lock point
DPP-4	dipeptidyl peptidase-4
EAC	Event Adjudication Committee
EASD	European Association for the Study of Diabetes
EPAR	European public assessment report
ESRD	end-stage renal disease
FDA	U.S. Food and Drug Administration
FMTC	familial medullary thyroid carcinoma
GLP-1	glucagon-like peptide-1
GVP	Good Pharmacovigilance Practices
HbA_{1c}	glycated haemoglobin
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia syndrome type 2
MTC	medullary thyroid cancer
NAACCR	North American Association of Central Cancer Registries
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PASS	post-authorisation safety studies
PL	package leaflet
PSUR	periodic safety update report
PT	preferred term
PYE	patient-years of exposure
QPPV	Qualified Person responsible for Pharmacovigilance
RA	receptor agonist
RET	rearranged during transfection
RMP	risk management plan
SAE	serious adverse event
s.c.	subcutaneous(-ly)
SmPC	Summary of Product Characteristics
SNAC	(salcaprozate sodium) sodium N-(8-[2-hydroxybenzoyl] amino) caprylate
SU	sulfonylurea
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
WM	weight management

1 Product overview

This risk management plan concerns semaglutide in a subcutaneous (s.c.) formulation (semaglutide s.c. for type 2 diabetes mellitus [T2D], Ozempic® and semaglutide s.c. 2.4 mg for weight management [WM], Wegovy®) and in an oral formulation (oral semaglutide for T2D, Rybelsus®); Table 1-1.

Table 1-1 Product overview

Active substance(s) (INN or common name)	Semaglutide
Pharmacotherapeutic group(s) (ATC Code)	Glucagon-like peptide (GLP-1) analogues (A10BJ06)
Marketing authorisation holder/applicant	Novo Nordisk A/S DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Ozempic®, Rybelsus® and Wegovy®
Marketing authorisation procedure	Centralised procedure
Brief description of the product	*Chemical class* Semaglutide is an analogue of human glucagon-like peptide-1 (GLP-1).
	Summary of mode of action Semaglutide acts as a GLP-1 receptor agonist (RA) that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone with multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain. Semaglutide works at pharmacological levels by lowering blood glucose and reducing body weight via a combination of effects described below. GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys from where it may mediate cardiovascular and microvascular effects. In addition to lowered systolic blood pressure, reduced selected inflammatory markers and increased heart rate seen in clinical studies, animal studies have shown that GLP-1 RA can be cardioprotective and attenuate cerebral stroke, atherosclerotic plaque size, and platelet aggregation, and increase stability of atherosclerotic plaques.
	Composition Semaglutide is produced by recombinant DNA technology in *Saccharomyces cerevisiae* followed by protein purification. Oral semaglutide is co-formulated with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC or salcaprozate sodium) which facilitates the absorption of semaglutide after oral administration.
Hyperlink to the Product Information	Ozempic® SmPC Rybelsus® SmPC Wegovy® SmPC

Indication(s) in the EEA	**Current – Ozempic®** Ozempic® is indicated for treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see Sections 4.4, 4.5 and 5.1 of the SmPC.
	Proposed – Ozempic® Not applicable
	Current – Rybelsus® Rybelsus® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in combination with other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see Sections 4.4, 4.5 and 5.1 of the SmPC.
	Proposed – Rybelsus® Not applicable
	Current – Wegovy® <u>Adults</u> Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial body mass index (BMI) of • ≥30 kg/m^2 (obesity), or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity, e.g., dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. <u>Adolescents (≥ 12 years)</u> Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with • obesity*and • body weight above 60 kg Treatment with Wegovy® should be discontinued and re-evaluated if patients have not lost at least 5% of their BMI after 12 weeks on the 2.4 mg dose or maximum tolerated dose.*Obesity (BMI ≥ 95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov).
	Proposed – Wegovy® Not applicable

Dosage in the EEA	**Current – Ozempic®** The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks, the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. After at least 4 weeks with a dose of 1 mg once weekly, the dose can be increased to 2 mg once weekly to further improve glycaemic control. Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm.
	Proposed – Ozempic® Not applicable
	Current – Rybelsus® The starting dose is 3 mg once daily. After 1 month, the dose should be increased to a maintenance dose of 7 mg once daily. After at least 1 month with a dose of 7 mg once daily, the dose can be increased to a maintenance dose of 14 mg once daily to further improve glycaemic control. Rybelsus® is a tablet for once-daily oral use. Rybelsus® should be swallowed whole on an empty stomach with up to half a glass of water (120 mL), followed by at least 30 minutes fasting.
	Proposed – Rybelsus® <u>Extension of marketing authorisation for addition of new strengths 1.5 mg, 4.0 mg and 9.0 mg</u> The starting dose of semaglutide is 1.5 mg once daily for one month. After one month, the dose should be increased to a maintenance dose of 4 mg once daily. After at least one month with a dose of 4 mg once daily, the dose can be increased to a maintenance dose of 9 mg once daily to further improve glycaemic control. The recommended single daily maintenance doses are 4 mg or 9 mg. The maximum recommended single daily dose of semaglutide is 9 mg. Taking more than one tablet a day should not be done to achieve the effect of a higher dose. Two formulations of the semaglutide tablets exists: - 1.5, 4, 9 mg (round tablets) - 3, 7 and 14 mg (oval tablets) Bioequivalent (=) doses of the two formulations are outlined in the table below: *Bioequivalent doses of the semaglutide formulations* **Dose** / **One tablet** / **Bioequivalent to** / **One tablet** Starting dose / 1.5 mg / = / 3 mg Maintenance doses / 4 mg / = / 7 mg Maintenance doses / 9 mg / = / 14 mg <u>Extension of marketing authorisation for addition of new strengths 25 mg and 50 mg</u> The starting dose of semaglutide is one 3 mg tablet once daily for one month. After one month, the dose should be increased to a maintenance dose of one 7 mg tablet once daily. If needed, escalation to the next maintenance dose can be made after minimum one month on the current dose. The recommended single daily maintenance doses are 7 mg, 14 mg, 25 mg or 50 mg and the maximum recommended dose of semaglutide is 50 mg. The 3 mg dosage is intended for treatment initiation (starting dose) and is not intended for glycemic control.

<table>
<tr><td></td><td>Taking more than one tablet should not be done to achieve the effect of a higher dose.</td></tr>
<tr><td></td><td>Current – Wegovy®
<u>Adults</u>
The maintenance dose of semaglutide 2.4 mg once weekly is reached by starting with a dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see table below). In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved.

Dose escalation schedule
<table>
<tr><th>Dose escalation</th><th>Weekly dose</th></tr>
<tr><td>Week 1–4</td><td>0.25 mg</td></tr>
<tr><td>Week 5–8</td><td>0.5 mg</td></tr>
<tr><td>Week 9–12</td><td>1 mg</td></tr>
<tr><td>Week 13–16</td><td>1.7 mg</td></tr>
<tr><td>Maintenance dose</td><td>2.4 mg</td></tr>
</table>
Weekly doses higher than 2.4 mg are not recommended.

<u>Adolescents</u>
For adolescents ages 12 years and above, the same dose escalation schedule as for adults should be applied. The dose should be increased until 2.4 mg (maintenance dose) or maximum tolerated dose has been reached. Weekly doses higher than 2.4 mg are not recommended.</td></tr>
<tr><td></td><td>Proposed – Wegovy®
Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current – Ozempic®
Solution for injection.

One (1) mL of solution contains 1.34 or 2.68 mg of semaglutide.</td></tr>
<tr><td></td><td>Proposed – Ozempic®
Not applicable.</td></tr>
<tr><td></td><td>Current – Rybelsus®
White to yellow oval-shaped tablets in three strengths: 3 mg, 7 mg and 14 mg.</td></tr>
<tr><td></td><td>Proposed – Rybelsus®
<u>Extension of marketing authorisation for addition of new strengths 1.5 mg, 4.0 mg and 9.0 mg</u>
The 1.5 mg, 4 mg and 9 mg tablets are white to light yellow, round, debossed with ‘1.5’, ‘4’ or ‘<u>9</u>’ on one side and ‘novo’ on the other side.

<u>Extension of marketing authorisation for addition of new strengths 25 mg and 50 mg</u>
The 25 mg and 50 mg tablets are white to light yellow, oval shaped, debossed with ‘25’ or ‘50’ on one side and ‘novo’ on the other side.</td></tr>
<tr><td></td><td>Current – Wegovy®
Solution for injection in a pre-filled pen.

• 0.25 mg solution for injection
Each single-use pre-filled pen contains 0.5 mg/mL semaglutide*</td></tr>
</table>

	• 0.5 mg solution for injection Each single-use pre-filled pen contains 1.0 mg/mL semaglutide* • 1 mg solution for injection Each single-use pre-filled pen contains 2.0 mg/mL semaglutide* • 1.7 mg solution for injection Each single-use pre-filled pen contains 2.27 mg/mL semaglutide* • 2.4 mg solution for injection Each single-use pre-filled pen contains 3.2 mg/mL semaglutide* *Human glucagon-like peptide-1 (GLP-1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.
	Proposed – Wegovy® Not applicable
Is/will the products be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = anatomical therapeutic chemical; EEA = European Economic Area; GLP-1 = glucagon-like peptide-1; INN = International Nonproprietary Name; RA = receptor agonist; SmPC = Summary of Product Characteristics.

2 Safety specification

2.1 Module SI: Epidemiology of the indication(s) and target population

2.1.1 Type 2 diabetes mellitus

Diabetes mellitus is a group of metabolic abnormalities characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[1] T2D is a heterogeneous, chronic and progressive disease characterised by insulin resistance, along with relatively impaired beta-cell function. While development of the disease is variable, it usually follows a predictable course of deteriorating beta-cell function and increasing insulin resistance.

2.1.1.1 Incidence and prevalence

The global prevalence and incidence rates of T2D are rising rapidly.[2-7] This is mainly driven by an increasingly ageing population, a better survival of patients with T2D and increasing levels of obesity and inactivity.[8] The incidence rates of T2D in adults range from 2.3 to 20.2 cases per 1,000 person-years, with wide geographical variation.[2-4, 9-21] In 2019, the estimated crude prevalence of diabetes in adults was 8.8% both globally and in Europe (the vast majority of cases are T2D). Estimated (crude) prevalence of diabetes in Europe is highest in Germany (15.3%) and Malta (12.2%), and the lowest (crude) European prevalence of diabetes has been reported in Greenland (3.2%), Ireland (4.4%) and Lithuania (5.4%).[7]

2.1.1.2 Demographics of the target population – Age, gender, racial and ethnic origin

T2D usually occurs in adults but is at the global level increasingly seen in children and adolescents.[7] The prevalence[7] and incidence[3] of T2D progressively increase with age. The incidence[3, 9, 10, 20] and prevalence[22] of T2D tend to be a little higher in men than in women. In the US, Whites have lower incidence[14] and prevalence[23] of T2D than other ethnic groups. The

prevalence is highest in African Americans[23] and the incidence is highest in Pacific Islanders and South Asians.[14]

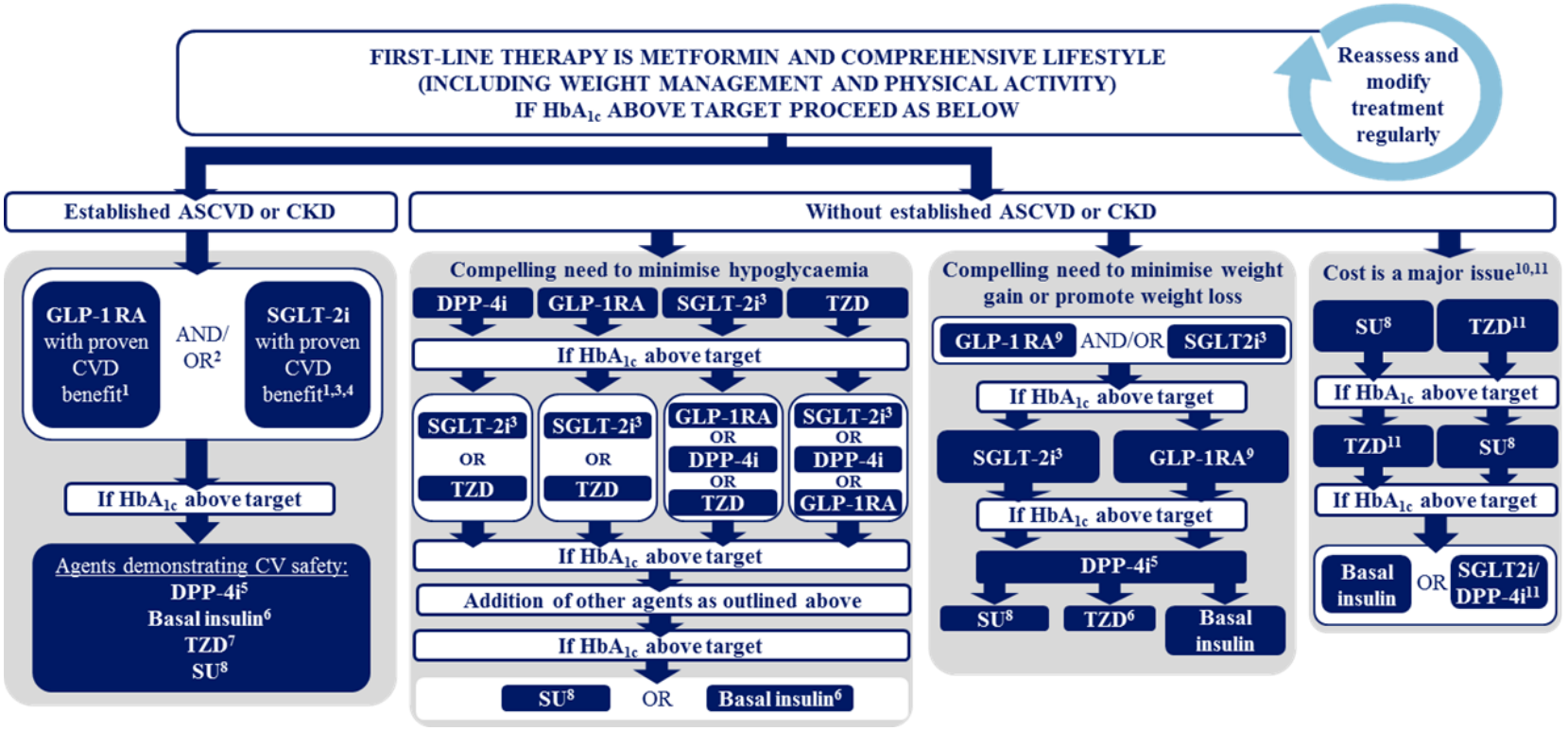
2.1.1.3 Risk factors for the disease

Although the exact causes for the development of T2D are still not known, there are several important risk factors. The most important are excess body weight (overweight and obesity), physical inactivity, genetics and dietary factors.[1] Additional risk factors include smoking, impaired glucose tolerance, abnormal lipids, hypertension, inflammation, intrauterine environment, age, sex, ethnicity, history of gestational diabetes and polycystic ovary syndrome.[24]

2.1.1.4 The main existing treatment options

The European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) consensus report on the management of hyperglycaemia in patients with T2D and the ADA guideline recommend, for most patients, to start with metformin in combination with lifestyle modifications (Figure 2-1).[25, 26] The choice of pharmacological agents for glycaemic management should have a patient-centred approach, and should take into account efficacy as well as patient and disease factors.

Figure 2-1 Glucose-lowering medication in T2D: overall approach



Note: Adapted from Davies *et al.*[25]

[1]Label indication of reducing CVD events (strongest evidence for liraglutide > semaglutide > exenatide extended release and for empagliflozin > canagliflozin). [2]If HF or CHD predominates, SGLT-2i is preferred. [3]SGLT-2i varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use. [4]Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs. [5]If not on GLP-1 RA. [6]Degludec/U100 glargine have demonstrated CVD safety. [7]Low dose may be better tolerated though less well studied for CVD effects. [8]Later generation SU with lower risk of hypoglycaemia. [9]With good efficacy for weight loss, i.e. semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide. [10]If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities). [11]Consider country- and region-specific cost of drugs.

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CHD = coronary heart disease; CKD = chronic kidney disease; CVD = cardiovascular disease; CVOT = cardiovascular outcomes trial; DPP-4 = dipeptidyl peptidase; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; SGLT2-i = sodium/glucose co-transporter 2; SU = sulfonylurea; T2D = type 2 diabetes mellitus; TZD = thiazolidinediones.

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

T2D is a heterogeneous, chronic and progressive disease characterised by insulin resistance, along with relatively impaired β-cell function. While the course of the disease is variable, it usually follows a predictable course. In the early stages, individuals with T2D have sufficient pancreatic reserves to compensate for insulin resistance and can maintain relatively normal blood glucose levels. However, over time, this ability to compensate decreases as β-cells gradually lose their ability to secrete insulin (β-cell insufficiency), eventually leading to a state of insulin dependency.[27]

The resulting insulin deficiency can be absolute or relative in the coexistence of insulin resistance (response to insulin in the target tissues, such as muscle, liver and adipose tissue). The result is chronic hyperglycaemia, caused by reduced insulin secretion, decreased insulin utilisation and increased liver glucose production, which leads to diabetic complications. Diabetes is a leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations, adult blindness and cardiovascular complications.[8, 27, 28]

T2D is associated with increased all-cause mortality.[29] Cardiovascular mortality (including death following heart failure[30] and myocardial infarction[31-33]) is increased and may account for 50% or more of deaths due to diabetes, in some populations.[1] Cancer patients with diabetes have poorer survival and higher mortality rates than cancer patients without diabetes,[34, 35] particularly so for liver, pancreatic, ovary and colorectal cancer.[36]

2.1.1.6 Important co-morbidities found in the target population

People with diabetes mellitus are at higher risk of developing a number of disabling and life-threatening health problems than people without diabetes (Table 2-1).[1] Persistent hyperglycaemia may lead to development of microvascular pathology in the eyes, the kidneys and peripheral nerves.[37] Diabetes is a leading cause of blindness, end-stage renal disease and a variety of debilitating neuropathies. Diabetes is also associated with accelerated atherosclerotic macrovascular disease, affecting arteries that supply blood to the heart, brain and lower extremities. As a result, people with diabetes have an increased risk of myocardial infarction, stroke and limb amputation.[1]

Table 2-1 Important co-morbidities/complications in the population with diabetes

Disorders	Important co-morbidities/complications
Microvascular disorders	Neuropathy, chronic kidney disease and nephropathy, retinopathy and extremity ulcers
Macrovascular disorders	Congestive heart failure, myocardial infarction, peripheral arterial disease and stroke
Acute complications	Diabetic ketoacidosis, hyperosmolar hyperglycaemic state
Other disorders and complications	Dyslipidaemia, hypertension, pancreatitis, obesity and several types of cancers (liver, pancreas, colorectal and breast)

2.1.2 Overweight and obesity

The European Association for the Study of Obesity (EASO),[38] World Obesity Federation,[39] American Medical Association (AMA)[40] and a number of leading institutions[41-44] have classified obesity as a disease, calling for dedicated efforts in prevention, diagnosis and treatment. The World

Health Organization (WHO) defines overweight as BMI ≥25 kg/m^2 and obesity as BMI ≥30 kg/m^2. Obesity is further divided into following classes:[45]

- Obesity class I equals a BMI between 30 kg/m^2 and 35 kg/m^2
- Obesity class II equals a BMI between 35 kg/m^2 and 40 kg/m^2
- Obesity class III equals a BMI of 40 kg/m^2 or higher

2.1.2.1 Incidence and prevalence

In 2016, there were more than 1.9 billion adults living with overweight, constituting almost 40% of the world's adult population. Of these, over 650 million adults had obesity, constituting about 13% of the world's adult population (11% of men and 15% of women). The worldwide prevalence of obesity nearly tripled between 1975 and 2016 in adults,[46] while the global prevalence of childhood obesity increased 10−12 fold in children and adolescents aged 5−19 years.[47] The prevalence of overweight and obesity in adults across WHO regions is presented in Table 2-2 and that in children is presented in Table 2-3. In Europe, roughly 50% of the population has overweight and over 20% of the population has obesity;[48] see Table 2-2.

Table 2-2 Age-standardised prevalence of overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2) in >20-year olds across WHO regions, 2016[48, 49]

Region	Overweight (%) BMI ≥25 kg/m^2		Obesity (%) BMI ≥30 kg/m^2	
	Males	Females	Males	Females
Global	38.5	39.2	11.1	15.1
Europe	63.1	54.3	21.9	24.5
Americas	64.1	60.9	25.9	31.0

Abbreviations: BMI = body mass index; WHO = World Health Organization.

Table 2-3 Obesity prevalence amongst children aged 5−9 years and 10−19 years in 2020 and 2030, by WHO region[50]

Region	Children aged 5-9 years (%)		Children aged 10-19 years (%)	
	2020	2030	2020	2030
Global	11%	15%	7%	11%
Europe	13%	16%	8%	11%
Americas	19%	23%	15%	19%

Abbreviations: WHO = World Health Organization.

The prevalence of obesity in children and adolescents, as well as in adults, has been increasing steadily during the past decades and has reached alarming proportions worldwide.[51-53]

2.1.2.2 Demographics of the target population – age, gender, racial and ethnic origin

Once considered a high-income country problem, overweight and obesity are now on the rise in low and middle-income countries, particularly in urban settings.[46] This is also reflected in the increasing prevalence and incidence of T2D (see Section 2.1.1.1).

The prevalence of obesity has also increased exponentially among children and adolescents, estimated to affect more than 157 million adolescents and children aged 5 to 19 years worldwide.[50]

The second round of the European Health Interview Survey (EHIS), conducted between 2013 and 2015 and included people aged 15 years and above, showed that the proportion of adults who have overweight or obesity varies in terms of region, gender and socio-economic background. There was no systematic difference in obesity prevalence across the member states. However, for overweight, the proportion of men was consistently higher than the proportion of women in all member states. With few exceptions, the 18 to 24-year-old age group presented the lowest shares of population with overweight, while the 65 to 74-year-old age group had the highest shares. Finally, regarding educational attainment, the proportion of women who had overweight was lower among those with higher levels of education. For men, there was no clear picture.[54]

In the US, the prevalence of obesity is lower among non-Hispanic Asian adults (12.7%) than among all other races and Hispanic-origin groups. Hispanic (47.0%) and non-Hispanic black (46.8%) adults have a higher prevalence of obesity than non-Hispanic white adults (37.9%). The prevalence of obesity among non-Hispanic black (22.0%) and Hispanic (25.8%) youth aged 2–19 years is higher than both non-Hispanic white (14.1%) and non-Hispanic Asian (11.0%) youth. There are no significant differences in the prevalence of obesity between non-Hispanic white and non-Hispanic Asian youth or between non-Hispanic black and Hispanic youth.[55]

2.1.2.3 Risk factors for the disease

The scientific understanding of the pathophysiology of obesity has advanced, and it is now viewed as a complex chronic disease with interacting genetic, environmental and biological determinants.[56]

Most cases of childhood obesity also arise from interactions between genetic factors that enhance susceptibility and environmental factors that increase food intake and decrease energy expenditure, specifically those related to a sedentary lifestyle and unfavourable eating patterns.[57, 58]

2.1.2.4 The main existing treatment options

The risk of obesity-related complications increases with increasing BMI, and a weight loss of 5–10% has significant health benefits in terms of slowing progression to T2D,[28-31] and improvement of non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), dyslipidaemia, hypertension and dysglycaemia as well as physical symptoms and quality of life. Further, studies suggest a weight loss of 10−15% has a beneficial impact on sleep apnoea, non-alcoholic steatohepatitis (NASH), cardiovascular risk and mortality in both people with diabetes and obesity.[59, 60, 61, 62] Furthermore, a weight loss of 5–10% improves many other obesity-related comorbidities as well as physical symptoms and quality of life. Studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in both people with diabetes and obesity.[63-65]

Main treatment options for obesity include:[64, 65]

- non-surgical and non-pharmacotherapeutical treatment options, including lifestyle modifications (diet and exercise) and psychological support
- pharmacological treatment
- bariatric surgery.

Family-centred lifestyle modifications is the standard of care treatment of adult as well as childhood obesity, with the aim of helping patients adopt healthier eating habits, increase physical activity,

and decrease sedentary time. There is evidence that the effect of lifestyle modifications can be enhanced through behavioural and cognitive-behavioural strategies.[66] However, data indicate that more than 50% of the patients who lose weight through lifestyle modifications return to their baseline weight within 5 years.[67]

Bariatric surgery offers an effective treatment option for some people with severe obesity, but surgery carries a risk in connection with the procedure and for complications afterwards, and requires close follow-up which can be cumbersome and costly.[43, 68-74] In paediatric population, use of bariatric surgery is primarily restricted to adolescents with unsuccessful weight loss and with comorbidities, after implementation of lifestyle modifications and/or pharmacotherapy. There remains a treatment gap for children and adolescents who have failed lifestyle modifications but do not meet criteria for bariatric surgery.[75] As in adults, most children and adolescents with obesity, especially those with severe obesity, struggle to achieve and maintain weight loss.[76,77-80]

In between lifestyle intervention and surgery is pharmacological intervention. In Europe, there are currently 3 marketed products licensed for the chronic treatment of obesity: orlistat (Xenical®), naltrexone/bupropion (Mysimba®) and liraglutide (Saxenda®). Only Saxenda® is approved in adolescents for chronic WM.

2.1.2.5 Natural history of the indicated condition including mortality and morbidity

Obesity is a chronic condition associated with a 5–10 years decreased life expectancy as well as several major comorbidities/complications, including hypertension, dysglycaemia (prediabetes and diabetes), dyslipidaemia, certain types of cancer, obstructive sleep apnoea and cardiovascular disease.[81] The WHO has estimated that the burden of disease (defined as mortality and loss of health due to disease) that can be attributed to overweight or obesity is 44% for diabetes, 23% for ischaemic heart disease and 7–41% for certain cancer types. Currently, excess weight is responsible for about 3.4 million annual deaths and 3.8% of the global burden of disease.[82]

Increasing BMI is associated with an increased risk of all-cause mortality. A large meta-analysis of more than 200 prospective studies showed an increasing risk of all-cause mortality with increasing BMI category compared to normal-weight individuals. Individuals with obesity grade 1, grade 2 and grade 3 have 45%, 94% and 176% higher risk of all-cause mortality, respectively, compared to normal-weight individuals.[83]

2.1.2.6 Important co-morbidities found in the target population

Overweight and obesity are defined as an abnormal or excessive fat accumulation that may impair health.[46] Obesity is associated with multiple medical complications that lead to increased morbidity and reduced life expectancy. These complications include CVDs, T2D, non-alcoholic fatty liver disease, metabolic syndrome, cholelithiasis, hypertension, cancer, sleep apnoea, osteoarthritis and reduced psychosocial function.[84] The most serious or common co-morbidities/complications are presented in Table 2-4.

Table 2-4 Important co-morbidities/complications in the target population – overweight and obesity

Disorders	Important co-morbidities/complications
Metabolic disorders	Metabolic syndrome or any of its components (including dyslipidaemia, hypertension and central obesity), non-alcoholic fatty liver disease (NAFLD), prediabetes and type 2 diabetes mellitus
Gastrointestinal disorders	Gastro-oesophageal reflux disease (GERD)
Cardiovascular disorders	Hypertension, coronary artery disease (CAD), stroke and cerebrovascular disease
Reproductive disorders	Polycystic ovary syndrome (PCOS), infertility, adverse pregnancy outcomes and menstrual disorder
Other disorders and complications	Malignant neoplasms, gallbladder disease, osteoarthritis, hypothyroidism, obstructive sleep apnoea (OSA), depression, urinary incontinence in women and gout

Abbreviations: CAD = coronary artery disease; GERD = gastro-oesophageal reflux disease; NAFLD = non-alcoholic fatty liver disease; OSA = obstructive sleep apnoea; PCOS = polycystic ovary syndrome.

2.2 Module SII: Nonclinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

In the nonclinical studies, semaglutide was generally administered by subcutaneous route. In addition, a dedicated programme of oral toxicology studies as well as studies with the absorption enhancer SNAC (or salcaprozate sodium) was conducted to support the oral route of administration. All pivotal nonclinical safety studies were conducted in accordance with the principles of Good Laboratory Practice (GLP).

Table 2-5 summarises the important nonclinical safety findings along with assessments of human relevance.

Table 2-5 Important nonclinical safety findings and their relevance to human use

Key nonclinical safety findings	Relevance to human usage
Acute toxicity, including important results from safety pharmacology studies	
Central Nervous System (CNS) In the CNS function study in rats, a decrease in activity was observed at the highest dose tested (0.095 mg/kg s.c.). Decreased activity is a known GLP-1 receptor-mediated effect in rats following acute doses of GLP-1 RAs[85] and is considered to be related to decrease of appetite, a desired pharmacological effect.	The clinical study data do not indicate a safety concern related to the CNS. However, 'fatigue' and 'decreased appetite' have been included as ADRs in Section 4.8 of the Summary of Product Characteristics (SmPC) for both semaglutide s.c. for T2D and oral semaglutide for T2D. For semaglutide s.c. 2.4 mg for WM, 'fatigue' has been included as an ADR in Section 4.8 of the SmPC. 'Decreased appetite' is reflected as part of the mode of action for semaglutide s.c. 2.4 mg for WM.

Key nonclinical safety findings	Relevance to human usage
Renal In the renal function study in rats, semaglutide caused an acute transient increase in diuresis and excretion of sodium at the highest doses (0.023 mg/kg and 0.089 mg/kg s.c.). These are well-known effects of GLP-1 RAs in the rat.[86, 87]	In humans, native GLP-1 has been shown to increase natriuresis and diuresis, whereas a similar effect has not been reported in studies with chronic administration of other GLP-1 RAs.[88, 89] The clinical study data do not indicate a safety concern related to renal failures. The nonclinical finding is therefore not considered to be relevant for humans.
Heart In the 52-week repeat-dose toxicity study in cynomolgus monkeys, electrocardiogram (ECG) evaluations revealed a chronic left-bundle-branch block recording in one female of eight animals receiving 0.36 mg/kg s.c. twice weekly (≥10-fold above the exposure at MRHD [2.4 mg/week]). The animal exhibited no clinical signs attributable to the ECG finding and histopathology revealed no correlating changes.	Cardiac bundle-branch blocks are an occasional finding in monkeys[90] and humans,[91] and are in most cases a consequence of other underlying cardiac diseases.[91] The occurrence of left-bundle-branch blocks in the clinical programmes with semaglutide (including the CVOTs [SUSTAIN 6 and PIONEER 6], which are the most appropriate clinical studies to assess the human relevance of this finding due to the study population; see Section 2.3.1) was very low and with no imbalance between semaglutide and comparators. Based on the clinical evidence, the nonclinical finding is not considered to be relevant for humans.
Repeat-dose toxicity	
Brunner's glands in duodenum Dilated lumen and hypertrophy of Brunner's glands of the duodenum were observed in mice and rats, respectively. Brunner's glands show high GLP-1 receptor expression[92, 93] and it is considered likely that the treatment-related changes in Brunner's glands were due to GLP-1 receptor activation by semaglutide. The findings were not considered adverse as they were not associated with inflammation or cellular damage in the Brunner's glands or intestinal mucosa, recovery occurred following the cessation of treatment, and there was no progression to hyper- or neoplasia in the rodent carcinogenicity studies.	Based on the low severity and reversibility in the rat, the observed changes in Brunner's glands in rodents are not considered to pose a safety concern in humans.

Key nonclinical safety findings	Relevance to human usage
Carcinogenicity	
Thyroid C-cell tumours in rodents have been observed for all currently approved long-acting GLP-1 RAs tested in carcinogenicity studies. For semaglutide, thyroid C-cell hyperplasia, adenomas or carcinomas were seen in both mouse and rat 2-year carcinogenicity studies at all dose levels, precluding establishment of NOAELs for these studies. In both mouse and rat, plasma calcitonin was shown to increase before proliferative C-cell changes were observed. The findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism.[94] In toxicity studies in cynomolgus monkeys, no plasma calcitonin increases and no C-cell changes were observed after 52 weeks of semaglutide treatment at exposures (≥10-fold above the MRHD (2.4 mg/week), which is consistent with the absence of GLP-1 receptors on normal monkey thyroid C-cells.[92]	Published data indicate that the GLP-1 receptor is not expressed in the normal human thyroid C-cells.[93, 95, 96] There was no effect of treatment with semaglutide on plasma calcitonin levels. Details regarding the important potential risk of MTC are provided in Section 2.7.3.3. Based on data for semaglutide and other GLP-1 RAs, the human relevance of the rodent C-cell tumours is considered to be low.
Reproductive and developmental toxicity	
Nonclinical findings for GLP-1 RAs Reproductive toxicity in animals has generally been observed among currently approved GLP-1 RAs, together with pharmacologically mediated reductions in maternal body weight.	General population Weight loss in pregnant women is reported to cause reduced neonatal birth weights, reduced placental weights and reduced umbilical cord length compared to controls, adjusted for BMI.[97]
Embryo–foetal development In rats, semaglutide adversely affected embryo–foetal development, causing foetal mortality, reduced growth, and skeletal and visceral malformations. Mechanistic studies demonstrated involvement of a GLP-1 receptor-mediated process impaired function of the inverted yolk sac during a period of gestation, when the rat embryo is entirely dependent on the inverted yolk sac for its nutrient supply.	Due to species differences in yolk sac anatomy and function, and due to the lack of GLP-1 receptor expression in cynomolgus monkey yolk sac, this mechanism is considered unlikely to be of relevance to humans.
Pregnancy losses and foetal abnormalities In rabbits and cynomolgus monkeys, pregnancy losses and foetal abnormalities were observed at exposures below (rabbit) or ≥1-fold above (monkey) the MRHD (2.4 mg/week).	The nonclinical observations of pregnancy losses and foetal abnormalities might be either incidental or related to the reduced maternal body weight, but a direct effect of semaglutide could not be excluded.

Key nonclinical safety findings	Relevance to human usage
Lactation In lactating rats, semaglutide was observed in milk at levels 3–12-fold below maternal plasma levels.	Due to the possibility of semaglutide transferring into milk, the use of semaglutide while breastfeeding is not recommended.
Not applicable	Conclusion The relevance to humans of the nonclinical observations with semaglutide cannot be excluded. Therefore, based on the totality of available clinical and nonclinical data semaglutide should not be used during pregnancy or breastfeeding (SmPC Section 4.6). Use in pregnancy is included as missing information (Section 2.7.3.4). Use during lactation is included as missing information for semaglutide s.c. for T2D and WM (Section 2.7.3.5).
Juvenile toxicity	
In juvenile rats, semaglutide caused pharmacologically mediated reductions in food consumption and body weight gain, and delays in the attainment of sexual maturation in both males and females. These delays were not considered adverse, as they had no long-term impact upon the oestrous cycle regularity of the females, reproductive capacity of either sex, or on the ability of the females to maintain pregnancy to mid-gestation.	The human relevance of delayed sexual maturation in rats is unknown. In pre-pubertal children, sexual maturation is influenced by body weight and body fat mass, particularly in females.[98] Use in children and adolescents will be investigated within the agreed paediatric investigation plan (PIP)/paediatric study plan (PSP).
Other toxicity-related information or data	
Unintended injection (i.m., i.v., i.a., semaglutide s.c.) Single dosing of semaglutide by an unintended route in rabbits resulted in mild histopathological changes (minimal or slight inflammatory cell reaction, perivascular or vascular necrosis, intima proliferation or haemorrhage). The effects were similar after administration of the vehicle and were thus considered to represent minor variations of local tissue reactions caused by the procedure itself.	It is expected that the effects in humans are similar to the nonclinical findings. No safety concerns relating to unintended injections have been identified in the clinical programme.

Key nonclinical safety findings	Relevance to human usage
Effect of SNAC on cellular respiration (oral semaglutide) SNAC was associated with adverse clinical signs and mortality in all toxicology species, in particular at doses >500 mg/kg/day. The mortality observed following administration of SNAC to animals is considered to be due to inhibition of cellular respiration, mainly via an inhibition of complex I in the electron transport chain, located on the inner mitochondrial membrane. The inhibition of cellular respiration caused an increase in plasma lactate in animals. The mortality was found to be related to very high initial plasma concentration levels of SNAC in animals and occurred in animals at exposure levels more than 272-fold above the human exposure ($C_{max,free}$: at 300 mg SNAC/day).	Adverse clinical signs and mortality occurred at very high plasma concentration in animals. Similarly, high plasma concentrations have not been observed in humans and are not considered achievable following administration of oral semaglutide in humans. Consistent with this, SNAC had no effect on plasma lactate in the clinical studies (lactate and SNAC exposure levels were measured concurrently at two visits in the PIONEER 1 and 2 studies). Therefore, based on current data and understanding the effect is not considered of clinical relevance for humans.

Abbreviations: ADR = adverse drug reaction; BMI = body mass index; CNS = central nervous system; CVOT = cardiovascular outcome trial; ECG = electrocardiogram; GLP-1 RA = glucagon-like peptide-1 receptor agonist; i.a. = intra-arterial; i.m. = intramuscular; i.v. = intravenous; MRHD = maximum recommended human dose; MTC = medullary thyroid cancer; NOAEL = no observed adverse effect level; PIP = paediatric investigation plan; PSP = paediatric study plan; RA = receptor agonist; SmPC = Summary of Product Characteristics; SNAC = sodium N-(8-[2-hydroxybenzoyl] amino) caprylate; T2D = type 2 diabetes mellitus.

2.2.2 Conclusions on nonclinical data

In conclusion, the comprehensive nonclinical programme did not identify any safety concerns prohibiting chronic subcutaneous or oral administration of semaglutide to humans. Based on the evaluations, the risks related to C-cell tumours in rodents and to observations in the embryo–foetal development studies are further brought forward as safety concerns (Table 2-6).

Table 2-6 Nonclinical summary of safety concerns

Safety concerns
Important identified risks (confirmed by clinical data) • None
Important potential risks (not refuted by clinical data or which are of unknown significance) • Medullary thyroid cancer
Missing information • Pregnancy and lactation

2.3 Module SIII: Clinical study exposure

2.3.1 Overall clinical study exposure to semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM

The phase 3 clinical development programmes are denoted as follows:

- ‘SUSTAIN’ for semaglutide s.c. for T2D

- 'PIONEER' for oral semaglutide for T2D.The clinical pharmacology study NN9924-4799, relevant for the use of oral semaglutide formulation D (1.5 mg, 4 mg and 9 mg), is presented separately from the phase 3 studies throughout this risk management plan (RMP).
- 'STEP' for semaglutide s.c. 2.4 mg for WM. The phase 3b CVOT study EX9536-4388 is denoted as 'SELECT'.

The clinical studies included in this RMP and their corresponding study IDs are listed in Table 2-7.

Table 2-7 Overview of clinical studies included in the RMP

Semaglutide s.c. for T2D[a]		Oral semaglutide for T2D[b]		Semaglutide s.c. 2.4 mg for WM[e]	
Trial name	**Study ID**	**Study name**	**Study ID**	**Study name**	**Study ID**
SUSTAIN 1	NN9535-3623	PIONEER 1	NN9924-4233	STEP 1	NN9536-4373
SUSTAIN 2	NN9535-3626	PIONEER 2	NN9924-4223	STEP 2	NN9536-4374
SUSTAIN 3	NN9535-3624	PIONEER 3	NN9924-4222	STEP 3	NN9536-4375
SUSTAIN 4	NN9535-3625	PIONEER 4	NN9924-4224	STEP 4	NN9536-4376
SUSTAIN 5	NN9535-3627	PIONEER 5	NN9924-4234	STEP TEENS	NN9536-4451
SUSTAIN 6 (CVOT)	NN9535-3744	PIONEER 6 (CVOT)	NN9924-4221	SELECT (CVOT)	EX9536-4388
SUSTAIN 7	NN9535-4216	PIONEER 7	NN9924-4257[c]	–	–
SUSTAIN 8	NN9535-4270	PIONEER 8	NN9924-4280	–	–
SUSTAIN 9	NN9535-4269	PIONEER 9	NN9924-4281	–	–
SUSTAIN 10	NN9535-4339	PIONEER 10	NN9924-4282	–	–
SUSTAIN JP	NN9535-4091	PIONEER PLUS	NN9924-4635	–	–
SUSTAIN JP	NN9535-4092	–	NN9924-4799[d]	–	–
SUSTAIN China	NN9535-4114	–	–	–	–
SUSTAIN FORTE	NN9535-4506	–	–	–	–

[a]Phase 3a studies include SUSTAIN 1, 2, 3, 4, 5, 6, JP and China; Phase 3b studies include SUSTAIN 7, 8, 9, 10 and FORTE. [b]All PIONEER studies included in the table are phase 3a studies except PIONEER PLUS which is a phase 3b study. [c]Study NN9924-4257 includes both the main phase and the extension phase. [d]Study NN9924-4799 is presented separately in this RMP since it is a phase 1 clinical pharmacology bioequivalence study in healthy volunteers comparing semaglutide exposures of oral semaglutide formulation D (1.5 mg, 4 mg and 9 mg) to the initially approved formulation (3 mg, 7 mg and 14 mg) for T2D. [e]All STEP studies included in the table are phase 3a studies, SELECT (EX9536-4388) is a phase 3b study.

Abbreviations: CVOT = cardiovascular outcomes trial; RMP = risk management plan; s.c. = subcutaneous(-ly); T2D = type 2 diabetes mellitus; WM = weight management.

A total of 27,516 participants have been exposed to semaglutide in the clinical studies (including CVOTs) included in this RMP.

Exposure and data from the cardiovascular outcomes studies (CVOTs [SUSTAIN 6, PIONEER 6 and SELECT]) are presented separately in Section 2.3.1.1, Section 2.3.1.2 and Section 2.3.1.5 as the populations in these studies differ from the populations included in the remaining studies. In the CVOTs SUSTAIN 6 and PIONEER 6, the participants were diagnosed with T2D and were either ≥50 years with the presence of cardiovascular disease or ≥60 years with the presence of

cardiovascular risk factors only. In the CVOT SELECT (EX9536-4388), the participants were ≥45 years with established cardiovascular disease and no history of type 1 or type 2 diabetes.

For data pertaining to the semaglutide s.c. for T2D development programme, the presentation is split into the CVOT (SUSTAIN 6) and the remaining phase 3 clinical studies throughout the RMP (except in Table 2-8, Table 2-9 and Table 2-10, where CVOTs are included in the pooled studies).

For data pertaining to the oral semaglutide for T2D development programme, the presentation is split into the CVOT (PIONEER 6) and all the remaining phase 3 clinical studies throughout the RMP (except in Table 2-8, Table 2-9 and Table 2-10, where CVOTs are included in the pooled studies). The *placebo pool* comprises the multinational placebo-controlled phase 3a studies (PIONEER 1, 4, 5 and 8) throughout the RMP. Exposure data from study NN9924-4635 (PIONEER PLUS) with high doses of oral semaglutide (25 mg and 50 mg) is presented separately in Section 2.3.1.3 by duration, age range, gender and race. The exposure from this study is also included in the cumulative exposure in Section 2.3.1 and Section 2.3.1.2. Exposure data from study NN9924-4799 with oral semaglutide formulation D is presented separately in Section 2.3.1.4 by duration, age range, gender and race.

For data pertaining to the semaglutide s.c. 2.4 mg for WM development programme, the *phase 3a pool* comprises the phase 3a studies (STEP 1–4 and STEP TEENS) comparing semaglutide 2.4 mg to placebo during the randomised, controlled study period throughout the RMP. The presentation is split into the CVOT SELECT (EX9536-4388) and all the remaining phase 3 clinical studies throughout the RMP (except in Table 2-8, Table 2-9 and Table 2-10, where CVOTs are included in the pooled studies) and include the total number of participants exposed to semaglutide (2.4 mg or 1.0 mg). Participants exposed to both semaglutide and placebo in STEP 4 are counted in both semaglutide and placebo in Table 2-8 and Table 2-9 but only included as per the randomised treatment group in Table 2-10. The exposure from the CVOT SELECT (EX9536-4388) is included in the cumulative exposure in Section 2.3.1 and Section 2.3.1.5.

Table 2-8 Exposure in completed phase 3 studies (incl. CVOTs) – semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM

	Number of participants	PYE
Semaglutide	27,516	46,452
All comparators	19,226	38,718

Note: The table includes exposure from all studies included in Table 2-7. PYE is calculated as the time from first drug date to last drug date plus 42 days for semaglutide s.c for T2D, plus 38 days for oral semaglutide for T2D and plus 49 days for semaglutide s.c. 2.4 mg for weight management.

Abbreviations: s.c. = subcutaneous(-ly); PYE = patient-years of exposure; T2D = type 2 diabetes mellitus.

The majority of the participants in the clinical studies were exposed to semaglutide or comparator for at least 15 months (see Table 2-9).

Table 2-9 Duration of exposure in completed phase 3 studies (incl. CVOTs) – semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM

Duration of exposure (at least)	Semaglutide		All comparators	
	Number of participants	Percentage	Number of participants	Percentage
1 month	27,507	100.0%	19,221	100.0%
3 months	26,579	96.6%	18,790	97.8%
6 months	24,848	90.3%	18,188	94.6%
9 months	21,408	77.8%	16,124	83.9%
12 months	19,551	71.1%	15,196	79.1%
15 months	15,309	55.7%	11,844	61.6%
18 months	10,415	37.9%	9,926	51.6%
21 months	8,755	31.8%	9,032	47.0%
24 months	8,584	31.2%	8,864	46.1%
27 months	6,811	24.8%	7,077	36.8%
30 months	6,162	22.4%	6,416	33.4%
33 months	5,408	19.7%	5,613	29.2%
36 months	4,831	17.6%	5,032	26.2%
39 months	4,406	16.0%	4,554	23.7%
42 months	3,463	12.6%	3,597	18.7%
45 months	2,419	8.8%	2,530	13.2%
48 months	1,487	5.4%	1,529	8.0%
51 months	518	1.9%	520	2.7%
55 months	9	0.0%	9	0.0%

Note: The table includes exposure from all studies included in Table 2-7.

Abbreviations: s.c. = subcutaneous(-ly); T2D = type 2 diabetes mellitus.

In the completed phase 3 clinical studies, more than half of the participants exposed to semaglutide were males (see Table 2-10). The majority were adults between 18 and 64 years old and of White or Asian (including Japanese) origin.

The demographic disposition of the participants exposed to placebo or active comparator was similar to that for semaglutide-treated participants.

Table 2-10 Exposure by gender, age and race in completed phase 3 studies (incl. CVOTs) – semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM

	Semaglutide				All comparators			
	N		PYE		N		PYE	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
12–<18 years	50	83	69	113	26	41	36	54
18–64 years	10,703	7,739	19,370	11,342	7,550	4,848	16,163	8,201
65–74 years	4,409	2,604	8,288	4,226	3,629	1,871	8,074	3,561
75–84 years	971	541	1,739	892	804	410	1,749	786
≥85 years	30	19	47	25	31	16	66	28
Total	**16,163**	**10,986**	**29,514**	**16,597**	**12,040**	**7,186**	**26,088**	**12,630**
Race								
White	20,026		35,894		14,850		31,105	
Black/African American	1,451		2,211		1,012		1,709	
Asian	4,801		6,438		2,688		4,498	
American Indian/Alaska native	89		138		70		124	
Native Hawaiian/other Pacific Islander	19		23		12		21	
Other	489		971		403		933	
Unknown/Not reported	274		435		191		326	
Total	**27,149**		**46,111**		**19,226**		**38,718**	

Note: The table includes exposure from all studies included in Table 2-7. The overall numbers are lower compared to Table 2-8 and Table 2-9 as participants who were exposed to both semaglutide and comparator in study NN9536-4376 are counted just once as per randomisation in the main part of the study.

Abbreviations: s.c. = subcutaneous(-ly); PYE = patient-years of exposure; T2D = type 2 diabetes mellitus.

2.3.1.1 Clinical study exposure in the semaglutide s.c. for T2D development programme (SUSTAIN)

A total of 6,118 participants (corresponding to 5,052 patient-years of exposure [PYE][1]) have been exposed to semaglutide s.c. for T2D in the completed phase 3 clinical studies, excluding a cardiovascular outcomes trial (CVOT [SUSTAIN 6]; NN9535-3744) in which 1,642 participants (2,932 PYE) were exposed to semaglutide s.c. The exposure to semaglutide in the clinical studies was almost double that of the comparators. More than half of the participants were exposed to 1.0 mg (60%), followed by 0.5 mg (32%) and 2.0 mg (8%); see Table 2-11.

[1]PYE is calculated as the time from first drug date to last drug date plus 42 days.

Table 2-11 Summary of exposure in completed phase 3 studies – semaglutide s.c. for T2D

Completed phase 3 studies, excluding the CVOT (SUSTAIN 6)[a]									
Semaglutide s.c. 0.5 mg		**Semaglutide s.c. 1.0 mg**		**Semaglutide s.c. 2.0 mg**		**All semaglutide s.c.**		**All comparators[b]**	
N	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**
1,961	1,596	3,678	3,051	479	404	6,118	5,052	3,377	2,857

CVOT (SUSTAIN 6)							
Semaglutide s.c. 0.5 mg		**Semaglutide s.c. 1.0 mg**		**All semaglutide s.c.**		**Placebo**	
N	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**
823	1,488	819	1,444	1,642	2,932	1,644	3,035

[a]Exposure from the SUSTAIN studies included in Table 2-7, except the CVOT (SUSTAIN 6). [b]All comparators include both active comparators and placebo.

Abbreviations: CVOT = cardiovascular outcomes trial; N = number of participants; s.c. = subcutaneous(-ly); PYE = patient-years of exposure; T2D = type 2 diabetes mellitus.

Participants were exposed to semaglutide s.c. for up to 14 months in the completed phase 3 studies (excluding the CVOT [SUSTAIN 6]; see Table 2-12). In the CVOT (SUSTAIN 6), the majority of the participants were exposed to semaglutide s.c. for 24 months (see Table 2-12).

Table 2-12 Duration of exposure in completed phase 3 studies – semaglutide s.c. for T2D

Number of participants (%)					
Completed phase 3 studies, excluding the CVOT (SUSTAIN 6)[a]					
Duration of exposure (at least)	**Semaglutide s.c. 0.5 mg**	**Semaglutide s.c. 1.0 mg**	**Semaglutide s.c. 2.0 mg**	**All semaglutide s.c.**	**All comparators[b]**
1 month	1,961 (100.0%)	3,678 (100.0%)	479 (100.0%)	6,118 (100.0%)	3,377 (100.0%)
3 months	1,876 (95.7%)	3,508 (95.4%)	474 (99.0%)	5,858 (95.8%)	3,252 (96.3%)
6 months	1,769 (90.2%)	3,262 (88.7%)	454 (94.8%)	5,485 (89.7%)	3,111 (92.1%)
9 months	848 (43.2%)	1,942 (52.8%)	449 (93.7%)	3,239 (52.9%)	1,723 (51.0%)
12 months	583 (29.7%)	1,214 (33.0%)	1 (0.2%)	1,798 (29.4%)	1,159 (34.3%)
14 months	500 (25.5%)	774 (21.0%)	0 (0.0%)	1,274 (20.8%)	738 (21.9%)
15 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)

CVOT (SUSTAIN 6)				
Duration of exposure (at least)	**Semaglutide s.c. 0.5 mg**	**Semaglutide s.c. 1.0 mg**	**All semaglutide s.c.**	**Placebo**
1 month	820 (100.0%)	815 (100.0%)	1,635 (100.0%)	1,641 (100.0%)
3 months	780 (95.1%)	781 (95.8%)	1,561 (95.5%)	1,587 (96.7%)
6 months	743 (90.6%)	720 (88.3%)	1,463 (89.5%)	1,527 (93.1%)
9 months	719 (87.7%)	690 (84.7%)	1,409 (86.2%)	1,481 (90.2%)
12 months	703 (85.7%)	673 (82.6%)	1,376 (84.2%)	1,444 (88.0%)
15 months	685 (83.5%)	662 (81.2%)	1,347 (82.4%)	1,400 (85.3%)
18 months	670 (81.7%)	651 (79.9%)	1,321 (80.8%)	1,366 (83.2%)
21 months	655 (79.9%)	637 (78.2%)	1,292 (79.0%)	1,340 (81.7%)
24 months	642 (78.3%)	623 (76.4%)	1,265 (77.4%)	1,307 (79.6%)
28 months	1 (0.12%)	0 (0.00%)	1 (0.06%)	0 (0.00%)

[a]Exposure from SUSTAIN studies included in Table 2-7, except the CVOT (SUSTAIN 6). [b]All comparators include both active comparators and placebo.
Abbreviations: CVOT = cardiovascular outcomes trial; N = number of participants; s.c. = subcutaneous(-ly); T2D = type 2 diabetes mellitus.

In the completed phase 3 clinical studies, except the CVOT (SUSTAIN 6), 56.7% of the participants exposed to semaglutide s.c for T2D. were males. The majority (76.2%) were adults between 18 years and 64 years old and of White (63.3%) or Asian (29.8%; including Japanese) origin.

In the CVOT (SUSTAIN 6), a higher percentage of males (61.3%) were exposed to semaglutide s.c. for T2D than females (38.7%); see Table 2-13. Almost half of the participants exposed to semaglutide s.c. for T2D were more than 64 years old (48.0%) and the majority were White (83.9%).

The demographic disposition of the participants exposed to placebo or active comparator was similar to that of semaglutide s.c. for T2D-treated participants in the phase 3 studies and the CVOT (Table 2-13).

Table 2-13 Exposure by gender, age and race in completed phase 3 studies – semaglutide s.c. for T2D

Completed phase 3 studies, excluding the CVOT (SUSTAIN 6)[a]								
	Semaglutide s.c.				**All comparators[b]**			
	N		**PYE**		**N**		**PYE**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	2,617	2,046	2,209	1,687	1,435	1,136	1,202	972
65–74 years	732	531	583	430	409	298	351	254
75–84 years	120	71	86	57	68	29	50	27
≥85 years	1	0	1	0	1	1	1	1
Total	**3,470**	**2,648**	**2,878**	**2,173**	**1,913**	**1,464**	**1,604**	**1,253**
Race								
White	3,874		3,214		2,224		1,895	
Black/African American	302		234		176		144	
Asian	1,138		845		650		520	
Japanese	685		662		223		208	
American Indian/Alaska native	7		5		6		6	
Native Hawaiian/other Pacific Islander	1		0		2		2	
Other	63		52		50		45	
Unknown	48		39		46		37	
Total	**6,118**		**5,052**		**3,377**		**2,857**	
CVOT (SUSTAIN 6)								
	Semaglutide s.c.				**Placebo**			
	N		**PYE**		**N**		**PYE**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	529	325	970	597	497	346	920	648
65–74 years	381	250	675	449	395	243	750	442
75–84 years	90	57	145	86	90	64	157	103
≥85 years	7	3	8	1	5	4	10	7
Total	**1,007**	**635**	**1,798**	**1,134**	**987**	**657**	**1,836**	**1,199**
Race								
White	1,378		2,462		1,347		2,492	
Black/African American	108		177		113		188	
Asian	121		233		152		298	
Other	35		61		32		57	
Total	**1,642**		**2,932**		**1,644**		**3,035**	

[a]Exposure from SUSTAIN studies included in Table 2-7, except the CVOT (SUSTAIN 6). [b]All comparators include both active comparators and placebo.

Abbreviations: CVOT = cardiovascular outcomes trial; N = number of participants; s.c. = subcutaneous(-ly); PYE = patient-years of exposure; T2D = type 2 diabetes mellitus.

2.3.1.2 Clinical study exposure in the oral semaglutide for T2D development programme (PIONEER)

A total of 5,818 participants (corresponding to 6,699 PYE)[2] have been exposed to oral semaglutide for T2D in the phase 3 pool (including PIONEER and PIONEER PLUS), whereas 1,591 participants (1,927 PYE) were exposed to semaglutide in the CVOT (PIONEER 6); see Table 2-14.

[2] PYE is calculated as the time from first drug date to last drug date plus 38 days.

The exposure to semaglutide in the clinical studies was more than double that of the comparators. The largest proportion of participants received a dose of 14 mg daily of oral semaglutide.

Table 2-14 Summary of exposure in completed phase 3 studies – oral semaglutide for T2D

Phase 3 pool[a]															
Oral semaglutide 3 mg		**Oral semaglutide 7 mg**		**Oral semaglutide 14 mg**		**Oral semaglutide 25 mg**		**Oral semaglutide 50 mg**		**Oral semaglutide flex[b]**		**Oral semaglutide total**		**All comparators[c]**	
N	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**
1,005	1,147	1,001	1,140	2,391	2,559	534	651	534	665	353	536	5,818	6,699	2,236	2,463

CVOT (PIONEER 6)			
Oral semaglutide (3 mg, 7 mg and 14 mg)		**Placebo**	
N	**PYE**	**N**	**PYE**
1,591	1,927	1,591	1,985

[a]Exposure from the PIONEER studies included in Table 2-7, except the CVOT (PIONEER 6).

[b]Participants in PIONEER 7 received oral semaglutide using a flexible dose adjustment (3 mg, 7 mg or 14 mg) based on clinical evaluation.

[c]All comparators include both active comparators and placebo.

Abbreviations: CVOT = cardiovascular outcomes trial; N = number of participants; PYE = patient-years of exposure; T2D = type 2 diabetes mellitus.

Participants were exposed to oral semaglutide for T2D for up to 19 months in the completed phase 3 studies (Table 2-15). The majority of the participants were exposed to oral semaglutide for at least 12 months (Table 2-15).

Table 2-15 Duration of exposure in completed phase 3 studies – oral semaglutide for T2D

Phase 3 pool[a]								
Duration of exposure (at least)	**Number of participants (%)**							
	Oral semaglutide 3 mg	**Oral semaglutide 7 mg**	**Oral semaglutide 14 mg**	**Oral semaglutide 25 mg**	**Oral semaglutide 50 mg**	**Oral semaglutide flex[b]**	**Oral semaglutide all**	**All comparators[c]**
1 month	1,005 (100%)	1,001 (100%)	2,391 (100%)	533 (100%)	534 (100%)	353 (100%)	5,817 (100%)	2,236 (100%)
3 months	965 (96.0%)	952 (95.1%)	2,275 (95.1%)	517 (97.0%)	519 (97.2%)	332 (94.1%)	5,560 (95.6%)	2,163 (96.7%)
6 months	933 (92.8%)	917 (91.6%)	2,111 (88.3%)	469 (88.0%)	477 (89.3%)	317 (89.8%)	5,224 (89.8%)	2,087 (93.3%)
9 months	749 (74.5%)	742 (74.1%)	1,770 (74.0%)	446 (83.7%)	457 (85.6%)	311 (88.1%)	4,475 (76.9%)	1,744 (78.0%)
12 months	730 (72.6%)	730 (72.9%)	1,738 (72.7%)	430 (80.7%)	442 (82.8%)	303 (85.8%)	4,373 (75.2%)	1,714 (76.7%)
15 months	393 (39.1%)	402 (40.2%)	840 (35.1%)	423 (79.4%)	436 (81.6%)	184 (52.1%)	2,678 (46.0%)	508 (22.7%)
19 months	384 (38.2%)	392 (39.2%)	372 (15.6%)	0	0	183 (51.8%)	1,331 (22.9%)	406 (22.2%)
20 months	1 (0.1%)	0	1 (<0.1%)	0	0	183 (51.8%)	185 (3.2%)	97 (4.3%)
25 months	0	0	0	0	0	175 (49.6%)	175 (3.0%)	93 (4.2%)

CVOT (PIONEER 6)		
Duration of exposure (at least)	**Oral semaglutide**	**Placebo**
1 month	1,591 (100%)	1,591 (100%)
3 months	1,534 (96.4%)	1,554 (97.7%)
6 months	1,464 (92.0%)	1,518 (95.4%)
9 months	1,426 (89.6%)	1,487 (93.5%)
12 months	1,385 (87.1%)	1,441 (90.6%)
15 months	915 (57.5%)	950 (59.7%)
19 months	6 (0.4%)	0 (0.0%)

[a]Exposure from the PIONEER studies included in Table 2-7, except the CVOT (PIONEER 6).

[b]Participants in PIONEER 7 received oral semaglutide using a flexible dose adjustment (3 mg, 7 mg or 14 mg) based on clinical evaluation.

[c]All comparators include both active comparators and placebo.

Abbreviations: CVOT = cardiovascular outcomes trial; N = number of participants; T2D = type 2 diabetes mellitus.

In the phase 3 pool, half of the participants exposed to oral semaglutide were males (Table 2-16). The majority (70%) were adults between 18 years and 64 years old and of White (67.2%) or Asian (24%, including Japanese) origin.

Within the phase 3 pool, exposure by age, sex, race and region was similar between oral semaglutide and comparators, with the exception of a higher proportion of Asians in the oral semaglutide group. This reflected the study design and randomisation ratios of PIONEER 9 and 10 conducted in Japanese participants only.

In the CVOT (PIONEER 6), the majority of the participants exposed to oral semaglutide were male (68.2%); see Table 2-16. More than half of the participants exposed to oral semaglutide were more than 64 years old (56.0%) and the majority were White (72.2%).

Table 2-16 Exposure by gender, age and race in completed phase 3 studies – oral semaglutide for T2D

Phase 3 pool[a]								
	Oral semaglutide				**All comparators**			
	N		**PYE**		**N**		**PYE**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	2,306	1,760	2,732	2,036	836	728	947	820
65–74 years	814	656	925	729	313	239	337	251
75–84 years	153	118	161	109	56	63	54	55
≥85 years	2	9	1	6	0	1	0	1
Total	**3,275**	**2,543**	**3,820**	**2,879**	**1,205**	**1,031**	**1,337**	**1,126**
Race								
White	3,909		4,558		1,562		1,701	
Black/African American	312		359		146		163	
Asian	1,400		1,552		431		486	
American Indian/Alaska native	18		22		9		12	
Native Hawaiian/other Pacific Islander	4		4		1		1	
Other	82		95		32		36	
Unknown	93		108		55		63	
Total	**5,818**		**6,699**		**2,236**		**2,463**	

CVOT (PIONEER 6)								
	Oral semaglutide				Placebo			
	N		PYE		N		PYE	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	471	229	588	278	433	201	539	251
65–74 years	469	222	566	266	512	234	646	293
75–84 years	141	55	163	61	138	63	168	76
≥85 years	3	1	2	0	8	2	9	3
Total	**1,084**	**507**	**1,321**	**606**	**1,091**	**500**	**1,362**	**622**
Race								
White	1,148		1,395		1,151		1,452	
Black/African American	89		113		103		129	
Asian	324		385		306		367	
American Indian/Alaska native	14		17		15		18	
Native Hawaiian/other Pacific Islander	5		5		1		2	
Other	11		13		15		17	
Total	**1,591**		**1,927**		**1,591**		**1,985**	

[a]Exposure from the PIONEER studies included in Table 2-7, except the CVOT (PIONEER 6), and study NN9924-4257-ext.

Abbreviations: CVOT = cardiovascular outcomes trial; N = number of participants; PYE = patient-years of exposure; T2D = type 2 diabetes mellitus.

2.3.1.3 Clinical study exposure in the completed high dose study with oral semaglutide for T2D, NN9924-4635 (PIONEER PLUS)

This was a 68-week randomised, active-controlled, double-blinded, three-armed, multi-centre, multinational clinical study to compare the efficacy, safety and tolerability of oral semaglutide 14 mg, 25 mg and 50 mg in adults with T2D. Table 2-17 shows the total exposure to oral semaglutide for T2D split by dose in the clinical study NN9924-4635. A total of 1,602 participants (corresponding to 1,979 PYE)[3] have been exposed to oral semaglutide for T2D in this study. From these, 1,068 participants (corresponding to 1,308 PYE) were exposed to high doses of oral semaglutide (25 mg and 50 mg).

Participants were exposed to oral semaglutide for T2D for up to 18 months (Table 2-18). In all treatment groups, the majority of the participants were males (~58%) and of White origin (~78%); see Table 2-19.

Table 2-17 Summary of exposure in the completed high dose study– oral semaglutide for T2D, NN9924-4635 (PIONEER PLUS)

Oral semaglutide 14 mg		Oral semaglutide 25 mg		Oral semaglutide 50 mg		Oral semaglutide total	
N	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**
534	671	534	647	534	661	1,602	1,979

Abbreviations: N = number of participants; PYE = patient-years of exposure; T2D = type 2 diabetes mellitus

[3] PYE is calculated as the time from first drug date to last drug date plus 38 days.

Table 2-18 Duration of exposure in the completed high dose study– oral semaglutide for T2D, NN9924-4635 (PIONEER PLUS)

Duration of exposure (at least)	Number of participants (%)			
	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	Oral semaglutide total
1 month	534 (100%)	533 (100%)	534 (100%)	1,601 (100%)
3 months	514 (96.3%)	517 (97.0%)	519 (97.2%)	1,550 (96.8%)
6 months	481 (90.1%)	469 (88.0%)	477 (89.3%)	1,427 (89.1%)
9 months	470 (88.0%)	446 (83.7%)	457 (85.6%)	1,373 (85.8%)
12 months	458 (85.8%)	430 (80.7%)	442 (82.8%)	1,330 (83.1%)
15 months	451 (84.5%)	423 (79.4%)	436 (81.6%)	1,310 (81.8%)
18 months	2 (0.4%)	0	4 (0.7%)	6 (0.4%)

Abbreviations: N = number of participants; T2D = type 2 diabetes mellitus.

Table 2-19 Exposure by gender, age and race in the completed high dose study– oral semaglutide for T2D, NN9924-4635 (PIONEER PLUS)

	Oral semaglutide 14 mg				Oral semaglutide 25 mg				Oral semaglutide 50 mg				Oral semaglutide total			
	N		PYE		N		PYE		N		PYE		N		PYE	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	231	136	293	171	218	150	268	184	213	162	269	200	662	448	830	555
65–74 years	83	63	110	75	69	66	83	80	81	54	100	64	233	183	293	219
75–84 years	11	12	14	11	17	13	21	13	13	12	17	16	41	37	52	40
≥85 years	0	0	0	0	0	2	0	2	0	0	0	0	0	0	2	2
Total	**325**	**211**	**417**	**258**	**304**	**231**	**372**	**278**	**307**	**228**	**386**	**279**	**936**	**670**	**1175**	**815**
Race																
White	424		546		432		531		398		504		1,254		1,581	
Black/African American	19		19		22		27		18		20		59		66	
Asian	85		101		73		83		111		132		269		316	
American Indian/Alaska native	1		1		0		0		0		0		1		1	
Native Hawaiian/other Pacific Islander	0		0		2		3		0		0		2		3	
Other	7		8		6		6		8		9		21		23	
Unknown	0		0		0		0		0		0		0		0	
Total	**536**		**675**		**535**		**651**		**535**		**665**		**1,606**		**1,991**	

Abbreviations: N = number of participants; PYE = patient-years of exposure; T2D = type 2 diabetes mellitus

2.3.1.4 Clinical study exposure in the completed formulation D bioequivalence study with oral semaglutide for T2D, NN9924-4799

This was an interventional, multi-centre, randomised, three-group, full-replicate cross-over, open-label study with a study period of up to 31 weeks (including screening [4 weeks], dose escalation [2 weeks], 4 steady-state periods [20 weeks] and a follow-up period [5 weeks]). The objective of the study was to confirm the bioequivalence between oral semaglutide formulation D and the initially approved formulation at steady state in healthy participants.

The majority of the participants were exposed to both formulations of oral semaglutide due to the cross-over design of the study; see total exposure in Table 2-20. Participants were exposed to oral semaglutide for T2D for up to 6 months (Table 2-21). Approximately half of the participants exposed to oral semaglutide were males (Table 2-22). All the participants were adults between 18 years and 64 years of age and the majority were of White origin, followed by Black/African American.

Table 2-20 Summary of exposure in completed clinical pharmacology study NN9924-4799 – oral semaglutide for T2D

NN9924-4799 (Phase 1)
Oral semaglutide total
N
544

Note: study with cross over design where all participants are randomized to receive both formulations (oral semaglutide formulation D and the initially approved formulation of oral semaglutide) over several periods with no washout periods in between. Therefore, it is not meaningful to present the exposure by formulation, but only by total numbers.
Patient-years of exposure not shown since NN9924-4799 is a clinical pharmacology study with healthy participants.
Abbreviations: N = number of participants; T2D = type 2 diabetes mellitus.

Table 2-21 Duration of exposure in completed clinical pharmacology study NN9924-4799 – oral semaglutide for T2D

Phase 1	
NN9924-4799	**Number of participants (%)**
Duration of exposure (at least)	**Oral semaglutide total**
1 month	542 (100%)
2 months	520 (95.9%)
3 months	495 (91.3%)
4 months	485 (89.5%)
5 months	480 (88.6%)
6 months	199 (36.7%)

Note: study with cross over design where all participants are randomized to receive both formulations (oral semaglutide formulation D and the initially approved formulation of oral semaglutide) over several periods with no washout periods in between. Therefore, it is not meaningful to present the exposure by formulation, but only by total numbers.
Abbreviations: N = number of participants; T2D = type 2 diabetes mellitus.

Table 2-22 Exposure by gender, age and race in completed clinical pharmacology study NN9924-4799 – oral semaglutide for T2D

NN9924-4799		
	Oral semaglutide	
	N	
Age group	**Male**	**Female**
18–64 years	286	258
65–74 years	0	0
75–84 years	0	0
≥85 years	0	0
Total	**286**	**258**
Race		
White	320	
Black/African American	185	
Asian	22	
American Indian/Alaska native	5	
Native Hawaiian/other Pacific Islander	1	
Other	11	
Total	**544**	

Note: study with cross over design where all participants are randomized to receive both formulations (oral semaglutide formulation D and the initially approved formulation of oral semaglutide) over several periods with no washout periods in between. Therefore, it is not meaningful to present the exposure by formulation, but only by total numbers.

Patient-years of exposure not shown since NN9924-4799 is a clinical pharmacology study with healthy participants.

Abbreviations: N = number of participants; T2D = type 2 diabetes mellitus.

2.3.1.5 Clinical study exposure in the semaglutide s.c. 2.4 mg for WM development programme (STEP and SELECT [EX9536-4388])

A total of 3,553 participants (corresponding to 4,363 PYE)[4] (excluding the CVOT) were exposed to semaglutide s.c. 2.4 mg for WM in the completed phase 3a clinical studies. In the CVOT SELECT (EX9536-4388) 8,794 participants (25,459 PYE) were exposed to semaglutide s.c. In STEP 2, two doses of semaglutide (1.0 mg and 2.4 mg) were administered. In the remaining STEP studies and the SELECT (EX9536-4388) study, all the participants exposed to semaglutide were assigned to the 2.4 mg dose. Most of the exposure (97%) was with the 2.4 mg dose (Table 2-23).

Table 2-23 Summary of exposure in completed phase 3 studies-semaglutide s.c. 2.4 mg for WM

Completed phase 3 studies[a]							
Semaglutide s.c. 1.0 mg		**Semaglutide s.c. 2.4 mg**		**All semaglutide s.c.**		**Placebo**	
N	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**
402	530	3,151	3,833	3,553	4,363	1,596	1,976
CVOT (SELECT [EX9536-4388])							
Semaglutide s.c. 2.4 mg				**Placebo**			
N		**PYE**		**N**		**PYE**	
8,794		25,459		8,782		26,381	

[4] PYE is calculated as the time from first drug date to last drug date plus 49 days.

[a]Exposure from the STEP studies included in Table 2-7, except the CVOT SELECT (EX9536-4388).

Abbreviations: N = number of participants; s.c. = subcutaneous(-ly); PYE= patient-years of exposure.

Participants were exposed to semaglutide s.c. 2.4 mg for WM for up to 18 months in the completed phase 3a studies (excluding the CVOT SELECT [EX9536-4388], see Table 2-24). In the CVOT SELECT (EX9536-4388), the participants were exposed to semaglutide s.c. for up to 55 months (see Table 2-24). The overall median on-treatment time for semaglutide was 37.3 months.

Table 2-24 Duration of exposure in completed phase 3 studies – semaglutide s.c. 2.4 mg for WM

Number of participants (%)				
Completed phase 3 studies[a]				
Duration of exposure (at least)	**Semaglutide s.c. 1.0 mg**	**Semaglutide s.c. 2.4 mg**	**All semaglutide s.c.**	**Placebo**
1 month	400 (99.5)	3,145 (99.8)	3,545 (99.8)	1,591 (99.7)
3 months	389 (96.8)	3,068 (97.4)	3,457 (97.3)	1,564 (98.0)
6 months	373 (92.8)	2,660 (84.4)	3,033 (85.4)	1,503 (94.2)
9 months	369 (91.8)	2,575 (81.7)	2,944 (82.9)	1,440 (90.2)
12 months	361 (89.8)	2,514 (79.8)	2,875 (80.9)	1,367 (85.7)
16 months	353 (87.8)	2,383 (75.6)	2,736 (77.0)	1,066 (66.8)
18 months	–	4 (0.1)	4 (0.1)	2 (0.1)
CVOT (SELECT [EX9536-4388])				
Duration of exposure (at least)	**Semaglutide s.c. 2.4 mg**		**Placebo**	
1 month	8,794 (100)		8,782 (100)	
3 months	8,596 (97.7)		8,664 (98.7)	
6 months	8,172 (92.9)		8,440 (96.1)	
9 months	7,913 (90.0)		8,247 (93.9)	
12 months	7,741 (88.0)		8,072 (91.9)	
15 months	7,563 (86.0)		7,884 (89.8)	
18 months	7,429 (84.5)		7,745 (88.2)	
21 months	7,277 (82.7)		7,593 (86.5)	
24 months	7,139 (81.2)		7,460 (84.9)	
27 months	6,808 (77.4)		7,074 (80.6)	
30 months	6,162 (70.1)		6,416 (73.1)	
33 months	5,408 (61.5)		5,613 (63.9)	
36 months	4,831 (54.9)		5,032 (57.3)	
39 months	4,406 (50.1)		4,554 (51.9)	
42 months	3,463 (39.4)		3,597 (41.0)	
45 months	2,419 (27.5)		2,530 (28.8)	
48 months	1,487 (16.9)		1,529 (17.4)	
51 months	518 (5.9)		520 (5.9)	
55 months	9 (0.1)		9 (0.1)	

[a]Exposure from the STEP studies included in Table 2-7, except the CVOT SELECT (EX9536-4388).

Abbreviations: s.c. = subcutaneous(-ly).

In the completed phase 3a clinical studies, except the CVOT SELECT (EX9536-4388), 69.2% of the participants exposed to semaglutide s.c. 2.4 mg for WM were females (Table 2-25). The majority (85%) were adults between 18 years and 64 years of age and of White origin (73.4%).

In the CVOT SELECT (EX9536-4388), the majority of the participants exposed to semaglutide s.c. for WM were males (72.2%), see Table 2-25. The majority of participants exposed the semaglutide s.c. for WM were adults between 18 and 64 years of age (61.8%), males (72.2%), and of white origin (83.9%).

The demographic disposition of the participants exposed to placebo was similar to that for semaglutide s.c.-treated participants in the phase 3 studies and the CVOT (Table 2-25).

Table 2-25 Exposure by gender, age and race in completed phase 3a studies – semaglutide s.c. 2.4 mg for WM

Completed phase 3 studies[a]								
	Semaglutide s.c.				**Placebo**			
	N		**PYE**		**N**		**PYE**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
12 − <18 years	50	83	69	113	26	41	36	54
18–64 years	795	1,919	1,016	2,392	391	971	493	1,182
65–74 years	123	188	160	240	61	93	75	118
75–84 years	12	15	13	17	4	9	6	12
≥85 years	–	1	–	1	–	–	–	–
Total	**980**	**2,206**	**1,258**	**2,763**	**482**	**1,114**	**610**	**1,366**
Race								
White	2,338		2,938		1,179		1,452	
Black/African American	293		362		152		172	
Asian	413		539		199		267	
American Indian/Alaska native	24		31		12		14	
Native Hawaiian/other Pacific Islander	3		4		3		3	
Other	77		98		34		43	
Unknown/Not reported	38		48		17		24	
Total	**3,186**		**4,021**		**1,596**		**1,976**	
CVOT (SELECT [EX9536-4388])								
	Semaglutide s.c.				**Placebo**			
	N		**PYE**		**N**		**PYE**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	3,981	1,458	11,841	4,345	3,957	1,466	12,053	4,326
65–74 years	1,893	759	5,378	2,112	1,938	764	5,908	2,199
75–84 years	456	224	1,171	562	450	182	1,316	514
≥85 years	17	6	35	16	17	8	46	18
Total	**6,347**	**2,447**	**18,425**	**7,034**	**6,362**	**2,420**	**19,324**	**7,057**
Race								
White	7,379		21,311		7,387		22,097	
Black/African American	347		964		322		911	
Asian	720		2,220		727		2,349	
American Indian/Alaska native	23		58		21		60	
Native Hawaiian/Pacific Islander	3		4		5		14	
Other	228		665		247		748	
Not reported	95		240		73		203	
Total	**8,794**		**25,459**		**8,782**		**26,381**	

Note: For PYE, the number in decimals have been rounded off to the nearest possible whole number, wherever applicable.

The overall numbers are lower compared to Table 2-23 and Table 2-24 as participants who were exposed to both semaglutide and placebo in study NN9536-4376 are counted just once in this table as per randomisation in the main part of the study.

[a]Exposure from the STEP studies included in Table 2-7, except the CVOT SELECT (EX9536-4388).

Abbreviations: N = number of participants; s.c. = subcutaneous(-ly); PYE = patient-years of exposure.

2.4 Module SIV: Populations not studied in clinical studies

2.4.1 Exclusion criteria in clinical studies within the development programme

This section summarises the important exclusion criteria, the reason for exclusion and the rationale for why an exclusion criterion is not classified as missing information for semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. for WM (Table 2-26).

Table 2-26 Exclusion criteria in clinical studies within the development programme

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Semaglutide s.c. for T2D and oral semaglutide for T2D: Experienced more than 3 episodes of severe hypoglycaemia within 6 months prior to screening, and/or hypoglycaemia unawareness.	*Semaglutide s.c. for T2D:* • SUSTAIN 5 (add-on to insulin) • SUSTAIN 4 (add-on to SU) *Oral semaglutide for T2D:* (hypoglycaemia unawareness only): • PIONEER 8 (add-on to insulin) *Semaglutide s.c. 2.4 mg for WM:* • Not applied	To not confound the results of the smaller studies.	No Similar proportions of participants and rate of events for severe hypoglycaemia were seen with semaglutide and placebo in the studies where background insulin medication was allowed and where this exclusion criterion was not present (i.e., the CVOTs [SUSTAIN 6 and PIONEER 6] and PIONEER 5 [where SU also was allowed as background medication]).
Semaglutide s.c. for T2D: Screening calcitonin value ≥50 ng/L or ≥100 ng/L *Semaglutide s.c. 2.4 mg for WM:* Screening calcitonin value ≥50 ng/L or ≥100 ng/L	*Semaglutide s.c. for T2D:* • All phase 3a studies • SUSTAIN 7 • SUSTAIN FORTE *Oral semaglutide for T2D:* • Not applied *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	Calcitonin levels >100 ng/L are highly predictive of MTC; interpretation of values between the UNL and 100 ng/L is more uncertain.[99] The limit was chosen in order to exclude participants with a pre-existing risk of MTC.	No MTC is included as an important potential risk in the RMP based on findings from nonclinical studies in rodents.

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Semaglutide s.c. for T2D and oral semaglutide for T2D: Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN2) *Semaglutide s.c. 2.4 mg for WM:* Personal or family history (first-degree relatives) of medullary thyroid carcinoma or MEN2	*Semaglutide s.c. for T2D:* • All phase 3 studies *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	To exclude participants with a pre-existing risk of MTC.	No MTC is included as an important potential risk in the RMP based on findings from nonclinical studies in rodents.
Semaglutide s.c. for T2D and oral semaglutide for T2D: History of pancreatitis (acute or chronic) *Semaglutide s.c. 2.4 mg for WM:* • *Adults:* Acute pancreatitis within 180 days of screening, any history or presence of chronic pancreatitis • *Adolescents:* History or presence of pancreatitis (acute or chronic)	*Semaglutide s.c. for T2D:* • All phase 3 studies *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	Treatment with other GLP-1 RA has been associated with acute pancreatitis, and history of pancreatitis is a risk factor for pancreatitis.	No • Acute pancreatitis is included as an important identified risk in the PSUR. • No additional pharmacovigilance activities. • The risk is considered to be appropriately managed. Therefore, the risk is not included in the RMP.
Semaglutide s.c. for T2D: • Acute coronary or cerebrovascular event within 90 days before randomisation (phase 3a studies) • Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening (phase 3b studies) *Oral semaglutide for T2D:* • Acute coronary or cerebrovascular event within 180 days (within 60 days for the CVOT [PIONEER 6]) before randomisation *Semaglutide s.c. 2.4 mg for WM:*	*Semaglutide s.c. for T2D:* • All phase 3 studies *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	To not jeopardise patient safety and confound the results of the studies.	No • There is no medical or scientific rationale for why a different safety profile would be expected in this population, based on the cumulative knowledge. • It is unlikely that ongoing or future pharmacovigilance activities will further characterise the safety profile of the product with respect to this selected population. • No additional pharmacovigilance activities are warranted.

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
• *Adults:* Acute coronary or cerebrovascular event within 60 days before randomisation • *Adolescents:* Not applicable			
Semaglutide s.c. for T2D: • Known proliferative retinopathy or maculopathy requiring acute treatment (phase 3a studies) • Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation (SUSTAIN 7, 8, 9, 10 and China) • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or during the period between screening and randomisation (SUSTAIN FORTE) *Oral semaglutide for T2D:* • Known proliferative retinopathy or maculopathy requiring acute treatment *semaglutide s.c. 2.4 mg for WM:* • Known proliferative retinopathy or maculopathy requiring acute treatment • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy (verified by a fundus examination performed within the past 90 days prior to screening. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination)	*Semaglutide s.c. for T2D:* • All phase 3 studies, except CVOT (SUSTAIN 6) *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • STEP 2 • STEP TEENS	These participants were excluded from the phase 3 studies (excluding SUSTAIN 6) in order to not jeopardise their safety. For SUSTAIN 6, these participants were not excluded because a supportive endpoint on diabetic retinopathy complications was included, and a DMC was implemented.	No Diabetic retinopathy complications for patients with T2D are included in the RMP as an important identified risk for: • semaglutide s.c. for T2D • oral semaglutide for T2D • semaglutide s.c. 2.4 mg for WM This is based on the findings in the semaglutide s.c. CVOT (SUSTAIN 6).

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Semaglutide s.c. for T2D: • Severe and end-stage renal disease • Renal impairment measured as estimated glomerular filtration rate (eGFR) value of <60 mL/min/1.73 m^2 (SUSTAIN 7, 8, 9 and China) or <30 mL/min/1.73 m^2 (SUSTAIN 10 and FORTE) *Oral semaglutide for T2D:* • Severe and end-stage renal disease *Semaglutide s.c. 2.4 mg for WM:* • *Adults*: Renal impairement (eGFR <15 mL/min/1.73m^2) • *Adolescents*: Impaired renal function defined as serum-creatinine >upper normal range (UNR) for age in children unless renal function is proven normal by further assessments at the discretion of the investigator.	*Semaglutide s.c. for T2D*: • All phase 3 studies. • In the CVOT (SUSTAIN 6) the criterion was limited to dialysis. *Oral semaglutide for T2D*: • All phase 3a studies. • In the CVOT (PIONEER 6) the criterion was limited to dialysis. *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies.	Participants with end-stage renal disease (and on dialysis) are considered vulnerable and were excluded from studies in order not to jeopardise their safety. Participants with severe renal impairment were excluded in the non-CVOTs due to comparator label and participants safety considerations. These participants were not excluded in the CVOTs (SUSTAIN 6 and PIONEER 6) as a DMC was monitoring the safety of participants. A few studies in both the semaglutide s.c. and oral semaglutide development programme excluded participants with moderate renal impairment.	No • The SmPCs for semaglutide s.c. and oral semaglutide state that it is not recommended in participants with end-stage renal disease, and that experience in patients with severe renal impairment is limited. • There is no medical or scientific rationale for why a different safety profile would be expected in this population, based on the cumulative knowledge. • It is unlikely that ongoing or future pharmacovigilance activities will further characterise the safety profile of the product with respect to this selected population. • No additional pharmacovigilance activities are warranted.

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Semaglutide s.c. for T2D and oral semaglutide for T2D: • Heart failure, New York Heart Association (NYHA) Class IV *Semaglutide s.c. 2.4 mg for WM:* • *Adults*: Heart failure, New York Heart Association (NYHA) Class IV • *Adolescents:* Known history of heart disease (including history of clinically significant arrhythmias or conduction delays on ECG) within 180 days before screening, new clinically significant arrhythmias or conduction delays on ECG identified at screening.	*Semaglutide s.c. for T2D:* • All phase 3 studies *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	Participants with NYHA Class IV are considered vulnerable and were excluded not to confound the results of the studies.	No • The SmPCs state that the use of semaglutide s.c. and oral semaglutide is not recommended in this population and that there is no therapeutic experience in these patients. • There is no scientific rationale for why a different safety profile would be expected in this population, based on the cumulative knowledge from other GLP-1 RAs. • It is unlikely that ongoing or future pharmacovigilance activities will further characterise the safety profile of the product with respect to this selected population. • No additional pharmacovigilance activities are warranted.
Semaglutide s.c. for T2D and oral semaglutide for T2D: • ALT >2.5 × ULN	*Semaglutide s.c. for T2D:* • SUSTAIN 8, 9 and 10 *Oral semaglutide for T2D:* • All phase 3a studies except PIONEER 3, 9, 10 and the CVOT (PIONEER 6) *Semaglutide s.c. 2.4 mg for WM:* • Not applied	To ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedures and study results, and in order not to jeopardise safety of participants.	No • There is no medical or scientific rationale for why a different safety profile would be expected in this population. • It is unlikely that ongoing or future pharmacovigilance activities will further characterise the safety profile of the product with respect to this selected population. • No additional pharmacovigilance activities are warranted.

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Oral semaglutide for T2D: • History of major surgical procedures involving the stomach potentially affecting absorption *Semaglutide s.c. 2.4 mg for WM*: • Previous or planned (during the study period) obesity treatment with surgery or a weight loss device. However, the following are allowed: • liposuction and/or abdominoplasty, if performed > 1 year before screening, • lap banding, if the band has been removed > 1 year before screening, • intragastric balloon if the balloon has been removed > 1 year before screening or • duodenal-jejunal bypass sleeve if the sleeve has been removed > 1 year before screening.	*Semaglutide s.c. for T2D:* • Not applied *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	*Oral semaglutide for T2D:* These participants were excluded because of the potential impact of a surgical procedure on the uptake of oral semaglutide and thereby the potential lack of effect. *Semaglutide s.c. 2.4 mg for WM*: These treatments may influence dietary metabolism and thus, potentially, the study results.	No Lack of effect is not considered an important risk to be included in the list of safety concerns in the RMP, as it is expected to have a minimal clinical impact on the patient.
Semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM (adults): • Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma *in situ* is allowed *Semaglutide s.c. 2.4 mg for WM (adolescents):* • History or presence of malignant neoplasms within the past 5 years prior to the day of screening.	*Semaglutide s.c. for T2D:* • All phase 3 studies *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	Participants with malignant neoplasms are considered vulnerable and were excluded not to jeopardise their safety and to confound the results of the studies.	No • There is no scientific rationale for why a different safety profile would be expected in this population, based on the cumulative knowledge from semaglutide and other GLP-1 RAs. • In addition, the specific neoplasms of interest ‘MTC’ and ‘pancreatic cancer’ are included as important potential risks in the RMP.

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Semaglutide s.c. 2.4 mg for WM: • History of major depressive disorder within 2 years before screening • Diagnosis of other severe psychiatric disorders (e.g., schizophrenia, bipolar disorder) • A Patient Health Questionnaire-9 (PHQ-9) score of ≥15 at screening • A lifetime history of suicidal attempt • Suicidal behaviour within 30 days before screening • Suicidal ideation corresponding to type 4 or 5 based on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening Additionally, for adolescents: • Participants with confirmed diagnosis of bulimia nervosa disorder	*Semaglutide s.c. for T2D:* • Not applied *Oral semaglutide for T2D:* • Not applied *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	To ensure safety of the study population due to a history of adverse neuropsychiatric events among other medicinal products for weight management with different mode of action compared to GLP-1 RAs. These participants are considered vulnerable and excluded from studies in order not to jeopardise their safety and confound the results of the studies.	No • There is no medical or scientific rationale for why a different safety profile would be expected in this population based on the cumulative knowledge. • It is unlikely that ongoing or future pharmacovigilance activities will further characterise the safety profile of the product with respect to this selected population. • No additional pharmacovigilance activities are warranted.
Semaglutide s.c. 2.4 mg for WM: Treatment with any medication for the indication of obesity within the past 90 days before screening	*Semaglutide s.c. for T2D:* Not applied *Oral semaglutide for T2D:* Not applied *Semaglutide s.c. 2.4 mg for WM:* All phase 3a studies	Treatment with such medications will influence the study results (primary endpoint).	No The exclusion criterion was included in the clinical studies to avoid influence on the primary endpoint (change in body weight) and is not considered related to a safety concern.

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Semaglutide s.c. for T2D and oral semaglutide for T2D: History of diabetic ketoacidosis	*Semaglutide s.c. for T2D:* • SUSTAIN 8, 9 and 10 *Oral semaglutide for T2D:* • PIONEER 2, 4, 7 and 10 and the CVOT (PIONEER 6) *Semaglutide s.c. 2.4 mg for WM:* • Not applied	The participants were excluded in the PIONEER studies, where SGLT2 inhibitors were either comparator (PIONEER 2) or allowed as background treatment. Participants are considered vulnerable and excluded to not jeopardise safety and confound study results.	No • There is no medical or scientific rationale for why a different safety profile would be expected in this population, based on the cumulative knowledge from semaglutide and other GLP-1 RAs. • It is stated in the SmPCs that semaglutide should not be used for treatment of diabetic ketoacidosis. • It is unlikely that ongoing or future pharmacovigilance activities will further characterise the safety profile of the product with respect to this selected population. • No additional pharmacovigilance activities are warranted.

Criteria	Applied in	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Semaglutide s.c. for T2D, Oral semaglutide for T2D and Semaglutide s.c. 2.4 mg for WM: Female who is pregnant, breast-feeding or intends to become pregnant, or is of childbearing potential and not using a highly effective contraceptive method.	*Semaglutide s.c. for T2D:* • All phase 3 studies *Oral semaglutide for T2D:* • All phase 3a studies *Semaglutide s.c. 2.4 mg for WM:* • All phase 3a studies	This population was excluded due to the potential reproductive and developmental toxicity effects of semaglutide, based on observations from nonclinical studies.	Yes 'Pregnancy' is included as a missing information in the RMP for all semaglutide products. 'Lactation' is included as a missing information in the RMP only for semaglutide s.c. for T2D and semaglutide s.c. for WM. No 'Lactation' is not considered missing information for oral semaglutide for T2D. A study on lactating females exposed to oral semaglutide for T2D showed that: • SNAC was present in breastmilk and some of its metabolites were excreted in breastmilk at low concentrations. • No measurable concentrations of semaglutide were found in breastmilk (values below the lower limit for quantification). It is stated in the SmPC that Rybelsus® should not be used during breast-feeding.

Abbreviations: ALT = alanine aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; CVOT = cardiovascular outcomes trial; DMC = Data Monitoring Committee; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer; NYHA = New York Heart Association; PHQ-9 = Patient Health Questionnaire-9; PSUR = periodic safety update report; RMP = risk management plan; s.c. = subcutaneous(-ly); SGLT2 = sodium-glucose co-transporter-2; SNAC = salcaprozate sodium; SU = sulfonylurea; T2D = type 2 diabetes mellitus; UNL = upper normal limit; UNR = upper normal range; WM = weight management.

2.4.2 Limitations of ADR detection common to clinical study development programmes

The clinical development programmes are unlikely to detect certain types of adverse reactions, such as:

- rare adverse reactions
- adverse reactions with a long latency
- adverse reactions caused by prolonged or cumulative exposure

2.4.3 Limitations with respect to populations typically under-represented in clinical study development programmes

Table 2-27 provides an overview of exposure in special populations in the phase 3 clinical studies and relevant phase 1 clinical studies completed before the data lock point (DLP).

The target population for marketed use of semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM is comparable to the patient population included in the clinical development programme. No safety concerns were identified irrespective of lack of exposure in sub-populations.

Table 2-27 Exposure by indication in special populations – semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM

Type of special population	Participants exposed to semaglutide s.c. for T2D	Participants exposed to oral semaglutide for T2D	Participants exposed to semaglutide s.c. 2.4 mg for WM
Pregnant females			
	NA (excluded from clinical studies)	NA (excluded from clinical studies)	NA (excluded from clinical studies)
Lactating females			
	NA (excluded from clinical studies)	Completed clinical pharmacology study NN9924-4669	NA (excluded from clinical studies)
	-	14	-
Renal impairment (eGFR[a])			
	Completed phase 3 studies	**Completed phase 3a studies and phase 1 study NN9924-4079**	**Completed phase 3a studies**
Mild (eGFR 60–89 mL/min)	2,529	1,878	833
Moderate (eGFR 30–59 mL/min)	570	617	63
Severe (eGFR 15–29 mL/min)	41	31	2
End-stage (eGFR <15 mL/min)	5	20	0
	Phase 1 study NN9535-3616	NA	NA
Mild (eGFR >50–≤80mL/min)	11		
Moderate (eGFR >30–≤50 mL/min)	11		
Severe (eGFR ≤30 mL/min)	13[b]		
End-stage (dialysis)	13[b]		

Type of special population	Participants exposed to semaglutide s.c. for T2D	Participants exposed to oral semaglutide for T2D	Participants exposed to semaglutide s.c. 2.4 mg for WM
Hepatic impairment (Child-Pugh)			
	Completed phase 3 studies	**Completed phase 3a studies**	**Completed phase 3a studies**
	Not assessed at baseline	Not assessed at baseline	Not assessed at baseline
	Phase 1 study NN9535-3651	**Phase 1 study NN9924-4082**	**NA**
Mild (5–6 points)	8	12	
Moderate (7–9 points)	10	12	
Severe (10–15 points)	7	8	
Heart failure (NYHA Class I-IV)			
	Completed phase 3 studies	**Completed phase 3a studies**	**Completed phase 3a studies**
NYHA Class I	138	121	4
NYHA Class II	306	297	10
NYHA Class III	51	35	None included
NYHA Class IV	None included	None included	

Note: The table includes exposure from all studies included in Table 2-7.

[a]The renal function categories are based on the eGFR; for studies SUSTAIN 8, 9, 10 and FORTE, the eGFR is calculated using CKD-EPI, and for the remaining studies, the eGFR is calculated using MDRD. [b]Six of the participants with renal impairment (3 with severe renal impairment and 3 with end-stage renal disease) in study NN9535-3616 were dosed with 10 µg/kg (approximately 0.8 mg); however, subsequently the study protocol was amended and the dose was reduced to 0.5 mg. The remaining participants with renal impairment enrolled in this study after the dose was reduced.

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CVOT = cardiovascular outcomes trial; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; NA = not applicable; NYHA = New York Heart Association; T2D = type 2 diabetes mellitus; WM = weight management.

2.5 Module SV: Post-authorisation experience

2.5.1 Post-authorisation exposure

2.5.1.1 Method used to calculate exposure – Ozempic®, Rybelsus® and Wegovy®

The post-authorisation exposure is calculated using sales figures, based on the total volume (including samples) of Ozempic®, Rybelsus® and Wegovy® released from Novo Nordisk to external customers cumulatively. The exposure may be over- or underestimated as the calculation is based on volume distributed and average usage rather than actual patient exposure. A summary of post-authorisation exposure can be found in Table 2-28.

Table 2-28 Summary of post-authorisation exposure

Product	First Marketing authorisation (US)	Marketing authorisation (EU)	Launched	Estimated exposure (PYE[a])
Ozempic®	05 Dec 2017	08 Feb 2018	Globally	16,349,236
Rybelsus®	20 Sep 2019	03 Apr 2020	Globally	2,570,332
Wegovy®	04 Jun 2021	06 Jan 2022	US, Denmark, Norway, Germany, UK, Iceland, Switzerland, Japan and UAE	591,495

Abbreviation: EU = European Union, UAE = United Arab Emirates; UK = United Kingdom; US = United States, PYE =Patient-years of exposure

[a]Calculated until 05 Mar 2024. Patient-years of exposure (PYE) = (reported sales [G] × 1,000) / (defined daily dose × 365), where 365 indicates days in a year. The defined daily dose (DDD) as defined by the World Health Organization (WHO) for Ozempic®, Rybelsus® and Wegovy® is 0.11 mg, 10.5 mg and 0.34 mg, respectively.

2.5.2 Post-authorisation use and off-label use − Ozempic®, Rybelsus® and Wegovy®

Post-marketing reports received cumulatively for Ozempic® and Rybelsus® indicate that the off-label use was mainly related to patients not following the dosing regimen described in the label and use in unapproved indication (mainly weight management).

For Wegovy®, the off-label use was related to patients not being prescribed/dispensed the dosing escalation indicated in the label and mainly concerned a starting dose too high. The exact root cause could not be established.

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes – semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM

Currently, no potential for misuse has been identified. The potential for use as a recreational drug or as a drug facilitating assault is very limited. The chemical structure and basic pharmacology of semaglutide does not resemble drugs associated with abuse or dependence. Semaglutide has not shown any relevant binding to receptors/transporters of neurotransmitter systems associated with abuse or dependence potential (e.g., opiates and narcotics). Based on this and nonclinical studies of cardiovascular effects, body temperature and spontaneous activity, semaglutide is not considered to be associated with any abuse or dependence potential. There are no accounts of abuse/dependency for already marketed GLP-1 RAs. Overdosing will, in a worst-case scenario, result in severe gastrointestinal adverse events (AEs). Semaglutide is not known to be addictive.

Conclusion

Based on the clinical development programme and post-marketing experience, there is no indication that semaglutide could be an abuse substance or be used to facilitate assault, and this area is hence not considered a safety concern.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

This section is not applicable for semaglutide s.c. for T2D as the initial RMP for semaglutide s.c. for T2D was submitted prior to the implementation of revision 2 of the Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems (Rev 2). The details of the important risks for semaglutide s.c. for T2D are included in Section 2.7.3.

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP – oral semaglutide for T2D

Risks that are not considered important for the purpose of planning of risk management for oral semaglutide are grouped based on the rationale for non-inclusion (Table 2-29). Overall, the impact of the risks on the overall benefit–risk balance is considered to be low. The risks are considered to be fully characterised in the clinical development programme for oral semaglutide and are considered to be appropriately managed in the proposed product labelling for oral semaglutide.

Table 2-29 Risks not considered important for inclusion in the list of safety concerns – oral semaglutide for T2D

Risk	Benefit−risk impact
Risks with minimal clinical impact on patients	
Decreased appetite	Decreased appetite is listed as a common ADR in the SmPC Section 4.8. All events of PT Decreased appetite in the phase 3a pool were non-serious and the majority were mild in severity. A dose-dependent increase in decreased appetite was observed in both PIONEER 3 and the placebo dose pool.
Weight decreased	Weight decreased is listed as an uncommon ADR in the SmPC Section 4.8. Participants treated with oral semaglutide had a dose-dependent weight loss that was larger than observed with comparator. The majority of events were mild or moderate, reported as probably or possibly related to study product and the participants were reported as recovered. Oral semaglutide is indicated for participants with T2D, a population where the majority have overweight and will benefit from losing weight. Few participants with low BMI reported weight loss. A decrease in body weight could potentially be serious in these participants; however, considering the low frequency, the risk is considered to be acceptable.
Fatigue	Fatigue is listed as a common ADR in the SmPC Section 4.8 (also covering PT Asthenia). The majority of the events in the phase 3a pool were non-serious. The median onset date for fatigue was during the dose escalation period in the phase 3a pool. Fatigue was frequently co-reported with gastrointestinal adverse events.
Medication errors (including lack of effect)	In general, medication errors could result in either increased or decreased exposure to semaglutide, which in turn could lead to gastrointestinal AEs or lack of efficacy. In the oral semaglutide phase 3a pool, AEs related to medication errors were rare (0.5 events per 100 SYE) and reported in a smaller proportion of participants randomised to oral semaglutide than to comparators. Co-reported events (PTs Nausea, Vomiting and Decreased appetite) with a temporal relationship to an event of overdose were reported in 1 case. No other co-reported events were clinically related and/or timely associated with the medication error events. No events related to hypoglycaemia were reported in participants treated with oral semaglutide and reporting medication errors. In the SmPC Section 4.9, it is described that effects of overdose may be associated with gastrointestinal disorders and that appropriate supportive treatment should be initiated according to the patient's signs and symptoms in the event of overdose. There could be a hypothetical risk of lack of efficacy connected to patients dispensing the tablets in advance, as this might affect the degradation of oral semaglutide. However, this has not been observed in the clinical development programme. Directions are included in the SmPC, PL and on the pack to inform patients to store the tablets in the original blister package until administration.
Increased heart rate	Increased heart rate is listed as an uncommon ADR in the SmPC Section 4.8 and seems to be a class effect for GLP-1 RAs. In the phase 3a pool, mean increase of 2 beats per minute (bpm) was observed with oral semaglutide. All events of PT Heart rate increased in the phase 3a pool were non-serious and of mild to moderate severity. In the CVOT (PIONEER 6), the mean pulse rate increased from baseline to end-of-treatment with oral semaglutide (4 bpm), whereas no changes were seen with placebo. The estimated HR of first EAC-confirmed MACE was 0.79 [0.57; 1.11]95% CI for oral semaglutide relative to placebo.

Risks where serious consequences occur at low frequencies and therefore are considered to be acceptable	
Gastrointestinal adverse reactions	Nausea and diarrhoea are listed as very common ADRs in the SmPC Section 4.8 and vomiting is listed as a common ADR. Gastrointestinal adverse reactions were the most frequently reported events in the clinical studies with oral semaglutide, primarily driven by nausea, vomiting and diarrhoea. Most events in the phase 3a pool were mild to moderate in severity and of short duration. The events were most frequently reported during the first 3−4 months on treatment. Gastrointestinal adverse reactions is a class effect for GLP-1 RAs and are listed events for Rybelsus® in Section 4.8 of the SmPC. In addition, a warning is included in the SmPC Section 4.4 stating that gastrointestinal adverse reactions can cause dehydration, which in rare cases can lead to a deterioration of renal function.
Hypoglycaemia (in combination with other anti-glycaemic agents)	Hypoglycaemia in combination with insulin/SU or with other OADs is listed as very common or common ADRs, respectively, in the SmPC Section 4.8. Hypoglycaemia is a well-known risk for all insulin and SU medicinal products and for GLP-1 RAs when administered in combination with other anti-glycaemic agents. The rate for severe hypoglycaemia (level 3)[a] in the phase 3a pool was 0.3 events per 100 SYE. Severe hypoglycaemia was primarily observed when oral semaglutide was used with insulin. Few episodes were observed with oral semaglutide in combination with SU or other oral glucose-lowering drugs. A warning of the increased risk of hypoglycaemia when semaglutide is used in combination with SU or insulin is included in Section 4.4 of the SmPC in line with the labelling of other marketed GLP-1 RAs.
Allergic reactions	Anaphylactic reaction is listed as a rare ADR in the SmPC Section 4.8. Allergic reaction is a hypothetical risk for all protein-based drugs. No events of anaphylactic reactions have been observed in participants treated with oral semaglutide in the completed clinical studies. The rate of adverse events related to immunogenicity was 2.9 events per 100 SYE, whereas it was <0.1 event per 100 SYE for serious adverse events in the phase 3a pool. The majority of the immunogenicity-related events were of mild or moderate severity and deemed by the investigator to be unlikely related to study product. Hypersensitivity to semaglutide or any of the excipients is included as a contraindication in the SmPC Section 4.3.
Lipase and amylase increased	Lipase and amylase increased are listed as a common ADR in Section 4.8 of the SmPC. The elevations of lipase or amylase activities seen with oral semaglutide were not predictive of later development of pancreatitis in the absence of other signs or symptoms of pancreatitis. The elevated lipase and amylase enzymes observed with oral semaglutide are therefore not considered a safety concern.
Cholelithiasis	Cholelithiasis is listed as an uncommon ADR in Section 4.8 of the SmPC. In the phase 3a pool, few events of cholelithiasis were SAEs. All participants had recovered or were recovering by the end of the studies. Potential complications of cholelithiasis, cholecystitis and pancreatitis were reported at a comparable rate for oral semaglutide and comparator/placebo.

[a]According to ADA classification (severe: requiring assistance from another person for recovery).[100]

Abbreviations: ADA = American Diabetes Association; ADR = adverse drug reaction; AE = adverse event; BMI = body mass index; bpm = beats per minute; EAC = event adjudication committee; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; OAD = oral antidiabetic drug; PL = package leaflet; SAE = serious adverse event; SmPC = Summary of Product Characteristics; SU = sulfonylurea; SYE = subject-years of exposure; T2D = type 2 diabetes mellitus.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP – oral semaglutide for T2D

The risks included in Table 2-30 are considered the important risks for inclusion in the list of safety concerns for oral semaglutide. They are further characterised in Section 2.7.3.

Table 2-30 Brief presentation of important safety concerns – oral semaglutide for T2D

Safety concerns	Benefit−risk impact
Important identified risks	
Diabetic retinopathy complications	The risk is included as an important identified risk for oral semaglutide based on the findings in the semaglutide s.c. clinical development programme. Based on the totality of data on diabetic retinopathy collected across the oral semaglutide phase 3a studies, there was no increased risk of diabetic retinopathy with oral semaglutide. Most events were non-serious, of mild or moderate severity, and found by routine examination. There was no treatment difference in the distribution of events by severity or treatment requirements. Participants with events typically had pre-existing diabetic retinopathy and longer diabetes duration with no treatment differences.
Important potential risks	
Pancreatic cancer	The risk is included as an important potential risk, based on the outcome of the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369). Pancreatic metaplastic changes have been observed in animal models following administration of incretin mimetic drugs, which may suggest that prolonged exposure to incretin mimetic drugs lead to an increased risk of pancreatic cancer. Therefore, the risk is included as an important potential risk for oral semaglutide. There was no indication of an increased relative risk in the oral semaglutide treatment group vs. comparator, including placebo, in the phase 3a pool and in the CVOT (PIONEER 6). Pancreatic cancer is a serious medical condition and most of the events reported in participants receiving oral semaglutide were serious, however assessed as unlikely related to study drug by investigator. One of the events reported in the oral semaglutide treatment arm was fatal.
Medullary thyroid cancer	This potential class risk is based on findings in mice and rats for all currently approved GLP-1 RAs. Data from the monitoring of calcitonin (a marker for MTC) in plasma in the oral semaglutide clinical development programme did not support a semaglutide effect on calcitonin in humans. One event of MTC was reported in the CVOT (PIONEER 6), in a participant with a medical history of thyroid micronodules and elevated calcitonin at baseline; hence a causal relationship to oral semaglutide is not very likely. No other events of MTC were reported in the phase 3a studies.
Neoplasms (malignant and non-malignant)	There is no evidence from clinical studies that GLP-1-based therapies increase the risk of neoplasms. However, the number of participants exposed to oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms, and therefore the risk is included in the RMP. In the phase 3a studies, the proportion of participants with neoplasms (malignant and non-malignant) were comparable, albeit slightly higher with semaglutide than with comparator. The majority of the neoplasm events were non-serious, mild and deemed by the investigator as unlikely to be related to the study product.

Abbreviations: CVOT = cardiovascular outcomes trial; MTC = medullary thyroid cancer; T2D = type 2 diabetes mellitus.

2.7.1.3 Risks not considered important for inclusion in the list of safety concerns in the RMP – semaglutide s.c. 2.4 mg for WM

Risks that are not considered important for the purpose of planning of risk management for semaglutide s.c. 2.4 mg for WM are grouped based on the rationale for non-inclusion (Table 2-31). Overall, the impact of the risks on the overall benefit–risk balance is considered to be low. The risks are considered to be fully characterised in the clinical development programme for semaglutide s.c. 2.4 mg for WM and appropriately managed in the proposed product labelling for semaglutide s.c. 2.4 mg for WM.

Table 2-31 Risks not considered important for inclusion in the list of safety concerns – semaglutide s.c. 2.4 mg for WM

Risk	Benefit−risk impact
Risks with minimal clinical impact on patients	
Fatigue	Fatigue is listed as a common ADR in the SmPC Section 4.8 (also covering the PT Asthenia). The majority of the events in the phase 3a pool were non-serious. Fatigue was more frequent during the dose escalation.
Medication errors (including lack of effect)	In general, medication errors could result in either increased or decreased exposure to semaglutide, which in turn could lead to gastrointestinal AEs or lack of efficacy. In the semaglutide phase 3a pool, AEs related to medication errors were rare (0.7 events per 100 SYE) and reported at a similar rate as that for placebo (0.6 events per 100 SYE). The majority of events occurred during the first 20 weeks of treatment, i.e., the dose escalation period. The most common reasons for medication error events were distraction of the participants and misunderstanding of the dosing schedule. In the phase 3a pool, AEs reported within 14 days of a medication error event were primarily related to the gastrointestinal system, such as nausea, vomiting and abdominal pain. The reported AEs were all non-serious, and the majority were mild or moderate in severity. In the SmPC Section 4.9, it is described that overdose with semaglutide may be associated with gastrointestinal disorders, which could lead to dehydration. In the event of overdose, the patient should be observed for clinical signs and appropriate supportive treatment initiated. The dispensing (and patient availability) of several pre-filled pens with different strengths holds a risk of overdose due to mix-up. The instructions for use include “Warning: Warn user that verifying the correct drug product is important”. In case of an overdose of semaglutide due to a mix-up of the pre-filled pens, the guidance in the SmPC Section 4.9 should be adhered to.
Increased heart rate	Increased heart rate is listed as an uncommon ADR in the SmPC Section 4.8 and seems to be a class effect for GLP-1 RAs. In the phase 3a dose escalation group, mean increase of 3 beats per minute (bpm) was observed with semaglutide 2.4 mg. All events of PT Heart rate increased in the phase 3a dose escalation group were non-serious, and the majority were mild to moderate in severity.
Headache	Headache is listed as a very common ADR in the SmPC Section 4.8. All but one of the events in the phase 3a pool were non-serious. Headache was more frequently reported in the dose escalation period.
Injection site reactions	Injection site reactions is listed as a common ADR in the SmPC Section 4.8. All of the events in the phase 3a pool were non-serious, and the majority were mild to moderate in severity.
Hair loss	Hair loss is listed as a common ADR in the SmPC Section 4.8. All events in the phase 3a pool were non-serious. The events were mainly mild in severity, and most of the patients recovered while on continued treatment. Hair loss was reported more frequently in patients with a greater weight loss (≥20%).
Risks where serious consequences occur at low frequencies and therefore are considered to be acceptable	
Gastrointestinal adverse reactions	Nausea, vomiting, diarrhoea, constipation and abdominal pain are listed as very common ADRs in the SmPC Section 4.8. Gastrointestinal adverse reactions were the most frequently reported events in the clinical studies with semaglutide 2.4 mg, primarily driven by nausea, vomiting, constipation and diarrhoea. Most of the events in the phase 3a dose escalation group were non-serious and mild to moderate in severity. The events were most frequently reported during the first 3−4 months of treatment. Gastrointestinal adverse reactions is a class effect for GLP-1 RAs and are listed events in Section 4.8 of the SmPC. In addition, a warning is included in the SmPC Section 4.4 stating that gastrointestinal adverse reactions can cause dehydration, which in rare cases can lead to deterioration of renal function.

Risk	Benefit−risk impact
Acute pancreatitis	A class labelling exists for all incretin-based therapies concerning the risk of pancreatitis. Published clinical data with a range of incretin-based therapies have indicated that there is no causal relationship between treatment with incretins and acute pancreatitis.[101-105] Acute pancreatitis is included as an uncommon ADR in Section 4.8 of the SmPC, and the class labelling text is included in Section 4.4.
Allergic reactions	Anaphylactic reactions is listed as a rare ADR in the SmPC Section 4.8. Allergic reactions is a hypothetical risk for all protein-based drugs. No events of anaphylactic reactions were observed in participants treated with semaglutide 2.4 mg in the completed clinical studies. In the phase 3a pool, the proportion of participants reporting AEs of allergic reactions were similar with semaglutide 2.4 mg and placebo. The majority of the events were non-serious, mild or moderate in severity and assessed by the investigator as unlikely related to the study product. The most frequently reported PTs were Rash, Eczema, Urticaria, Dermatitis contact and Rhinitis allergic, all reported by a similar proportion of participants exposed to semaglutide 2.4 mg and placebo. Hypersensitivity to semaglutide or any of the excipients is included as a contraindication in the SmPC Section 4.3.
Lipase and amylase increased	Lipase and amylase increased is listed as an uncommon ADR in Section 4.8 of the SmPC. The elevations of lipase or amylase activities seen with semaglutide 2.4 mg were not predictive of later development of pancreatitis in the absence of other signs or symptoms of pancreatitis. The elevated lipase and amylase enzymes observed with oral semaglutide are therefore not considered a safety concern.
Cholelithiasis	Cholelithiasis is listed as a common ADR in Section 4.8 of the SmPC. In the phase 3a pool, cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of the patients treated with semaglutide 2.4 mg. All events resolved, and none led to permanent discontinuation of the trial product.
Hypoglycaemia (in patients with T2D)	Hypoglycaemia in patients with T2D is listed as a common ADR in the SmPC Section 4.8. Hypoglycaemia is a well-known risk for all insulin and SU medicinal products and for GLP-1 RAs when administered in combination with other anti-glycaemic agents. One event of severe hypoglycaemia (level 3[a]) was reported in the STEP 2 study. A warning of the increased risk of hypoglycaemia when semaglutide is used in combination with SU or insulin is included in Section 4.4 of the SmPC in line with the labelling of other marketed GLP-1 RAs.

[a]According to ADA classification (severe: requiring assistance from another person for recovery).[100]

Abbreviations: ADA = American Diabetes Association; ADR = adverse drug reaction; AE = adverse event; BMI = body mass index; bpm = beats per minute; GLP-1 RA = glucagon-like peptide-1 receptor agonist; PT = preferred term; SmPC = Summary of Product Characteristics; SU = sulfonylurea; SYE = subject-years of exposure; T2D = type 2 diabetes mellitus.

2.7.1.4 Risks considered important for inclusion in the list of safety concerns in the RMP – semaglutide s.c. 2.4 mg for WM

The risks included in Table 2-32 are considered the important risks for inclusion in the list of safety concerns for semaglutide s.c. for WM. They are further characterised in Section 2.7.3.

Table 2-32 Brief presentation of important safety concerns – semaglutide s.c. 2.4 mg for WM

Safety concerns	Benefit−risk impact
Important identified risks	
Diabetic retinopathy complications	The risk is included as an important identified risk for semaglutide for WM in patients with T2D based on the findings in the semaglutide s.c. clinical development programme. In the STEP 2 study, diabetic retinopathy was reported by 2.7% of participants treated with semaglutide s.c. 1.0 mg, 4.0% of participants treated with semaglutide s.c. 2.4 mg and 2.7% of participants treated with placebo. None of the events were serious, and the majority of the events were mild in severity. Diabetic retinopathy at baseline was more prevalent in participants with events compared to participants without events across all treatment arms. The majority of the events were identified at the two scheduled eye examinations and not due to emergence of eye-related symptoms. For the majority of the events, no treatment was deemed necessary, only observation.
Important potential risks	
Pancreatic cancer	The risk is included as an important potential risk based on the outcome of the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369). Pancreatic metaplastic changes have been observed in animal models following administration of incretin mimetic drugs, which may suggest that prolonged exposure to incretin mimetic drugs leads to an increased risk of pancreatic cancer. Therefore, the risk is included as an important potential risk for semaglutide s.c. 2.4 mg for WM. There was no indication of an increased relative risk in the semaglutide s.c. 2.4 mg for WM treatment group compared to placebo in the phase 3a pool, with no events of pancreatic cancer being reported in any of the studies. Pancreatic cancer is a serious medical condition and as it is considered an important potential risk for semaglutide in type 2 diabetes mellitus, it is also included as a risk for WM.
Medullary thyroid cancer	This potential class risk is based on findings in mice and rats for all currently approved GLP-1 RAs. Data from the monitoring of calcitonin (a marker for MTC) in plasma in the oral semaglutide clinical development programme did not support a semaglutide effect on calcitonin in humans. No events of MTC were reported in phase 3a studies.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; CVOT = cardiovascular outcomes trial; EAC = event adjudication committee; GLP-1 RA = glucagon-like peptide-1 receptor agonist; MTC = medullary thyroid cancer; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus; ULN = upper limit normal.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns for semaglutide s.c. for T2D, oral semaglutide for T2D or semaglutide s.c. 2.4 mg for WM.

The safety concern ‘lactation’ has been proposed to be removed from the missing information for oral semaglutide for T2D in the current version of the RMP. In accordance with GVP Module V, Rev. 2, fully characterised and appropriately managed risks do not require further risk management. Details can be found in Section 2.7.2.1.

2.7.2.1 Removal of missing information

Novo Nordisk has proposed to remove the safety concern ‘lactation’ from the missing information for oral semaglutide for T2D in the semaglutide RMP. This is based on the results from study NN9924-4669, which investigated semaglutide and SNAC concentrations in breastmilk following the administration of oral semaglutide in healthy, lactating females. No measurable concentrations

of semaglutide were found in breastmilk of lactating females. SNAC was present in breastmilk and some of its metabolites were excreted in breastmilk at low concentrations. As a risk to a breast-fed child cannot be excluded, Rybelsus® should not be used during breast-feeding. This is reflected in the SmPC of Rybelsus®. According to GVP Module V, Rev. 2, fully characterised and appropriately managed risks do not require further risk management.

Study NN9924-4669 was designed to investigate the concentrations of semaglutide, SNAC and SNAC metabolites in breastmilk of lactating females following oral dosing with semaglutide. No dedicated studies have been conducted to investigate semaglutide concentrations in breastmilk upon s.c. dosing. As such, lactation will remain as missing information for semaglutide s.c. for T2D and WM.

2.7.3 Details of important identified risks, important potential risks, and missing information

The important risks and missing information described in detail below and summarized in Table 2-38 apply to semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM. The important identified risk of diabetic retinopathy complications only applies to patients with T2D.

2.7.3.1 Important identified risk: Diabetic retinopathy complications (only for patients with T2D)

Potential mechanisms

It is well established that a rapid decline in blood glucose can lead to initial worsening of diabetic retinopathy.[106] Treatment with semaglutide is associated with rapid initial decline in blood glucose, and analyses from the semaglutide s.c. CVOT (SUSTAIN 6) indicate this as the most likely mechanism underlying the increased risk of diabetic retinopathy complications with semaglutide s.c. treatment. The treatment difference observed in the CVOT (SUSTAIN 6) was primarily seen in the subset of participants characterised by a longer duration of diabetes, history of diabetic retinopathy at baseline, a high baseline HbA_{1c} and insulin use.

Other studies, such as the Diabetes Control and Complications Trial (DCCT),[106] have shown that despite the detriment of the initial early worsening, participants experienced a substantial long-term benefit from good glycaemic control with respect to diabetic retinopathy.

Evidence source and strength of evidence

The risk of diabetic retinopathy complications was identified for semaglutide s.c. based on findings in the CVOT (SUSTAIN 6), where a total of 3,297 participants with T2D and high cardiovascular risk were included. In the CVOT (SUSTAIN 6), participants with known proliferative retinopathy or maculopathy requiring acute treatment were not excluded.

The risk is included for oral semaglutide based on the findings in the semaglutide s.c. clinical development programme. Based on the totality of data on diabetic retinopathy collected across the oral semaglutide phase 3a studies, there was no increased risk of diabetic retinopathy with oral semaglutide (see details below).

The risk is included for semaglutide s.c. 2.4 mg for WM in patients with T2D based on the findings in the semaglutide s.c. for T2D clinical development programme.

In STEP 2 study, few diabetic retinopathy events were reported, but with higher rates and proportions with semaglutide 2.4 mg than with placebo.

Participants with known proliferative retinopathy or maculopathy requiring acute treatment were excluded from the clinical studies with oral semaglutide for T2D and STEP 2 (see Table 2-26).

Characterisation of the risk

Impact on quality of life

Diabetic retinopathy is reported to significantly reduce health-related quality of life.[107-109] Diabetic retinopathy is often asymptomatic, particularly in the early stages of the disease. For patients experiencing complications in the later stages of the disease, e.g., significantly reduced vision (including blindness), the impact is considered major. However, for most patients, the impact is considered to be low as the condition is manageable with appropriate monitoring and treatment.

Data from clinical studies with semaglutide s.c. for T2D

In the semaglutide s.c. CVOT (SUSTAIN 6), a composite endpoint to assess diabetic retinopathy complications was included. This endpoint was adjudicated using the four individual criteria (an event could fulfil one or more criteria):

- need for treatment with photocoagulation
- need for treatment with intravitreal agents
- vitreous haemorrhage
- development of diabetes-related blindness

No exclusion criteria regarding diabetic retinopathy were implemented in the CVOT (SUSTAIN 6). The frequencies shown in Table 2-33 (reported rates per 100 subject-years of observation) are based on the first event reported during the CVOT (SUSTAIN 6), regardless of treatment adherence and confirmed by the event adjudication committee (EAC).

Table 2-33 EAC-confirmed events (in-study) of diabetic retinopathy complications in the CVOT (SUSTAIN 6) – semaglutide s.c. for T2D

	0.5 mg semaglutide	1.0 mg semaglutide	All semaglutide	Placebo
Number of participants	826	822	1,648	1,649
SYO	1,708	1,700	3,408	3,401
Number of participants with diabetic retinopathy reported at baseline	270 (32.7%)	240 (29.2%)	510 (30.9%)	459 (27.8%)
	N/%/E/R	**N/%/E/R**	**N/%/E/R**	**N/%/E/R**
Diabetic retinopathy complication	25/3.0/28/1.64	25/3.0/34/2.00	50/3.0/62/1.82	29/1.8/36/1.06
Need for treatment with photocoagulation	21/2.5/21/1.23	17/2.1/22/1.29	38/2.3/43/1.26	20/1.2/24/0.71
Need for treatment with intravitreal agents	6/0.7/6/0.35	10/1.2/12/0.71	16/1.0/18/0.53	13/0.8/14/0.41
Vitreous haemorrhage	7/0.8/7/0.41	9/1.1/12/0.71	16/1.0/19 0.56	7/0.4/8/0.24
Development of diabetes-related blindness	4/0.5/4/0.23	1/0.1/1/0.06	5/0.3/5/0.15	1/0.1/1/0.03

Note: E: number of events, N: number of participants experiencing at least one event, %: percentage of participants experiencing at least one event, R: event rate per 100 SYO, SYO: subject-years of observation is calculated from the time period from when a participant was randomised until the final scheduled visit.

Abbreviations: CVOT = cardiovascular outcome trial; EAC = event adjudication committee; s.c. = subcutaneous(-ly); SYO = subject-years of observation; T2D = type 2 diabetes mellitus.

A higher proportion of semaglutide-treated participants than placebo-treated participants with EAC-confirmed events of diabetic retinopathy complications were observed shortly after study initiation; this continued throughout the study (3.0% vs. 1.8%). An imbalance was observed for all four components of the endpoint (Table 2-33). No dose effect of semaglutide was seen. Of the 79 participants who experienced diabetic retinopathy complications, 83.5% (n = 66) had pre-existing diabetic retinopathy and most had been treated with insulins. For participants without a history of diabetic retinopathy at baseline, the number of events was similar for semaglutide and placebo, indicating no increased relative risk.

Evaluation of seriousness, severity and outcome is not available for the EAC-confirmed events of diabetic retinopathy complications, as the adjudicators were not asked to evaluate this for any of the criteria of the endpoint.

In the remaining phase 3 studies, involving 9,495 participants, the number of reported AEs related to diabetic retinopathy was the same for semaglutide (2.1%) and comparators (2.1%). Participants requiring acute treatment for proliferative retinopathy or maculopathy were excluded from these studies. No adjudicated endpoint for diabetic retinopathy complications was included in these studies. The events of diabetic retinopathy in these studies were captured in Novo Nordisk databases.

Two of the AEs led to treatment discontinuation.

A randomised clinical study (NN9535-4352, FOCUS) is being conducted to evaluate the long-term effects of semaglutide on diabetic retinopathy development and progression when added to standard of care in participants with T2D (see Section 3.2.1).

Data from clinical studies with oral semaglutide for T2D

In the oral semaglutide phase 3a programme, the risk of diabetic retinopathy and related complications has been evaluated based on investigator-reported AEs using a pre-defined MedDRA search to capture events of diabetic retinopathy and related complications. The events were not adjudicated; instead, the investigator was to report all retinopathy events during the study on a standard AE form and provide additional relevant details about the events on a dedicated diabetic retinopathy form, which was implemented in all PIONEER studies. The in-study observation period has been used for the evaluations of diabetic retinopathy and related complications due to the potentially long latency between onset and diagnosis.

The proportion of participants with events and the rate of events were slightly higher with oral semaglutide than with comparators in the phase 3a pool (4.9% vs. 3.3% and 4.4 vs. 3.2 events per 100 subject-years of observation [SYO], Table 2-34) and slightly higher with oral semaglutide than with placebo in the placebo pool (3.8% vs. 2.9% and 4.9 vs. 3.5 events per 100 SYO, data not shown) and in the CVOT (PIONEER 6 [7.1% vs. 6.3% and 6 vs. 5 events per 100 SYO, data not shown]). Few events were serious and with no treatment difference. No consistent pattern was seen across the individual studies. Consistent with the differences in patient population between the CVOT (PIONEER 6) and the other phase 3a studies, the proportion of participants with events and the rate of events were higher in the CVOT (PIONEER 6) than in the phase 3a pool and the placebo pool. No dose–response relationship was observed for oral semaglutide.

Results described below are from the phase 3a pool; however, the same overall pattern was observed in the CVOT (PIONEER 6).

The most frequently reported events were PTs Diabetic retinopathy and Retinopathy; the remaining event types were reported in low numbers. There was no apparent difference between oral semaglutide and comparators when looking at events by PT. Most events were non-serious, of mild or moderate severity and did not require treatment, and there was no treatment difference in the distribution of events by severity (Table 2-34).

Table 2-34 Events of diabetic retinopathy and related complications (in-study) in the phase 3a pool – oral semaglutide for T2D

	Oral semaglutide	**All comparators[a]**
Number of participants	4,216	2,236
SYO	5,024	2,555
	N/%/E/R	**N/%/E/R**
All events	206/4.9/223/4.4	74/3.3/83/3.2
Serious events	2/<0.1/2/0.0	3/0.1/4/0.2
	N/%/E/R	**N/%/E/R**
Mild	165/3.9/174/3.5	64/2.9/67/2.6
Moderate	42/1.0/47/0.9	11/0.5/13/0.5
Severe	1/<0.1/2/0.0	2/<0.1/3/0.1
Relationship to study product		

	Oral semaglutide	All comparators[a]
Probable	15/0.4/16/0.3	6/0.3/6/0.2
Possible	52/1.2/54/1.1	13/0.6/13/0.5
Unlikely	140/3.3/153/3.0	57/2.5/64/2.5
Leading to premature study discontinuation		
Yes	1/<0.1/1/0.0	0

Note: Includes all PIONEER studies in Table 2-7 except the CVOT (PIONEER 6). %: the proportion of participants with at least one event. R: event rate per 100 subject-years of observation. Relationship to study product is as judged by the investigator. N: number of participants with at least one event; SYO: subject-years of observation, calculated from time period from when a participant was randomised until the final scheduled visit; E: number of events.
[a]All comparators include both active comparators and placebo.

Abbreviations: CVOT = cardiovascular outcomes trial; SYO = subject-years of observation; T2D = type 2 diabetes mellitus.

Most of the reported events (>93%) in both treatment groups were identified in relation to routine examinations (as part of the clinical studies) and not based on symptoms. A small proportion of the events in both treatment groups were proliferative diabetic retinopathy (oral semaglutide: 3.1%; comparators: 5.3%).

Participants with events of diabetic retinopathy and related complications had longer diabetes duration (~2 years longer) and a larger proportion of the participants had a history of diabetic retinopathy at baseline (31–34% vs. 15–16%), regardless of treatment with oral semaglutide or comparators. These results are consistent with the known risk factors for diabetic retinopathy and related complications (see details below). Furthermore, when comparing within each treatment group, a larger proportion of the participants with events were on insulin at baseline compared to the participants without events (oral semaglutide: 21.0% vs. 14.9%; comparator 14.9% vs. 10.6%). This is likely reflecting a more progressed diabetes stage as also indicated by the longer diabetes duration.

Results from the study NN9535-4352 (FOCUS) for semaglutide s.c. will be relevant also for the ongoing evaluation of the risk for oral semaglutide.

Data from clinical studies with semaglutide s.c. 2.4 mg for WM

Adult population:

The increased risk of diabetic retinopathy complications observed in SUSTAIN 6 led to the inclusion of retinal disorders as a safety focus area for the STEP 2 study in the semaglutide 2.4 mg for WM programme. Retinal disorders were evaluated in STEP 2 as this study included a T2D population. The evaluation was based on AEs from a pre-specified MedDRA search as well as results of eye exams performed at baseline, week 52 and week 68 (end-of-treatment). In STEP 2, participants with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were not eligible for enrolment in the study. The investigator was to report AEs related to retinal disorders on the standard AE form and only if the event was assessed as a new onset or a worsening of diabetic retinopathy should additional relevant details about these AEs be provided on the dedicated diabetic retinopathy form. The additional details included type of event, how the event was identified and whether the event required treatment. This information has been used as a supplement to the standard AE information to enable a more comprehensive evaluation of these events.

The events of retinal disorders, as identified by the pre-specified MedDRA search, were reported by a larger proportion of participants with semaglutide 1.0 mg and 2.4 mg than with placebo (6.2%, 6.9% and 4.2%, respectively; Table 2-35) with no clear dose–response relationship between the two semaglutide doses.

No serious AEs were reported for any of the treatment groups.

The majority of the events were mild in severity and assessed as unlikely related to the study product.

One participant discontinued treatment with the study product permanently and one participant had a dose reduction of the study product, both participants were treated with semaglutide 1.0 mg. The former participant did not recover from the event and also did not receive any treatment for the event but was under observation only, and the latter participant recovered from the event and completed treatment with semaglutide.

Table 2-35 Events of diabetic retinopathy and related complications (in-study) in STEP 2 (NN9536-4374) – semaglutide s.c. 2.4 mg for WM

	1.0 mg semaglutide	2.4 mg semaglutide	Placebo
Number of participants	402	403	402
SYO	569.1	572.8	566.6
	N/%/E/R	**N/%/E/R**	**N/%/E/R**
All events	25/6.2/30/5.3	28/6.9/36/6.3	17/4.2/19/3.4
Serious events	0	0	0
	N/%/E/R	**N/%/E/R**	**N/%/E/R**
Mild	23/5.7/27/4.7	25/6.2/30/5.2	16/4.0/18/3.2
Moderate	2/0.5/2/0.4	5/1.2/6/1.0	1/0.2/1/0.2
Severe	1/0.2/1/0.2	0	0
Relationship to study product			
Probable	1/0.2/1/0.2	1/0.2/1/0.2	0
Possible	4/1.0/4/0.7	4/1.0/5/0.9	1/0.2/1/0.2
Unlikely	21/5.2/25/4.4	23/5.7/30/5.2	16/4.0/18/3.2
Leading to			
Permanent treatment discontinuation	1/0.2/1/0.2	0	0
Temporary interruption of study product	0	0	0
Dose reduction of study product	1/0.2/1/0.2	0	0
Events of PT Diabetic retinopathy	11/2.7/13/2.3	16/4.0/17/3.0	11/2.7/12/2.1

Note: N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, E: Number of events, R: Event rate per 100 years. SYO: The duration of the in-study period in years, calculated from time period from when a participant was randomised until the final scheduled visit. 'All events' represents the pre-defined MedDRA search of retinal disorders.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; s.c. = subcutaneous; SYO = subject-years of observation.

The majority of the events of retinal disorders were reported with the PT Diabetic retinopathy. For this PT, more events were reported for participants in the semaglutide 2.4 mg group compared to semaglutide 1.0 mg and placebo (4.0%, 2.7% and 2.7%, respectively). There was no apparent dose–response relationship with semaglutide as the proportion of participants with events was similar between semaglutide 1.0 mg and placebo.

The remaining events of retinal disorders were distributed across several PTs with few events within each PT with no clear treatment pattern with semaglutide compared to placebo, and no apparent dose–response relationship with semaglutide. Most of these PTs appeared to represent general age-related eye conditions rather than diabetic retinopathy.

All events reported with the PT Diabetic retinopathy for the on-treatment period in the phase 3a pool originated from the phase 3a with T2D study (STEP 2), i.e., no additional events with the PT Diabetic retinopathy were reported in STEP 1, 3 and 4.

Adolescent population (aged 12 to <18 years):

No events with PT Diabetic retinopathy were reported in study NN9536-4451 (STEP TEENS), and only one event with PT Visual impairment (by the Standardised MedDRA Query search (SMQ) Retinal disorders) was reported in this study for the on-treatment period with semaglutide s.c. 2.4 mg for WM. This non-serious event with moderate intensity was reported as unlikely related to the study product by the investigator, and the outcome was reported as recovered.

Data from literature sources: Incidence and prevalence in the background population

The incidence rate of diabetic retinopathy is in the range of 38–125 per 1,000 person-years in patients with T2D, and varies with the length of follow-up time and race.[110-116]

The global prevalence of any diabetic retinopathy and proliferative diabetic retinopathy in patients with T2D are 25.2% and 3.0%, respectively[117]

Risk factors and risk groups

Patient risk factors include increasing age, long duration of diabetes, poor glycaemic control, prior history of diabetic retinopathy and rapid decline in HbA_{1c}.[118]

Preventability

Patients with diabetes should have eye examinations performed as per clinical guidelines and any detected changes in the retina should be appropriately managed in order to prevent further complications of diabetic retinopathy. Additionally, caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. Good long-term glycaemic control decreases the risk of diabetic retinopathy.[106]

Impact on the benefit−risk balance of the product

Overall, the proportion of participants developing diabetic retinopathy complications was low in the 2-year semaglutide s.c. CVOT (SUSTAIN 6): 3% for semaglutide-treated vs. 1.8% for placebo-treated participants. The majority of the participants experiencing these events were treated with insulin (>75%) and/or had documented history of diabetic retinopathy (>80%) at baseline, and in participants with no diabetic retinopathy at baseline, there was no increased risk.

In the oral semaglutide phase 3a pool, placebo pool and in the CVOT (PIONEER 6), AEs of diabetic retinopathy and related complications were slightly more frequent with oral semaglutide than with comparators. However, the difference was small, and the events were overall of the same nature as with comparators. In addition, there was no indication of an increase in the severity of the events regardless of treatment group. No consistent pattern was seen across the individual studies.

Initial worsening of diabetic retinopathy has been seen with intensive treatment with glucose-lowering agents,[119-121] but continued intensive therapy provided a greater benefit for patients with diabetic retinopathy in the long term. In addition to this, the recently published ACCORD follow-up study demonstrated a ‘legacy effect’ with a post-treatment benefit of intensive glycaemic control on the progression of eye disease.[122]

Taken together, the benefits of the long-term improved glycaemic control, including reduction in diabetes complications and cardiovascular (CV) risk reduction, are considered to outweigh the risk of diabetic retinopathy complications during diabetes therapy intensification. The CV risk reduction was also observed in the subgroup of participants with documented medical history of diabetic retinopathy at baseline. In summary, the overall benefit–risk balance is considered favourable for both semaglutide s.c. and oral semaglutide.

Public health impact

The attributed risk (difference between semaglutide rate and comparator rate) for developing diabetic retinopathy complications when treated with semaglutide was 0.76 events per 100 SYO for the CVOT (SUSTAIN 6; all four endpoints). The attributed risk for diabetic retinopathy and related complications for oral semaglutide was 1 event per 100 SYO in the CVOT (PIONEER 6).

Considering the risk factors in relation to the size of the target population, the public health impact is anticipated to be minimal.

The risk is established with the use of insulin products, but not specifically for GLP-1 RA-based treatments. The risk is therefore not considered incorporated into clinical practice with this product class.

2.7.3.2 Important potential risk: Pancreatic cancer

Potential mechanisms

In 2010, a potential risk of pancreatic cancer was hypothesised for the incretin mimetic class of antidiabetic drugs (GLP-1 RAs and dipeptidyl peptidase 4 [DPP-4] inhibitors).[123] It was suggested that based on the mode of action of incretin mimetic drugs and pancreatic metaplastic changes seen in animal models following administration of incretin mimetic drugs, prolonged exposure to incretin mimetic drugs may lead to an increased risk of pancreatic cancer.

An association between the incretin-based therapy class and risk of pancreatic cancer is not supported by findings from the completed CVOTs of other GLP-1 RAs, including lixisenatide[102] and liraglutide,[101] dulaglutide,[124] and DPP-4 inhibitors (saxagliptin, sitagliptin and alogliptin).[103,104,105]

Evidence source and strength of evidence

Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer. There is no evidence from clinical studies, that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer is included as an important potential risk, based on the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369).

Characterisation of the risk

Impact on quality of life

Pancreatic cancer severely impacts the patient's quality of life. Treatment can involve chemotherapy, radiation therapy and/or surgery. More than 50% of the patients are diagnosed at an advanced stage with a 5-year survival rate less than 5%.[125]

Data from clinical studies with semaglutide s.c. for T2D

There is no indication of an increased relative risk in the semaglutide s.c. treatment group vs. comparator. In the semaglutide phase 3 development programme, rates of EAC-confirmed events of pancreatic cancer were consistently low across studies (2 events with semaglutide 0.5 mg, 2 events with semaglutide 1.0 mg and 6 events with comparators; Table 2-36). Likewise, the rates of pancreatic cancer events captured by the MedDRA search were low. However, since the data

collection period of the studies is relatively short, this will continue to be monitored in post-marketing data.

Evaluation of seriousness, severity and outcome is not available for the EAC-confirmed events of pancreatic cancer as the adjudicators were not asked to evaluate this for any of the criteria of the endpoint.

Pancreatic cancer is a serious medical condition and most of the investigator-reported events in the phase 3 studies were serious. The majority of the events were reported as 'not recovered' or 'fatal'.

Table 2-36 MedDRA search and EAC-confirmed events (in-study) of pancreatic cancer in the phase 3 studies – semaglutide s.c. for T2D

	Phase 3 studies (excl. SUSTAIN 6)		CVOT (SUSTAIN 6)	
	Semaglutide N/%/E/R	All comparators[a] N/%/E/R	Semaglutide N/%/E/R	Placebo N/%/E/R
Number of participants	6,118	3,377	1,648	1,649
SYO	5,372	2,962	3,408	3,401
Pancreatic cancer (MedDRA search)				
AEs	4/<0.1/4/0.1	2/<0.1/2/0.1	1/0.1/1/<0.1	4/0.2/4/0.1
EAC-confirmed events				
Number of participants	4,870	3,090	1,648	1,649
SYO	4,312	2,770	3,408	3,401
Pancreatic cancer (EAC confirmed)	3/<0.1/3/0.1	2/<0.1/2/0.1	1/0.1/1/0.03	4/0.2/4/0.12

Note: Includes all SUSTAIN studies included in Table 2-7. N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, E: Number of events, R: Event rate per 100 SYO, SYO: subject-years of observation, calculated from the time period from when a participant was randomised until the final scheduled visit. The events included for SUSTAIN 7 (NN9535-4216), SUSTAIN 10 (NN9535-4339) and SUSTAIN FORTE (NN9535-4506) are captured with a predefined MedDRA search only; events from other studies are also based on adjudication.
[a]All comparators include both active comparators and placebo.
Abbreviations: AE = adverse event; CVOT = cardiovascular outcomes trial; EAC = event adjudication committee; MedDRA = Medical Dictionary for Regulatory Activities; SYO = subject-years of observation; T2D = type 2 diabetes mellitus.

A post-marketing epidemiological database study is being conducted to estimate the risk of pancreatic cancer in users of semaglutide (see Section 3.2.3).

Data from clinical studies with oral semaglutide for T2D

There is no indication of an increased relative risk in the oral semaglutide treatment group vs. comparator, including placebo. Rates of EAC-confirmed events of pancreatic cancer were consistently low across studies (7 events with oral semaglutide and 6 events with comparators; Table 2-37).

Pancreatic cancer is a serious medical condition and most of the events reported in participants receiving oral semaglutide were serious, however assessed as unlikely related to study drug by investigator. One of the events reported in the oral semaglutide treatment arm was fatal, whereas the remaining events were reported as recovered/recovering (3 events) or not recovered (3 events). No dose–response was seen with oral semaglutide.

Table 2-37 MedDRA search and EAC-confirmed events (in-study) of pancreatic cancer in the phase 3a studies – oral semaglutide for T2D

	Phase 3a studies (excl. PIONEER 6)		CVOT (PIONEER 6)	
	Semaglutide N/%/E/R	All comparators[a] N/%/E/R	Semaglutide N/%/E/R	Placebo N/%/E/R
Number of participants	4,216	2,236	1,591	1,592
SYO	5,024	2,555	2,101	2,081
Pancreatic cancer (MedDRA search)				
AEs	2/<0.1/2/0.0	2/<0.1/2/0.1	4/0.3/4/0	5/0.3/5/0
EAC-confirmed events				
Number of participants	4,216	2,236	1,591	1,592
SYO	5,024	2,555	2,101	2,081
Pancreatic cancer (EAC confirmed)	2/<0.1/2/<0.0	2/<0.1/2/<0.1	5/0.3/5/0.2	4/0.3/4/0.2

Note: Includes all PIONEER studies included in Table 2-7. %: the proportion of participants with at least one event. R: event rate per 100 subject-years of observation. Relationship to study product is as judged by the investigator. N: number of participants with at least one event; SYO: subject-years of observation, calculated from the time period from when a participant was randomised until the final scheduled visit; E: number of events.

[a]All comparators include both active comparators and placebo.

Abbreviations: AE = adverse event; CVOT = cardiovascular outcomes trial; EAC = event adjudication committee; MedDRA = Medical Dictionary for Regulatory Activities; SYO = subject-years of observation; T2D = type 2 diabetes mellitus.

Results from the post-marketing database study NN9535-4447 for semaglutide s.c. will be relevant also for the ongoing evaluation of the risk for oral semaglutide.

Data from clinical studies with semaglutide s.c. 2.4 mg for WM

No cases of pancreatic cancer were reported in clinical studies with semaglutide s.c. 2.4 mg for WM (including study NN9536-4451 with adolescents aged 12 to <18 years).

Data from literature sources: Incidence and prevalence in the background population

People with T2D: Reported incidence rates of pancreatic cancer range from 0.1 to 2.4 per 1,000 person-years.[126-140]

A claims-based analysis found an incidence rate of pancreatic cancer of 0.20 for users of liraglutide (a GLP-1 RA structurally similar to semaglutide), compared with 0.33 per 1,000 person-years for users of non-incretin-based comparator therapies.[141]

People who have overweight or obesity: The incidence of pancreatic neoplasm in women who have overweight or obesity reported in the literature ranges from 0.12 to 0.34 per 1,000 person-years and from 0.15 to 0.40 per 1,000 person-years, respectively.[142-145] For men, the incidence in population with overweight and obesity is reported as 0.29 to 0.34 per 1,000 person-years and 0.53 to 0.68 per 1,000 person-years, respectively.[142, 145]

Risk factors and risk groups

Patient risk factors for neoplasms include diabetes, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasms and family history of pancreatic cancer, and other genetic predispositions.

Preventability

No causal relationship has been established between semaglutide (s.c. and oral) and pancreatic cancer, and preventability is therefore not applicable.

Impact on the benefit–risk balance of the product

Data from the semaglutide (s.c. and oral) development programmes do not indicate a causal association. This is further supported by clinical and post-marketing data for other GLP-1 RAs. Based on this the risk is considered to have a low impact on the benefit–risk profile of semaglutide s.c. and oral semaglutide.

Public health impact

Considering that pancreatic cancer is a rare event in the general population, the absolute risk is expected to be very low, and the potential impact on public health is expected to be minimal.

2.7.3.3 Important potential risk: Medullary thyroid cancer

Potential mechanisms

Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy arising from the parafollicular C cells. Thyroid C-cell tumours were observed in semaglutide carcinogenicity studies in mice and rats. Based on mechanistic data generated by Novo Nordisk and data from the literature, it has been shown that the C-cell tumours induced in mice and rats following dosing of semaglutide are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive, whereas monkeys and humans are not (Section 2.2.1).

Evidence source and strength of evidence

This potential class risk is based on findings in mice and rats for all currently approved long-acting GLP-1 RAs. Data from the monitoring of calcitonin (a marker for MTC) in plasma in the semaglutide s.c. and oral clinical development programmes did not support a semaglutide effect on calcitonin in humans.

Characterisation of the risk

Impact on the individual patient

The management of MTC will impact the patient's quality of life. Surgery is primarily required for the management of MTC, but chemotherapy or radiation therapy may also be required. MTC may result in death. The 10-year overall survival rate in unselected patients with MTC is approximately 75%, but it decreases to 40% or less in patients with locally advanced or metastatic disease.[146]

Data from clinical studies with semaglutide s.c. for T2D

In the semaglutide phase 3 clinical development programme, 1 event of MTC was reported in a participant treated with semaglutide. The onset date of the MTC event was reported by the

investigator as the randomisation date and was detected due to elevated calcitonin levels. The participant underwent thyroidectomy and discontinued semaglutide. The outcome for the event was reported as 'recovered'.

Semaglutide is included in an MTC registry designed to monitor the incidence of MTC in the US and establish a registry of MTC cases in adults in the US (MTC-22341; see Section 3.2.2).

Data from clinical studies with oral semaglutide for T2D
One event of MTC was reported in the oral semaglutide CVOT (PIONEER 6). The participant had a medical history of thyroid nodules, which is a risk factor for the development of MTC, and elevated levels of calcitonin prior to study drug initiation. The participant was treated with oral semaglutide for approximately 3 months before discontinuing the product. The EAC-reported onset date of MTC was at day 457 after first dose. The investigator reported a possible causality; however, due to the medical history, the event of MTC is not likely related to treatment with oral semaglutide.

No other events of MTC were reported from the clinical development programme.

Oral semaglutide will be included in the MTC registry (MTC-22341; see Section 3.2.2).

Data from clinical studies with semaglutide s.c. 2.4 mg for WM
No cases of MTC were reported in clinical studies with semaglutide s.c. 2.4 mg for WM (including study NN9536-4451 with adolescents aged 12 to <18 years). Semaglutide s.c. 2.4 mg for WM is included in the medullary thyroid cancer registry in the US (MTC-22341; see Section 3.2.2).

Data from literature sources: Incidence in the general population
Previous studies report that MTC accounts for a small percentage of thyroid cancer overall, with estimates of the proportion ranging from 1–2%.[147-149] Among patients with T2D, the incidence rate of thyroid cancer has been reported to be 0.24 per 1,000 person-years.[150]

No studies evaluating the incidence of MTC in patients with diabetes are available. In the general population, the incidence rate was between 0.0021–0.0028 per 1,000 person-years.[151, 152]

A meta-analysis reported that obesity was associated with a decreased risk of MTC (RR = 0.50; 95% CI, 0.27–0.97; I2 = 1%).[153] Additionally, another meta-analysis showed inverse relations between overweight and MTC, and obesity and MTC with risk estimates of 0.57 (95% CI = 0.36–0.88) and 0.50 (95% CI = 0.27–0.92), respectively.[154]

Risk factors and risk groups

Patient risk factors for MTC include previous family history or personal medical history of multiple endocrine neoplasia 2 (MEN2), a group of medical disorders associated with tumours of the endocrine system.

Preventability

No causal relationship between semaglutide s.c. or oral semaglutide and MTC has been established, and preventability is therefore not applicable.

Impact on the benefit−risk balance of the product

The impact on the benefit–risk balance will depend on the size of the attributed risk if a causal relationship is confirmed. Considering that MTC is a rare event in the general population, the absolute risk is expected to be very low, and the potential impact on the benefit–risk balance is expected to be minimal.

Public health impact

Considering that MTC is a rare event in the general population, the absolute risk is expected to be very low, and the potential impact on public health is expected to be minimal.

2.7.3.4 Missing information: Pregnancy

Evidence source

Weight loss in pregnant women is reported to cause reduced neonatal birth weights, reduced placental weights and reduced umbilical cord length compared to controls, adjusted for body mass index (BMI).[97]

Nonclinical observations of foetal mortality and malformations in rats, rabbits and cynomolgus monkeys have been reported with the use of semaglutide (Table 2-5). Although the findings are considered unlikely to be of relevance to humans, a different safety profile in this population cannot be excluded. Semaglutide should therefore not be used during pregnancy.

Within the semaglutide 2.4 mg for WM clinical development programme, despite the efforts to avoid pregnancies, 37 women reported that they had conceived a child. Most of the pregnancies (29) were reported in patients treated with semaglutide 2.4 mg.

In all cases, the foetuses were exposed to semaglutide for a short time until the pregnancy was discovered, and study product was discontinued. One child of a female participant exposed to semaglutide was born with a congenital anomality of the external ear. None of the elective abortions were reported to be due to congenital anomalies.

Population in need of further characterisation

The exposure during pregnancy is limited and the human relevance of the nonclinical observations with semaglutide cannot be excluded.

The anticipated use in this population is low based on the prescription-only status of the products and because the SmPCs clearly specifies that semaglutide should not be used in this population. Novo Nordisk will continue to monitor the population of pregnant patients in the post-marketing setting by routine pharmacovigilance activities.

2.7.3.5 Missing information: Lactation (semaglutide s.c. for T2D and semaglutide s.c. for WM)

Evidence source

Semaglutide was observed in milk in lactating rats. Although the findings are considered unlikely to be of relevance to humans, a different safety profile in this population cannot be excluded.

Clinical data from study NN9924-4669, conducted with oral semaglutide for T2D, shows that SNAC was present in breastmilk and some of its metabolites were excreted in breastmilk at low concentrations in lactating females following oral dosing with semaglutide. No measurable concentrations of semaglutide were found in breastmilk of lactating females. No dedicated studies have been conducted to investigate semaglutide concentrations in breastmilk upon subcutaneous dosing. Semaglutide should not be used in this population during breast-feeding.

Population in need of further characterisation

The exposure during breast-feeding is limited and the human relevance of the nonclinical observations with semaglutide cannot be excluded.

The anticipated use in this population is low based on the prescription-only status of the products and because the SmPCs clearly specifies that semaglutide should not be used in this population. Novo Nordisk will continue to monitor the population of lactating patients in the post-marketing setting by routine pharmacovigilance activities.

2.7.3.6 Missing information: Patients with severe hepatic impairment

Evidence source

Semaglutide is metabolised by enzymes widely distributed in the body, with no single organ responsible for its metabolism. The safety profile of semaglutide in patients with T2D or overweight/obesity and severe hepatic impairment is currently unknown; however, it is likely to be similar to the overall population due to the mode of action of semaglutide.

Baseline hepatic function (Child–Pugh score) has been measured in two phase 1 studies investigating the effect of hepatic impairment on semaglutide exposure (single-dose study NN9535-3651 [semaglutide s.c.] and multiple-dose study NN9924-4082 [oral semaglutide]; see Table 2-27). The studies included 42 participants with mild or moderate hepatic impairment and 15 participants with severe hepatic impairment. There was no inclusion criterion for participants with T2D or overweight/obesity in these studies. Hepatic impairment did not affect the PK exposure of semaglutide, except for the unbound fraction of semaglutide estimated *in vitro* which increased with increasing severity of hepatic impairment in study NN9924-4082. The two studies showed that semaglutide (s.c. and oral) was safe and well-tolerated in participants with mild, moderate or severe hepatic impairment.

Participants with hepatic impairment or hepatic disorders were not excluded from the semaglutide s.c. for T2D phase 3a studies, with the exception of participants with end-stage liver disease who were excluded from the CVOT. Severe hepatic impairment was not an exclusion criterion in the oral semaglutide phase 3a studies. Participants were not classified according to the Child–Pugh score at baseline in these studies. In some studies, participants with ALT >2.5 × ULN were excluded (see Table 2-26). The data showed that the safety profile was not affected to a clinically meaningful extent by hepatic impairment.

Population in need of further characterisation

The exposure of semaglutide (s.c. and oral) in patients with T2D or overweight/obesity and severe hepatic impairment is currently limited.

Novo Nordisk will continue to monitor the population of patients with severe hepatic impairment in clinical studies and in the post-marketing setting by routine pharmacovigilance activities.

2.8 Module SVIII: Summary of safety concerns

Table 2-38 Summary of safety concerns (semaglutide s.c. for T2D, oral semaglutide for T2D) and semaglutide s.c. 2.4 mg for WM)

Summary of safety concerns	
Important identified risks	• Diabetic retinopathy complications (only for patients with T2D)
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer
Missing information	• Pregnancy • Lactation (only for semaglutide s.c. for T2D and semaglutide s.c. for WM) • Patients with severe hepatic impairment

Abbreviations: s.c. = subcutaneous(-ly); T2D = type 2 diabetes mellitus.

3 Pharmacovigilance plan

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

No specific follow-up forms or questionnaires are used for the important risks associated with semaglutide s.c. for T2D, or oral semaglutide for T2D, or semaglutide s.c. 2.4 mg for WM. Routine case follow-up includes a number of targeted questions relating to the diagnosis and description of the event. Based on medical evaluation, the relevant questions are returned to the reporter in an attempt to get further information to be used in the evaluation of the events.

3.1.2 Other forms of routine pharmacovigilance activities

No other forms of routine pharmacovigilance activities are applied for semaglutide s.c. or oral semaglutide.

3.2 Additional pharmacovigilance activities

Results from the post-authorisation safety study (PASS) NN9535-4352 (FOCUS; see Section 3.2.1) for semaglutide s.c. for T2D will also be relevant for the ongoing evaluation of the risk Diabetic retinopathy complications for oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM in patients with T2D.

The PASS MTC registry (MTC-22341; see Section 3.2.2) is an activity for semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM.

The PASS NN9535-4447 (see Section 3.2.3; for the risk Pancreatic cancer) is an activity for both semaglutide s.c. for T2D and oral semaglutide for T2D and will also be relevant for the ongoing evaluation of the risk of pancreatic cancer for semaglutide s.c. 2.4 mg for WM.

3.2.1 NN9535-4352 summary (Diabetic retinopathy)

Study title:

Long-term effects of semaglutide on diabetic retinopathy in participants with type 2 diabetes (FOCUS).

Rationale and study objectives:

While it is well-established that long-term good glycaemic control will reduce the risk of diabetic retinopathy development and progression, intensification of glycaemic control has also been associated with an initial worsening of diabetic retinopathy. This phenomenon is known as 'early worsening'. The rationale of this study is to establish the long-term effects of semaglutide on diabetic retinopathy in participants with T2D using validated and standardised ophthalmic assessments.

The objectives of this study are:

- to assess the long-term effects of treatment with semaglutide compared to placebo, both added to standard-of-care, on diabetic retinopathy development and progression in participants with T2D
- to assess the effects of treatment with semaglutide compared to placebo, both added to standardof-care, with regards to visual acuity, diabetic retinopathy manifestations and diabetic retinopathy treatments.

Results from the study will be relevant also for the ongoing evaluation of the risk for oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM in patients with T2D.

Study design:

This study is a 5-year randomised, double-masked, parallel-group, placebo-controlled study comparing the effects of semaglutide versus placebo both administered subcutaneously once-weekly and added to standard-of-care in participants with inadequately controlled T2D. Participants will be randomised 1:1 to receive either semaglutide or placebo and stratified based on diabetic retinopathy severity at baseline.

Study populations:

Adult population, diagnosed with T2D and with an HbA_{1c} of 7.0–10.0% (53–86 mmol/mol) both inclusive.

Milestones:

Adopted protocol: 19 Nov 2018

Final report: February 2028

3.2.2 MTC Registry/MTC-22341 summary (Medullary thyroid cancer)

Study title:

Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry

Rationale and study objectives:

Nonclinical studies in rodents of clinically relevant doses of GLP-1 RAs showed dose-related and treatment duration-dependent increases in the incidence of thyroid C-cell tumours (adenomas and carcinomas). The clinical relevance of rodent thyroid findings observed with GLP-1 RAs is unknown.

MTC is the human equivalent of C-cell carcinoma in rodents. MTC is a rare form of human cancer.

A post-approval active surveillance programme for MTC has been established to monitor for any signal indicating a possible association between treatment with long-acting GLP-1 RAs and development of MTC.

The objectives of this MTC Surveillance Study are:
1. To systematically monitor the annual incidence of MTC in the U.S. through the North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market.
2. To establish a registry of cases of MTC in adults in the US in order to characterise their medical histories and possible risk factors, including history of treatment with long-acting GLP-1 RAs.

Study design:

Cancer registry data will be collected through NAACCR to monitor the annual incidence rates of MTC in the US population as a whole during the conduct of the active surveillance programme. Incidence rates from 2001 until the time of US market introduction of the first long-acting GLP-1 receptor agonist (January 2010) will serve as a baseline.

Annual incidence rates will be documented for the 15-year period after the approval of each long-acting GLP-1 RAs.

Study populations:

Each participating registry will be asked to identify all cases of MTC in their database that were diagnosed on or after FDA approval of the first long-acting GLP-1 RA in January 2010 with the date of first MTC diagnosis.

Milestones – semaglutide s.c. for T2D:

Protocol submission: February 2019

Final report: December 2033

Milestones – oral semaglutide for T2D:

Protocol submission: November 2020

Final report: February 2037

Milestones – semaglutide s.c. 2.4 mg for WM:

Protocol submission: August 2022

Final report: February 2039

3.2.3 NN9535-4447 summary (Pancreatic cancer)

Study title:

Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes – A cohort study based on Nordic registry data.

Rationale and study objectives:

In 2010, a safety hazard of pancreatic cancer was hypothesised for the incretin mimetic class of antidiabetic drugs (including the GLP-1 RAs). Until now, available clinical data have not indicated a potential risk of pancreatic cancer associated with the use of semaglutide. However, the follow-up of 2 years in the semaglutide development programme is too short for the assessment of association of semaglutide with pancreatic cancer, and this will be monitored with post-marketing data. Thus, an epidemiological study with longer follow-up time and a substantially larger patient population is warranted to assess whether the use of semaglutide is associated with an increased risk of pancreatic cancer.

The aim of this study is to evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D.

Results from the study will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM.

Study design:

A multi-national, non-interventional study based on healthcare data from Denmark, Sweden and Norway is conducted during the period 2018–2023.

Study population:

The study population consists of new users of Ozempic®/Rybelsus® and new users of active comparators if they:

1. initiate treatment with Ozempic®/Rybelsus® or active comparators from the date Ozempic®/Rybelsus® is available on the market in the respective country until 31 Dec 2022
2. fill at least 2 prescriptions of Ozempic®/Rybelsus® or active comparators with the second prescription filled less than one year after the initial prescription
3. are ≥18 years old at the date of the initial prescription and
4. have at least 10 years of continuous residency in the respective country before the first prescription of either Ozempic®/Rybelsus® or active comparators.

Patients will be excluded if they have rare but strong risk factors for developing pancreatic cancer before initiating treatment (e.g., a history of pancreatic cancer, acute or chronic pancreatitis, etc.).

Furthermore, patients initiating insulin as first-line antidiabetic treatment will be excluded (to limit inclusion of patients with T1D).

Milestones – semaglutide s.c. for T2D:

Adopted protocol: 20 Sep 2018

Final report: March 2026

Milestones – oral semaglutide for T2D:

Adopted protocol: 12 Nov 2020

Final report: March 2026

3.3 Summary table of additional pharmacovigilance activities

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk) **– semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM**				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk) **– semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM**				
None				
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA) **– semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM**				
MTC-22341 Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of semaglutide into the marketplace.	Medullary thyroid cancer	**Semaglutide s.c. for T2D**	
			Submitted protocol	February 2019
			Final report	December 2033
			Oral semaglutide for T2D	
			Submitted protocol	November 2020
			Final report	February 2037
			Semaglutide s.c. 2.4 mg for WM	
			Submitted protocol	August 2022
			Final report	February 2039

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
NN9535-4447 Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes Ongoing[a]	The study will evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D. (Results from the study will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM)	Pancreatic cancer	**Semaglutide s.c. for T2D**	
			Adopted protocol	20 Sep 2018
			Final report	March 2026
			Oral semaglutide for T2D	
			Adopted protocol	12 Nov 2020
			Final report	March 2026
NN9535-4352 Long-term effects of semaglutide on diabetic retinopathy in participants with type 2 diabetes (FOCUS). Ongoing	The study will assess the long-term effects of semaglutide treatment on development and progression of diabetic retinopathy (Results from the study will also be relevant for the ongoing evaluation of the risk for oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM in patients with T2D.)	Diabetic retinopathy complications (only for patients with T2D)	**Semaglutide s.c. for T2D**	
			Adopted protocol	19 Nov 2018
			Final report	February 2028

[a]Patient-level data on exposure to Ozempic® and Rybelsus® and follow-up for pancreatic cancer in the period 2018-2023 will be included in the study. The first extraction of data was done in 2020 and the last data extraction is planned in 2024 with final reporting of the study in 2025.

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; MTC = medullary thyroid cancer; NCA = national competent authority; PRAC = Pharmacovigilance Risk Assessment Committee; T2D = type 2 diabetes mellitus; TBD = to be determined.

4 Plans for post-authorisation efficacy studies

There are no imposed post-authorisation efficacy studies ongoing or planned for semaglutide.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

Table 5-1 Description of routine risk minimisation measures by safety concern – semaglutide s.c. for T2D

Safety concern	Routine risk minimisation measures
Diabetic retinopathy complications	**Routine risk communication:** SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** A recommendation to closely monitor patients with a history of diabetic retinopathy treated with insulin is included in the SmPC. Instructions to inform the HCP about history of diabetic eye disease are included in the PL.

Safety concern	Routine risk minimisation measures
	Other risk minimisation measures beyond the Product Information: By the legal status of the product; prescription only.
Pancreatic cancer	**Routine risk communication:** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Medullary thyroid cancer	**Routine risk communication:** SmPC Section 5.3 (Nonclinical findings). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pregnancy	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that semaglutide should not be used during pregnancy and should be discontinued at least 2 months in advance if a patient wishes to become pregnant. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Lactation	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that semaglutide should not be used during breastfeeding. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Patients with severe hepatic impairment	**Routine risk communication:** SmPC Sections 4.2 and 5.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC that caution should be exercised when treating patients with severe hepatic impairment. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.

Abbreviations: HCP = healthcare professional; PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Table 5-2 Description of routine risk minimisation measures by safety concern – oral semaglutide for T2D

Safety concern	Routine risk minimisation measures
Diabetic retinopathy complications	**Routine risk communication:** SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** A recommendation to monitor patients with a history of diabetic retinopathy is included in the SmPC. Instructions to inform the HCP about history of diabetic eye disease are included in the PL. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pancreatic cancer	**Routine risk communication:** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Medullary thyroid cancer	**Routine risk communication:** Nonclinical findings are presented in the SmPC Section 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pregnancy	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that semaglutide should not be used during pregnancy and breastfeeding and should be discontinued at least 2 months in advance if a patient wishes to become pregnant. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Patients with severe hepatic impairment	**Routine risk communication:** SmPC Sections 4.2 and 5.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC that caution should be exercised when treating patients with severe hepatic impairment. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.

Abbreviations: HCP = healthcare professional; PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Table 5-3 Description of routine risk minimisation measures by safety concern – semaglutide s.c. 2.4 mg for WM

Safety concern	Routine risk minimisation measures
Diabetic retinopathy complications (only for patients with T2D)	**Routine risk communication:** SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** A recommendation to monitor patients with a history of diabetic retinopathy is included in the SmPC. Instructions to inform the HCP about a history of diabetic eye disease are included in the PL. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pancreatic cancer	**Routine risk communication:** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Medullary thyroid cancer	**Routine risk communication:** Nonclinical findings are presented in the SmPC Section 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pregnancy	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that semaglutide should not be used during pregnancy and should be discontinued at least 2 months in advance if a patient wishes to become pregnant. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Lactation	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that semaglutide should not be used during breastfeeding.

Safety concern	Routine risk minimisation measures
	Other risk minimisation measures beyond the Product Information: By the legal status of the product; prescription only.
Patients with severe hepatic impairment	**Routine risk communication:** SmPC Sections 4.2 and 5.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC that caution should be exercised when treating patients with severe hepatic impairment. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.

Abbreviations: HCP = healthcare professional; PL = package leaflet; SmPC = Summary of Product Characteristics.

5.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Section 5.1 are sufficient to manage the safety concerns of the medicinal product (semaglutide s.c. for T2D, oral semaglutide for T2D, and semaglutide s.c. 2.4 mg for WM).

5.3 Summary table of pharmacovigilance and risk minimisation activities by safety concern

Table 5-4 Pharmacovigilance and risk minimisation activities by safety concern – semaglutide s.c. for T2D

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk Diabetic retinopathy complications	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Study NN9535-4352 (Long-term effects of semaglutide on diabetic retinopathy in participants with T2D [FOCUS])
Important potential risk Pancreatic cancer	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Study NN9535-4447 (see Section 3.2.3; Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D)
Important potential risk Medullary thyroid cancer	*Routine risk minimisation measures:* Non-clinical findings are presented in the SmPC Section 5.3 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry; see Section 3.2.2)
Missing information: Pregnancy	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Missing information: Lactation	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Missing information: Patients with severe hepatic impairment	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None

Abbreviations: MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Table 5-5 Pharmacovigilance and risk minimisation activities by safety concern – oral semaglutide for T2D

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk Diabetic retinopathy complications	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and in the PL Sections 2 and 4. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Results from the study NN9535-4352 (FOCUS; see Section 3.2.1) ongoing for semaglutide s.c. for T2D will also be relevant for the ongoing evaluation of the risk for oral semaglutide for T2D.
Important potential risk Pancreatic cancer	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Study NN9535-4447 (See Section 3.2.3; Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D).
Important potential risk Medullary thyroid cancer	*Routine risk minimisation measures:* Non-clinical findings are presented in the SmPC Section 5.3 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry; see Section 3.2.2).
Missing information: Pregnancy	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Missing information: Patients with severe hepatic impairment	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Table 5-6 Pharmacovigilance and risk minimisation activities by safety concern – semaglutide s.c. 2.4 mg for WM

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk Diabetic retinopathy complications (only for patients with T2D)	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Results from the study NN9535-4352 (FOCUS; see Section 3.2.1) ongoing for semaglutide s.c. for T2D will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM in patients with T2D.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk Pancreatic cancer	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Results from study NN9535-4447 (see Section 3.2.3; Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide patients with T2D) will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM.
Important potential risk Medullary thyroid cancer	*Routine risk minimisation measures:* Nonclinical findings are presented in the SmPC Section 5.3 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry; see Section 3.2.2)
Missing information: Pregnancy	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Missing information: Lactation	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Missing information: Patients with severe hepatic impairment	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

6 Summary of the risk management plan

6.1 Summary of the risk management plan for Ozempic (semaglutide s.c. for T2D)

This is a summary of the risk management plan (RMP) for Ozempic. The RMP details important risks of Ozempic, how these risks can be minimised, and how more information will be obtained about Ozempic's risks and uncertainties (missing information).

Ozempic's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ozempic should be used.

This summary of the RMP for Ozempic should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Ozempic's RMP.

6.1.1 The medicine and what it is used for

Ozempic is authorised for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication). It contains semaglutide as the active substance and it is injected by subcutaneous route.

Further information about the evaluation of Ozempic's benefits can be found in Ozempic's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: EPAR link.

6.1.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ozempic, together with measures to minimise such risks and the proposed studies for learning more about Ozempic's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status – the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

6.1.2.1 List of important risks and missing information

Important risks of Ozempic are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ozempic. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Diabetic retinopathy complications
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer
Missing information	• Pregnancy • Lactation • Patients with severe hepatic impairment

6.1.2.2 Summary of important risks

Table 6-2 Diabetic retinopathy complications

Evidence for linking the risk to the medicine	The risk of diabetic retinopathy complications was identified based on findings in the cardiovascular outcomes trial (CVOT; SUSTAIN 6), where a total of 3,297 participants with T2D and high cardiovascular risk were included. In the CVOT (SUSTAIN 6), participants with known proliferative retinopathy or maculopathy requiring acute treatment were not excluded.
Risk factors and risk groups	Patient risk factors include increasing age, long duration of diabetes, poor glycaemic control, prior history of diabetic retinopathy and rapid decline in HbA_{1c}.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8and PL Sections 2 and 4. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Study NN9535-4352 (Long-term effects of semaglutide on diabetic retinopathy in participants with T2D [FOCUS])* See Section 6.1.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: CVOT = cardiovascular outcomes trial; PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Table 6-3 Pancreatic cancer

Evidence for linking the risk to the medicine	Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer. There is no evidence from clinical studies, that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer is included as an important potential risk, based on the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369)
Risk factors and risk groups	Patient risk factors for neoplasms include diabetes, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasms and family history of pancreatic cancer and other genetic predispositions.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Study NN9535-4447 (Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D)* See Section 6.1.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: GLP-1 = glucagon-like peptide-1; T2D = type 2 diabetes mellitus.

Table 6-4 Medullary thyroid cancer

Evidence for linking the risk to the medicine	This potential class risk is based on findings in mice and rats for all currently approved long–acting GLP-1 RAs. Data from the monitoring of calcitonin (a marker for MTC) in plasma in the semaglutide s.c. and oral semaglutide clinical development programmes did not support a semaglutide effect on calcitonin in humans.
Risk factors and risk groups	Patient risk factors for MTC include previous family history or personal medical history of multiple endocrine neoplasia 2 (MEN2), a group of medical disorders associated with tumours of the endocrine system.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 5.3. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry)* See Section 6.1.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: MEN2 = multiple endocrine neoplasia 2; MTC = medullary thyroid cancer; s.c. = subcutaneous(-ly); SmPC = Summary of Product Characteristics.

Table 6-5 Pregnancy

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 6-6 Lactation

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 6-7 Patients with severe hepatic impairment

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None

Abbreviations: SmPC = Summary of Product Characteristics.

6.1.2.3 Post-authorisation development plan

6.1.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ozempic.

6.1.2.3.2 Other studies in post-authorisation development plan

NN9535-4352 (FOCUS)

Purpose of the study: The aim of this randomised clinical study is to establish the long-term effects of semaglutide on diabetic retinopathy in participants with type 2 diabetes mellitus (T2D) using validated and standardised ophthalmic assessments.

NN9535-4447

Purpose of the study: The aim of this study is to evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D.

MTC-22341

Purpose of the study: This active surveillance programme for MTC has been established to evaluate further a potential association between treatment with long-acting GLP-1 RAs and the occurrence of MTC in humans. The MTC registry is an FDA post-marketing requirement for long-acting GLP-1 RA products.

6.2 Summary of the risk management plan for Rybelsus (oral semaglutide for T2D)

This is a summary of the risk management plan (RMP) for Rybelsus. The RMP details important risks of Rybelsus, how these risks can be minimised, and how more information will be obtained about Rybelsus' risks and uncertainties (missing information).

Rybelsus' Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rybelsus should be used.

This summary of the RMP for Rybelsus should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Rybelsus' RMP.

6.2.1 The medicine and what it is used for

Rybelsus is authorised for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication). It contains semaglutide as the active substance and it is given by oral route of administration.

Further information about the evaluation of Rybelsus' benefits can be found in Rybelsus' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: EPAR link.

6.2.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Rybelsus, together with measures to minimise such risks and the proposed studies for learning more about Rybelsus' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status – the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

6.2.2.1 List of important risks and missing information

Important risks of Rybelsus are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rybelsus. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6-8 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Diabetic retinopathy complications
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer
Missing information	• Pregnancy • Patients with severe hepatic impairment

6.2.2.2 Summary of important risks

Table 6-9 Diabetic retinopathy complications

Evidence for linking the risk to the medicine	The risk is included as an identified risk for oral semaglutide based on findings in the semaglutide s.c. for T2D clinical development programme. Based on the totality of data on diabetic retinopathy collected across the oral semaglutide for T2D phase 3a studies, there was no increased risk of diabetic retinopathy with oral semaglutide.
Risk factors and risk groups	Patient risk factors include increasing age, long duration of diabetes, poor glycaemic control, prior history of diabetic retinopathy and rapid decline in HbA_{1c}.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Results from the study NN9535-4352 (*Long-term effects of semaglutide on diabetic retinopathy in participants with T2D [FOCUS]*) for semaglutide s.c. for T2D will also be relevant for the ongoing evaluation of the risk for oral semaglutide for T2D. See Section 6.2.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: CVOT = cardiovascular outcomes trial; MedDRA = Medical Dictionary for Regulatory Activities; PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Table 6-10 Pancreatic cancer

Evidence for linking the risk to the medicine	Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer. There is no evidence from clinical studies that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer is included as an important potential risk, based on the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369).
Risk factors and risk groups	Patient risk factors for neoplasms include diabetes, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasms and family history of pancreatic cancer and other genetic predispositions.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* *Study NN9535-4447 (Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D)* See Section 6.2.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: GLP-1 = glucagon-like peptide-1; T2D = type 2 diabetes mellitus.

Table 6-11 Medullary thyroid cancer

Evidence for linking the risk to the medicine	This potential class risk is based on findings in mice and rats for all currently approved long–acting GLP-1 RAs. Data from the monitoring of calcitonin (a marker for MTC) in plasma in the semaglutide s.c. and oral semaglutide clinical development programmes did not support a semaglutide effect on calcitonin in humans.
Risk factors and risk groups	Patient risk factors for MTC include previous family history or personal medical history of multiple endocrine neoplasia 2 (MEN2), a group of medical disorders associated with tumours of the endocrine system.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 5.3. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* *Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry)* See Section 6.2.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: MEN2 = multiple endocrine neoplasia 2; MTC = medullary thyroid cancer; SmPC = Summary of Product Characteristics.

Table 6-12 Pregnancy

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 6-13 Patients with severe hepatic impairment

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None

Abbreviations: SmPC = Summary of Product Characteristics.

6.2.2.3 Post-authorisation development plan

6.2.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Rybelsus.

6.2.2.3.2 Other studies in post-authorisation development plan

NN9535-4352 (FOCUS)

Purpose of the study: The aim of this randomised clinical study is to establish the long-term effects of semaglutide on diabetic retinopathy in participants with type 2 diabetes mellitus (T2D) using validated and standardised ophthalmic assessments. Results from the study will be relevant also for the ongoing evaluation of the risk for oral semaglutide for T2D.

NN9535-4447

Purpose of the study: The aim of this study is to evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D.

MTC-22341

Purpose of the study: This active surveillance programme for MTC has been established to evaluate further a potential association between treatment with long-acting GLP-1 RAs and the occurrence of MTC in humans. The MTC registry is an FDA post-marketing requirement for long–acting GLP-1 RA products.

6.3 Summary of the risk management plan for Wegovy (semaglutide s.c. 2.4 mg for WM)

This is a summary of the risk management plan (RMP) for Wegovy. The RMP details important risks of Wegovy, how these risks can be minimised and how more information will be obtained about Wegovy's risks and uncertainties (missing information).

Wegovy's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Wegovy should be used.

This summary of the RMP for Wegovy should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Wegovy's RMP.

6.3.1 The medicine and what it is used for

Wegovy is authorised for weight loss and weight maintenance. It contains the active substance semaglutide and it is given by subcutaneous route.

Wegovy is used together with diet and physical activity for weight loss and weight maintenance in adults who have:

- a BMI of 30 kg/m² or greater (with obesity) or
- a BMI of 27 kg/m² and less than 30 kg/m² (overweight) and weight-related health problems.

Wegovy is used together with diet and physical activity for WM in adolescents ages 12 years and above, who have

- obesity and

- body weight >60 kg

Use of Wegovy should only be continued if patients lost at least 5% of their BMI after 12 weeks on the 2.4 mg dose or maximum tolerated dose.

BMI (body mass index) is a measure of your weight in relation to your height.

Further information about the evaluation of Wegovy's benefits can be found in Wegovy's EPAR, including its plain-language summary, available on the EMA website under the medicine's webpage: EPAR link.

6.3.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Wegovy, together with measures to minimise such risks and the proposed studies for learning more about Wegovy's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status – the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and analysed regularly, including the PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

6.3.2.1 List of important risks and missing information

Important risks of Wegovy are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Wegovy. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6-14 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Diabetic retinopathy complications (only for patients with T2D)
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer

List of important risks and missing information	
Missing information	• Pregnancy • Lactation • Patients with severe hepatic impairment

Abbreviations: T2D = type 2 diabetes mellitus.

6.3.2.2 Summary of important risks

Table 6-15 Diabetic retinopathy complications (only for patients with T2D)

Evidence for linking the risk to the medicine	The risk is included for semaglutide s.c. 2.4 mg for WM in patients with T2D based on the findings in the semaglutide s.c. for T2D (Ozempic) clinical development programme. In STEP 2 study, few diabetic retinopathy events were reported, but with higher rates and proportions with semaglutide 2.4 mg than with placebo.
Risk factors and risk groups	Patient risk factors include increasing age, long duration of diabetes, poor glycaemic control, prior history of diabetic retinopathy and rapid decline in HbA_{1c}.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8, and PL Sections 2 and 4. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* Study NN9535-4352 (Long-term effects of semaglutide on diabetic retinopathy in participants with T2D [FOCUS]) will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM in patients with T2D. See Section 6.3.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: CVOT = cardiovascular outcomes trial; PL = package leaflet; s.c. = subcutaneous(-ly); SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Table 6-16 Pancreatic cancer

Evidence for linking the risk to the medicine	Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer. There is no evidence from clinical studies that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer is included as an important potential risk based on the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369).
Risk factors and risk groups	Patient risk factors for neoplasms include diabetes, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasms and family history of pancreatic cancer and other genetic predispositions.
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* Study NN9535-4447 (Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D) will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM. See Section 6.3.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: GLP-1 = glucagon-like peptide-1; s.c. = subcutaneous(-ly); T2D = type 2 diabetes mellitus.

Table 6-17 Medullary thyroid cancer

Evidence for linking the risk to the medicine	This potential class risk is based on findings in mice and rats for all currently approved long-acting GLP-1 RAs. Data from the monitoring of calcitonin (a marker for MTC) in plasma in the semaglutide s.c. and oral semaglutide clinical development programmes did not support a semaglutide effect on calcitonin in humans.
Risk factors and risk groups	Patient risk factors for MTC include previous family history or personal medical history of multiple endocrine neoplasia 2 (MEN2), a group of medical disorders associated with tumours of the endocrine system.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 5.3. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry) See Section 6.3.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: MEN2 = multiple endocrine neoplasia 2; MTC = medullary thyroid cancer; s.c. = subcutaneous(-ly); SmPC = Summary of Product Characteristics.

Table 6-18 Pregnancy

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 6-19 Lactation

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 6-20 Patients with severe hepatic impairment

Risk minimisation measures	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None

Abbreviations: SmPC = Summary of Product Characteristics.

6.3.2.3 Post-authorisation development plan

6.3.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Wegovy.

6.3.2.3.2 Other studies in post-authorisation development plan

NN9535-4352 (FOCUS)

Purpose of the study: The aim of this randomised clinical study is to establish the long-term effects of semaglutide on diabetic retinopathy in participants with type 2 diabetes mellitus (T2D) using validated and standardised ophthalmic assessments. Results from the study will be relevant also for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM in patients with T2D.

NN9535-4447

Purpose of the study: The aim of this study is to evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D. Results from the study will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM.

MTC-22341

Purpose of the study: This active surveillance programme for MTC has been established to evaluate further a potential association between treatment with long-acting GLP-1 RAs and the occurrence of MTC in humans. The MTC registry is an FDA post-marketing requirement for long–acting GLP-1 RA products.

7 Annexes

Table 7-1 Annexes

Annex	Title	Included (Yes/No)
1	EudraVigilance interface	No
2	Tabulated summary of planned, ongoing and completed pharmacovigilance study programme	Yes
3	Protocols for proposed and ongoing studies in Categories 1–3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part 3	Yes
4	Specific adverse event follow-up forms	No
5	Protocols for proposed and ongoing studies in RMP part IV	No
6	Details of proposed additional risk minimisation measures	No
7	Other supporting data (including referenced material) 7A: References	Yes
8	Summary of changes to the risk management plan over time	Yes

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