SCHEDULING STATUS

S4

WARNING: RISK OF THYROID C-CELL TUMOURS

- **In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures. It is unknown whether Ozempic® causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumours has not been determined (see 4.4 Special warnings and precautions for use).**
- **Ozempic® is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) (see 4.3 Contraindications). Counsel patients regarding the potential risk for MTC with the use of Ozempic® and inform them of symptoms of thyroid tumours (e.g. a mass in the neck, dysphagia, dyspnoea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Ozempic® (see 4.4 Special warnings and precautions for use).**

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1 NAME OF THE MEDICINE

Ozempic® 1,34 mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 1,34 mg of semaglutide (a human glucagon-like peptide-1 (GLP-1) receptor agonist produced in *Saccharomyces cerevisiae* by recombinant DNA technology), preserved with 5,50 mg/mL (0,55 % *m/v*) phenol.

Ozempic® 0,25 mg and 0,5 mg/dose pen:

Each pre-filled pen contains 2 mg semaglutide in 1,5 mL solution.

Ozempic® 1 mg/dose pen:

Each pre-filled pen contains 4 mg semaglutide in 3 mL solution.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless or almost colourless, isotonic solution: pH = 7,4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ozempic® is indicated:

- for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

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- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- as combination therapy with oral anti-diabetic medicines (metformin, thiazolidinediones, sulphonylurea), basal insulin with or without metformin and pre-mix insulin.

- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

4.2 Posology and method of administration

Posology

Ozempic® starting dose is 0,25 mg 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.

Ozempic® dose 0,25 mg is not a therapeutic dose.

Ozempic® can be used as monotherapy or as combination therapy with one or more antidiabetic medicines (see 4.1 Therapeutic indications for further information).

When Ozempic® is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged.

When Ozempic® is added to existing sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy, the current dose of SGLT2 inhibitor can be continued unchanged.

When Ozempic® is added to existing therapy of a sulphonylurea or insulin, a reduction in the

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dose of sulphonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see 4.4 Special warnings and precautions for use).

The use of Ozempic® does not require blood glucose self-monitoring. Self-monitoring should be performed when Ozempic® is used together with metformin, sulphonylurea or insulin in order to allow adjustment of the dose of these medicines.

Special populations

Elderly (≥ 65 years old): No dose adjustment is required based on age.

Gender and ethnicity:

No dose adjustment is required based on gender, age, race or ethnicity.

Patients with renal impairment:

No dose adjustment is required for patients with renal impairment. Experience with the use of Ozempic® in patients with end-stage renal impairment is limited. Caution should be exercised when treating these patients with Ozempic®.

Patients with hepatic impairment:

No dose adjustment is required for patients with hepatic impairment. Experience with the use of Ozempic® in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Ozempic®.

Children and adolescents:

Safety and efficacy of Ozempic® in children and adolescents below 18 years have not been studied.

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Method of administration

Ozempic® is to be administered once weekly at any time of the day, with or without meals.

Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment.
Ozempic® should not be administered intravenously or intramuscularly.

The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 2 days (> 48 hours).

Missed dose
If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

4.3 Contraindications

- Hypersensitivity to semaglutide or to any of the excipients listed in section 6.1.
- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) (see 4.4 Special warnings and precautions for use).
- Pregnancy and lactation. Women who may become pregnant should use effective contraception while using Ozempic® (see 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Ozempic® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

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Ozempic® is not a substitute for insulin.

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP 1 RAs undergoing general anaesthesia (GA) or deep sedation despite reported adherence to preoperative fasting recommendations. Therefore, the increased risk of residual gastric content because of delayed gastric emptying should be considered prior to performing procedures with GA or deep sedation.

Gastrointestinal effects

Ozempic® may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function as nausea, vomiting and diarrhoea may cause dehydration which could cause a deterioration of renal function.

Acute pancreatitis

Acute pancreatitis has been observed with the use of Ozempic®. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Ozempic® should be discontinued; if confirmed, Ozempic® should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Hypoglycaemia

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Patients treated with Ozempic® in combination with a sulphonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulphonylurea or insulin when initiating treatment with Ozempic®.

Diabetic retinopathy

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines.

Populations not studied

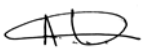
There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV.

There is limited experience in patients with a history of severe gastroparesis. Use with caution in these patients.

Risk of thyroid C-cell tumours

In mice and rats, semaglutide caused a dose dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumours (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether Ozempic® causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumours has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist have been reported in the post marketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

Signed: 

Ozempic® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of Ozempic® and inform them of symptoms of thyroid tumours e.g. mass in the neck, dysphaqia, dyspnoea, persistent hoarseness). Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values > 50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Hypersensitivity

Serious hypersensitivity reactions (e g anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists such as Ozempic® If hypersensitivity reactions occur, discontinue use of Ozempic®; treat promptly per standard of care and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to Ozempic® (see 4.3 Contraindications).

Effects on ability to drive and use machines

When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies have shown very low potential for Ozempic® to inhibit or induce CYP enzymes, and to inhibit drug transporters.

The delay of gastric emptying with Ozempic® may influence the absorption of concomitantly administered oral medicines. The potential effect of Ozempic® on the absorption of co-administered oral medicines was studied in trials at Ozempic® 1 mg steady state exposure.

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Paracetamol

Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardised meal test. Paracetamol $AUC_{0\text{-}60min}$ and C_{max} were decreased by 27% and 23%,

respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure ($AUC_{0\text{-}5h}$) was not affected. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2,4 mg, following 20 weeks of administration of semaglutide, probably due to a tolerance effect. No dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives

Semaglutide is not anticipated to decrease the effect of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0,03 mg ethinylestradiol/0,15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20 % was observed for levonorgestrel exposure at steady state. Cmax was not affected for any of the compounds.

Atorvastatin

Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin Cmax was decreased by 38%. This was assessed not to be clinically relevant.

Digoxin

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Semaglutide did not change the overall exposure or Cmax of digoxin following a single dose of digoxin (0.5 mg).

Metformin

Semaglutide did not change the overall exposure or C_{max} of metformin following dosing of 500 mg twice daily over 3.5 days.

Warfarin and other coumarin derivatives

Semaglutide did not change overall exposure or C_{max} of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, cases of decreased INR have been reported during concomitant use of acenocoumarol and semaglutide. Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

4.6 Fertility, pregnancy and lactation

Ozempic® is contraindicated during pregnancy and lactation (see 4.3 Contraindications).

Pregnancy

Studies in animals have shown reproductive toxicity. Semaglutide should not be used during pregnancy. The safety of Ozempic® in pregnant women has not been established. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Women who may become pregnant should use effective contraception while using Ozempic® and for 2 months after stopping the medicine.

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Lactation

It is unknown whether semaglutide is excreted in human milk. In lactating rats, semaglutide was excreted in milk. Women on treatment with Ozempic® should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

When it is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 Undesirable effects

Summary of safety profile

In 8 phase 3a trials, 4 792 patients were exposed to Ozempic® alone or in combination with other glucose lowering medicines. The duration of the treatment ranged from 30 weeks to 2 years.

The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting.

Tabulated list of adverse reactions

Table 1 lists adverse reactions identified in phase 3a trials in patients with type 2 diabetes (further described in section Description of selected adverse reactions). The frequencies of the adverse reactions are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial.

The reactions are listed below by system organ class and absolute frequency. Frequencies are defined as: very common: (≥ 1/10); common: (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare: (≥ 1/10 000 to < 1/1 000); and very rare: (< 1/10 000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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Table 1: Side effects from controlled phase 3a trials

MedDRA system organ class	Very common	Common	Uncommon	Rare	Unknown
Immune-system disorders			Hypersensitivity[c]	Anaphylactic reaction	
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulphonylurea	Hypoglycaemia[a] when used with other OADs Decreased appetite			
Nervous system disorders		Dizziness Headache	Dysgeusia		
Eye disorders		Diabetic retinopathy complications[b]			
Cardiac disorders			Increased heart rate		
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Eructation Flatulence	Acute pancreatitis Delayed gastric emptying		Intestinal obstruction[e]
Hepatobiliary disorders		Cholelithiasis			Cholecystitis[d]
Skin and subcutaneous tissue disorders					Angioedema[d]
General disorders and administration site conditions		Fatigue	Injection site reactions		
Investigations		Increased lipase Increased amylase Weight decreased			

[a] *Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose < 3,1 mmol/L*

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[b] *Diabetic retinopathy complications is a composite of: need for retinal photocoagulation, need for treatment with intravitreal agents, vitreous haemorrhage, onset of diabetes-related blindness. Frequency based on cardiovascular outcomes trial.*
[c] *Grouped term covering adverse events related to hypersensitivity such as rash and urticaria*
[d] *From post-marketing reports.*
[e] *Grouped term covering PTs Intestinal obstruction, Ileus, small intestinal obstruction*

2-year cardiovascular outcomes and safety trial

In a high cardiovascular risk population, the adverse reaction profile was similar to that seen in the other phase 3a trials.

Description of selected adverse reactions

Hypoglycaemia

One episode of severe hypoglycaemia was observed when Ozempic® was used as monotherapy. Severe hypoglycaemia was primarily observed when Ozempic® was used with a sulphonylurea (1,2 % of subjects, 0,03 events/patient year) or insulin (1,5 % of subjects, 0,02 events/patient year). Few severe episodes (0,1 % of subjects, 0,001 events/patient year) were observed with Ozempic® in combination with oral antidiabetics other than sulphonylureas.

Gastrointestinal adverse reactions

Nausea occurred in 17,0 % and 19,9 % patients when treated with Ozempic® 0,5 mg and 1 mg respectively, diarrhoea in 12,2 % and 13,3 % and vomiting in 6,4 % and 8,4 %. Most events were mild to moderate in severity and of short duration. The events led to treatment discontinuation in 3,9 % and 5,9 % of subjects. The events were most frequently reported during the first months on treatment.

Diabetic retinopathy complications

In a 2-year clinical trial involving 3 297 patients with type 2 diabetes and high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose, adjudicated events of diabetic retinopathy occurred in more patients treated with Ozempic® (3,0 %) compared to

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placebo (1,8 %). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline. In the patients that did not have a documented history of diabetic retinopathy the number of events were similar for Ozempic® and placebo.

Acute pancreatitis

The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0,3 % for semaglutide and 0,2 % for the comparator, respectively. In the 2-year cardiovascular outcomes trial the frequency of acute pancreatitis confirmed by adjudication was 0,5 % for semaglutide and 0,6 % for placebo (see 4.4 Special warnings and precautions for use).

Discontinuation due to an adverse event

The incidence of discontinuation of treatment due to adverse events was 8,7 % for patients treated with 1 mg of Ozempic®. The most frequent adverse events leading to discontinuation were gastrointestinal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website and to Novo Nordisk (Pty) Ltd at infoZa@novonordisk.com or telephone 010 500 8699 (toll free).

4.9 Overdose

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There is no specific antidote for overdose with Ozempic®. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of Ozempic® of approximately 1 week.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06

A 21.13 Other hormones

Mechanism of action

Semaglutide is a GLP-1 analogue with 94 % sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system and kidneys. 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 and immune system and kidney from where it may mediate cardiovascular and microvascular effects. In addition to lowered systolic blood pressure and reduced selected inflammatory markers seen in clinical studies, animal studies have shown that GLP-1 receptor agonists can be cardioprotective and attenuate cerebral stroke,

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atherosclerotic plaque size, and platelet aggregation, and increase stability of atherosclerotic plaques.

Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once weekly s.c. administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme.

Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia semaglutide diminishes insulin secretion and does not impair glucagon secretion.

Semaglutide reduces body weight and body fat mass through lowered energy intake. The mechanism involves an overall reduced appetite, which includes increased satiety and reduced hunger, as well as improved control of eating and decreased food cravings. Insulin resistance is also reduced, probably through reduction in body weight. In addition, semaglutide reduces the preference for high fat foods. In animal studies, semaglutide is taken up in specific brain regions and increases key satiety and decreases key hunger signals. Using isolated brain tissues sections semaglutide activates satiety related neurons and inhibits hunger related neurons.

Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies.

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In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

The mechanism of action of semaglutide for the kidney protective effect is likely multifactorial, driven by both indirect effects as seen in the beneficial effects on cardio-kidney risk factors (improved glucose metabolism and lipid profile, reduced systemic inflammation and systolic blood pressure and weight loss) as well as direct kidney-specific effects, such as reduced kidney-specific inflammation, potentially unique to semaglutide.

Clinical data showed that semaglutide lowered albuminuria, a biomarker for kidney damage in patients with kidney disease associated with higher rates of chronic kidney disease progression.

Pharmacodynamic data

All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg once weekly.

Fasting and Postprandial glucose

Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline (mmol/l / mg/dL) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/L / 29 mg/dL; 22 %), 2 hour postprandial glucose (4.1 mmol/L / 74 mg/dL; 37 %), mean 24 hour glucose concentration (1.7 mmol/L / 30 mg/dL; 22 % reduction) and postprandial glucose excursions over 3 meals (0.6-1.1 mmol/L / 11-20 mg/dl) compared to placebo (see Figure 1).

Semaglutide lowered fasting glucose after the first dose.

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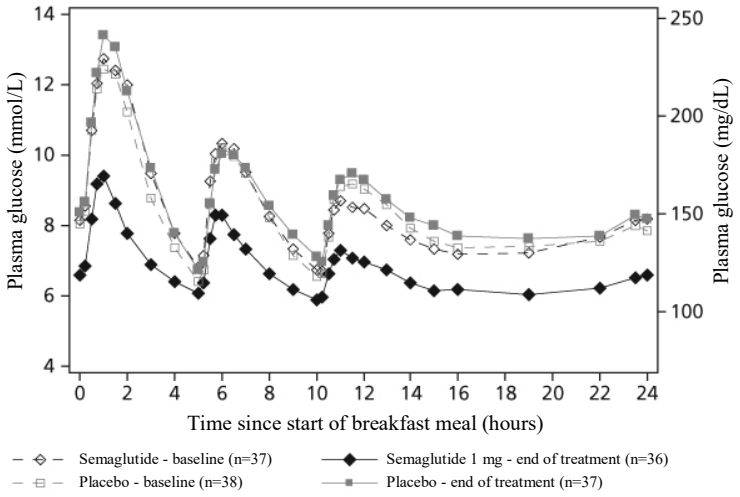

Figure 1 Mean 24 hour plasma glucose profiles (standardised meals) in patients with type 2 diabetes before (baseline) and after 12 weeks of treatment with semaglutide or placebo

Beta-cell function and insulin secretion

Semaglutide improves beta-cell function. Semaglutide, compared to placebo, improved first- and second-phase insulin response, with a 3 and 2 fold increase, respectively, following an intravenous bolus of glucose, and increased maximal beta-cell secretory capacity after an arginine stimulation test in patients with type 2 diabetes. In addition, semaglutide treatment increased fasting insulin concentrations compared to placebo.

Glucagon secretion

Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in glucagon compared to placebo: fasting glucagon (8-21 %), postprandial glucagon response (14-15 %) and mean 24 hour glucagon concentration (12 %).

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Glucose dependent insulin and glucagon secretion

Semaglutide lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that of healthy subjects (see Figure 2).

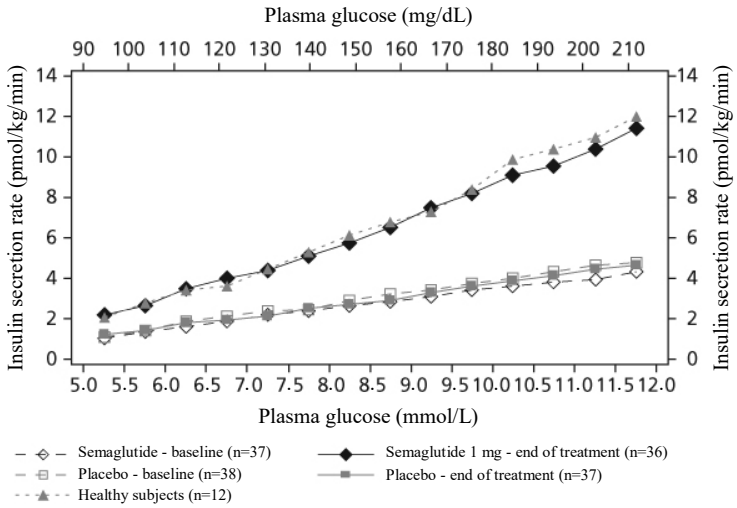

Figure 2 Mean insulin secretion rate versus glucose concentration in patients with type 2 diabetes during graded glucose infusion before (baseline) and after 12 weeks of treatment with semaglutide or placebo and in untreated healthy subjects

During induced hypoglycaemia, semaglutide compared to placebo did not alter the counter regulatory responses of increased glucagon and did not impair the decrease of C peptide in patients with type 2 diabetes.

Gastric emptying

Semaglutide caused a minor delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

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Body weight and body composition

A greater reduction in body weight was observed with semaglutide compared to studied comparators (placebo, sitagliptin, exenatide ER and insulin glargine) (section Body Weight). The body weight loss with semaglutide was predominantly from fat tissue with loss of fat mass being 3 fold larger than loss of lean mass.

Appetite, energy intake and food choice

Semaglutide compared to placebo lowered the energy intake of 3 consecutive *ad libitum* meals by 18-35 %. This was supported by a semaglutide-induced suppression of appetite in the fasting state as well as postprandially, improved control of eating, less food cravings and a relative lower preference for high fat food.

Fasting and postprandial lipids

Semaglutide compared to placebo lowered fasting triglyceride and VLDL cholesterol concentrations by 12 % and 21 %, respectively. The postprandial triglyceride and VLDL cholesterol response to a high fat meal was reduced by > 40 %.

Cardiac electrophysiology (QTc)

The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at dose levels up to 1,5 mg at steady state.

Clinical efficacy and safety data

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Improvement of glycaemic control and body weight, as well as reduction of cardiovascular morbidity and mortality and risk reduction of chronic kidney disease progression are integral parts of the treatment of type 2 diabetes.

The efficacy and safety of Ozempic® 0,5 mg and 1 mg once weekly were evaluated in six randomised controlled phase 3a trials. Of these, five trials (SUSTAIN 1-5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective.

These trials included in total 8 124 randomised patients with type 2 diabetes (4 792 treated with Ozempic®).

In addition, a phase 3b trial (SUSTAIN 7) including 1 201 patients was conducted to compare the efficacy and safety of Ozempic 0,5 mg and 1 mg once weekly versus dulaglutide 0,75 mg and 1,5 mg once weekly, respectively.

A phase 3b kidney outcomes trials (FLOW) including 3 533 patients was conducted to investigate the effects of semaglutide 1 mg once weekly versus placebo on the progression of kidney impairment in patients with type 2 diabetes and chronic kidney disease.

A phase 3b functional capacity trial (STRIDE) including 792 patients was conducted to investigate the effects of semaglutide 1 mg once weekly versus placebo in patients with type 2 diabetes and peripheral arterial disease.

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A phase 3b trial (SUSTAIN 9) including 302 patients, was conducted to investigate the efficacy and safety of semaglutide as add-on to SGLT2 inhibitor treatment (with or without metformin or sulfonylurea) in subjects with type 2 diabetes mellitus.

Treatment with Ozempic® demonstrated sustained, statistically superior and clinically meaningful reductions in HbA_{1c} (see Figure 3) and body weight for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide).

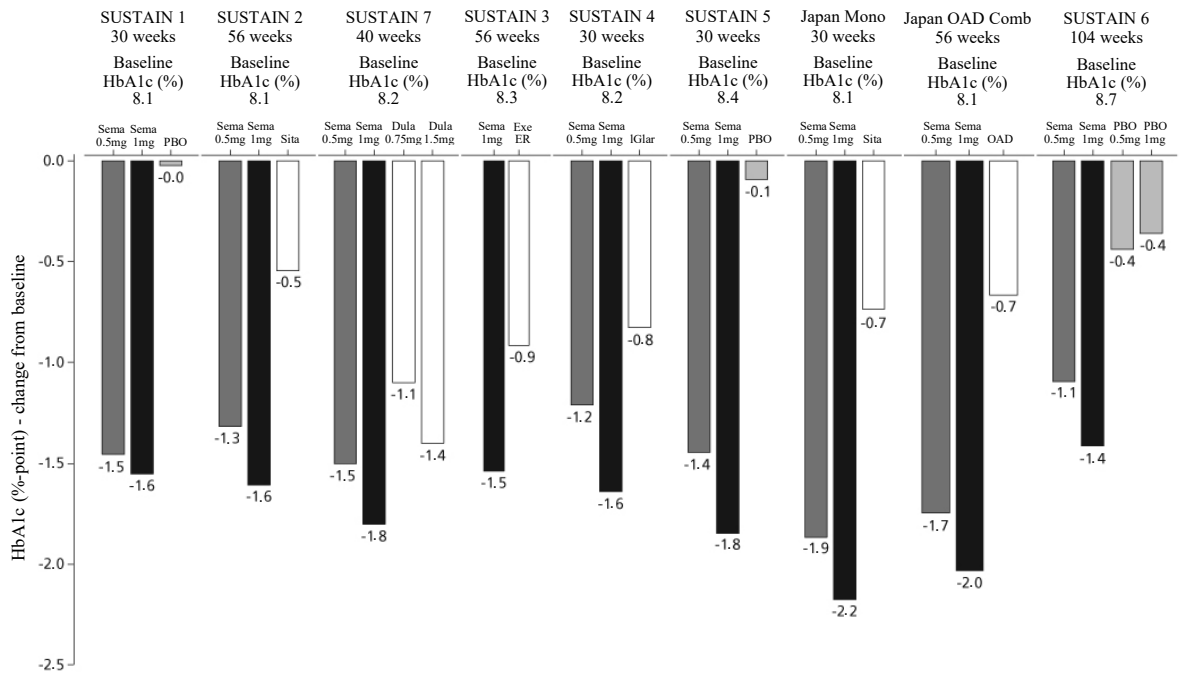

Figure 3 HbA_{1c} (%)-estimated change from baseline to end of treatment in SUSTAIN 1-7, Japan Monotherapy and Japan OAD Combination trials (semaglutide 0,5 mg dark grey, semaglutide 1 mg black, competitors white and placebo light grey)

The efficacy of Ozempic® was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

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Detailed information Is provided below.

SUSTAIN 1 – Monotherapy

In a 30-week double-blind trial, 388 patients inadequately controlled with diet and exercise were randomised to Ozempic® 0,5 mg or Ozempic® 1 mg once weekly or placebo.

Patients had a mean age of 54 years and a mean duration of type 2 diabetes of 4.2 years. There were 64 % White patients, 8% were Black or African Americans and 21 % were Asian. For ethnicity, 30 % of patients (n= 115) were Hispanic or Latino. The mean BMI was 33 kg/m^2

Monotherapy with Ozempic® 0,5 mg and 1 mg once weekly for 30 weeks resulted in statistically superior reductions in HbA_{1c} and body weight compared to placebo (see Table 2).

Table 2 Results of a at 30-week monotherapy trial (SUSTAIN 1)

	Ozempic® 0.5 mg	Ozempic® 1 mg		Placebo
Intent-to-Treat (ITT) Population (N)	128	130		129
HbA_{1c} (%)				
Baseline (mean)	8.1	8.1		8.0
Change from baseline at week 30	-1.5	-1.6		0
Difference from placebo [95% CI]	-1.4 [-1.7; -1.1][a]	-1.5 [-1.8; -1.2][a]		-
Patients (%) achieving HbA_{1c} < 7%	74[b]	72[b]		25
Patients (%) achieving HbA_{1c} ≤ 6.5%	59[b]	60[b]		13
FPG (mmol/l)				
Baseline (mean)	9.7	9.9		9.7
Change from baseline at week 30	-2.5	-2.3		-0.6

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Difference from placebo [95% CI]	-2.0 [-2.5; -1.4][b]	-1.8 [-2.3; -1.3][b]		-
Body weight (kg)				
Baseline (mean)	89.8	96.9		89.1
Change from baseline at week 30	-3.7	-4.5		-1.0
Difference from placebo [95% CI]	-2.7 [-3.9; -1.6][a]	-3.6 [-4.7; -2.4][a]		-
Patients (%) achieving weight loss ≥ 5%	37[b]	45[b]		7
Patients (%) achieving weight loss ≥ 10%	8[c]	13[c]		2

[a] $p < 0.0001$ (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA_{1c} and body weight

[b] $p < 0.0001$ for treatment difference, unadjusted for multiplicity

[c] $p < 0.05$ for treatment difference, unadjusted for multiplicity

SUSTAIN 2 – *Ozempic® vs. sitagliptin both in combination with 1-2 antidiabetic drugs (metformin and/ or thiazolidinediones)*

In a 56-week double-blind trial, 1 231 patients were randomised to Ozempic® 0,5 mg once weekly, Ozempic® 1 mg once weekly or sitagliptin 100 mg once daily, all in combination with metformin (94 %) and/or thiazolidinedioness (6 %). Patients had a mean age of 55 years and a mean duration of type 2 diabetes of 6,6 years. There were 68 % White patients, 5 % were Black or African American and 25 % were Asian. For ethnicity, 17 % of patients (n = 209) were Hispanic or Latino. Mean BMI was 32 kg/m^2.

Treatment with Ozempic® 0,5 mg and 1 mg once weekly for 56 weeks resulted in sustained and statistically superior reductions in HbA1c and body weight compared to sitagliptin (see Table 3). From a baseline of 132,6 mmHg, treatment with Ozempic® 0,5 mg and 1 mg significantly reduced systolic blood pressure compared to sitagliptin (5,1 mmHg; 5,6 mmHg vs 2,3 mmHg, P< 0,05). There were no changes in diastolic blood pressure.

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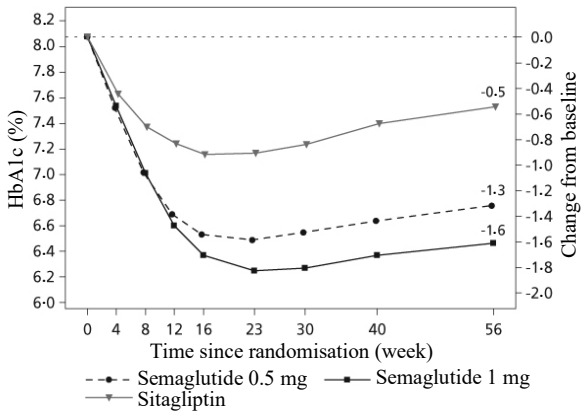
Table 3 Results of a 56-week trial of Ozempic® compared to sitagliptin (SUSTAIN 2)

	Ozempic® 0.5 mg	Ozempic® 1 mg		Sitagliptin 100 mg
Intent-to-Treat (ITT) Population (N)	409	409		407
HbA_{1c} (%)				
Baseline (mean)	8.0	8.0		8.2
Change from baseline at week 56	-1.3	-1.6		-0.5
Difference from sitagliptin [95% CI]	-0.8 [-0.9; -0.6][a]	-1.1 [-1.2; -0.9][a]		-
Patients (%) achieving HbA_{1c} < 7%	69[b]	78[b]		36
Patients (%) achieving HbA_{1c} ≤ 6.5%	53[b]	66[b]		20
FPG (mmol/l)				
Baseline (mean)	9.3	9.3		9.6
Change from baseline at week 56	-2.1	-2.6		-1.1
Difference from sitagliptin [95% CI]	-1.0 [-1.3; -0.7][b]	-1.5 [-1.8; -1.2][b]		
Body weight (kg)				
Baseline (mean)	89.9	89.2		89.3
Change from baseline at week 56	-4.3	-6.1		-1.9
Difference from sitagliptin [95% CI]	-2.3 [-3.1; -1.6][a]	-4.2 [-4.9; -3.5][a]		-
Patients (%) achieving weight loss ≥ 5%	46[b]	62[b]		18
Patients (%) achieving weight loss ≥ 10%	13[b]	24[b]		3

[a] p < 0.0001 (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA_{1c} and body weight

[b] p < 0.0001 for treatment difference, unadjusted for multiplicity



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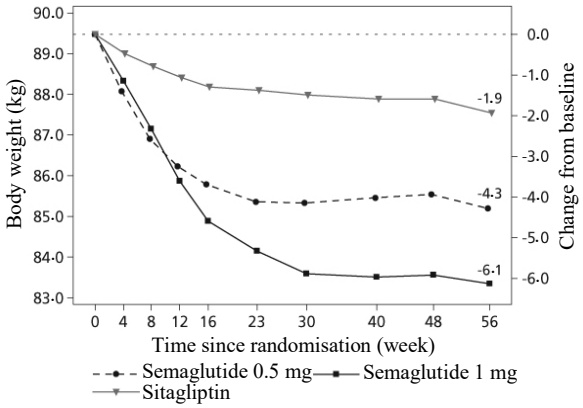

Figure 4 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 56 (SUSTAIN 2)

SUSTAIN 7 – *Ozempic® vs. dulaglutide both in combination with metformin*

In a 40-week open-label trial, 1 201 patients on metformin were randomised to either Ozempic® 0,5 mg or 1 mg once weekly or dulaglutide 0,75 mg or 1,5 mg once weekly. The trial compared 0,5 mg of semaglutide to 0,75 mg of dulaglutide and 1 mg of semaglutide to 1,5 mg of dulaglutide. Patients had a mean age of 56 years and a mean duration of type 2 diabetes of 7,4 years. There were 77 % White patients, 6 % were Black or African-American and 16 % were Asian. For ethnicity, 11 % of patients (n= 138) were Hispanic or Latino. Mean BMI was 33,5 kg/m^2.

Table 4 Results at week 40 trial of Ozempic® versus dulaglutide (SUSTAIN 7)

	Ozempic® 0.5 mg	Ozempic® 1 mg	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
Intent-to-Treat (ITT) Population (N)	301	300	299	299
HbA_{1c} (%)				
Baseline (mean)	8.3	8.2	8.2	8.2
Change from baseline at week 40	-1.5	-	-1.1	-1.4

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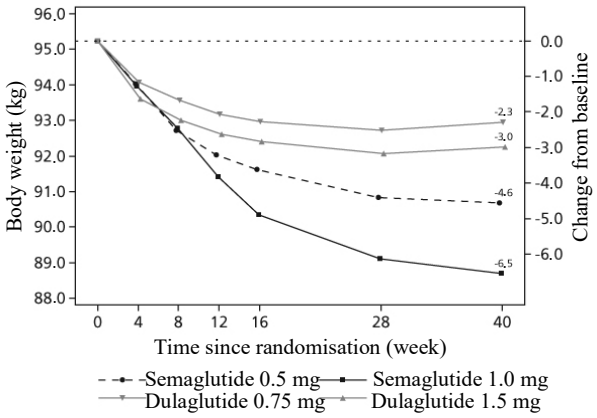
Difference from dulaglutide [95% CI]	-0.4 [-0.6; -0.2][a, c]	-0.4 [-0.6; -0.2] [a,d]	-	
Patients (%) achieving HbA_{1c} < 7%	68[b]	79[b]	52	67
Patients (%) achieving HbA_{1c} ≤ 6.5%	49[b]	67[b]	34	47
FPG (mmol/l)				
Baseline (mean)	9.8	9.8	9.7	9.6
Change from baseline at week 40	-2.2	-2.8	-1.9	-2.2
Difference from dulaglutide [95% CI]	-0.3 [-0.6; -0.0][b, c]	-0.6 [-0.9; -0.3] [b,d]		
Body weight (kg)				
Baseline (mean)	96.4	95.5	95.6	93.4
Change from baseline at week 40	-4.6	-6.5	-2.3	-3.0
Difference from dulaglutide [95% CI]	-2.3 [-3.0; -1.5][a, c]	-3.5 [-4.3; -2.8] [a,d]	-	
Patients (%) achieving weight loss ≥ 5%	44[b]	63[b]	23	30
Patients (%) achieving weight loss ≥ 10%	14[b]	27[b]	3	8

[a] p < 0.0001 (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA_{1c} and body weight

[b] p < 0.001 for treatment difference, unadjusted for multiplicity

[c] Ozempic® 0.5 mg vs. dulaglutide 0.75 mg

[d] Ozempic® 1 mg vs. dulaglutide 1.5 mg



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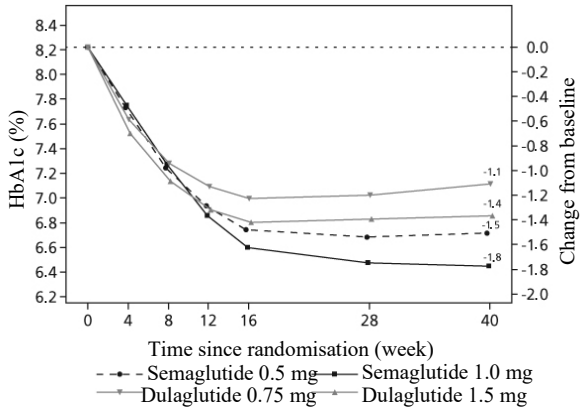

Figure 5 Mean change in HbA1c (%) and body weight (kg) from baseline to week 40

SUSTAIN 3 – *Ozempic® vs. exenatide ER both in combination with metformin or metformin with sulfonylurea*

In a 56-week open-label trial, 813 patients on metformin alone (49 %), metformin with sulfonylurea (45 %) or other (6 %) were randomised to Ozempic® 1 mg once weekly or exenatide ER 2,0 mg. Patients had a mean age of 57 years and a mean duration of type 2 diabetes of 9 years. There were 84 % White patients, 7 % were Black or African-American and 2 % were Asian. For ethnicity, 24 % of patients (n= 197) were Hispanic or Latino. Mean BMI was 34 kg/m^2.

Treatment with Ozempic® 1 mg once weekly for 56 weeks resulted in sustained and statistically superior reductions in HbA_{1c} and body weight compared to exenatide ER 2,0 mg.

Table 5 Results of a 56- week trial of Ozempic® versus exenatide ER (SUSTAIN 3)

	Ozempic® 1 mg	Exenatide ER 2.0 mg

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Intent-to-Treat (ITT) Population (N)	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change from baseline week 56	-1.5	-0.9
Difference from exenatide ER [95% CI]	-0.6 [-0.8; -0.4][a]	-
Patients (%) achieving HbA_{1c} < 7%	67[b]	40
Patients (%) achieving HbA_{1c} ≤ 6.5%	47[b]	22
FPG (mmol/l)		
Baseline (mean)	10.6	10.4
Change from baseline at week 56	-2.8	-2.0
Difference from exenatide ER [95% CI]	-0.8 [-1.2; -0.5][b]	-
Body weight (kg)		
Baseline (mean)	96.2	95.4
Change from baseline week 56	-5.6	-1.9
Difference from exenatide ER [95% CI]	-3.8 [-4.6; -3.0][a]	-
Patients (%) achieving weight loss ≥ 5%	52[b]	17
Patients (%) achieving weight loss ≥ 10%	21[b]	4

[a] p < 0.0001 (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA_{1c} and body weight

[b] p < 0.0001 for treatment difference, unadjusted for multiplicity

SUSTAIN 4 – *Ozempic® vs. insulin glargine both in combination with 1–2 oral antidiabetic drugs (metformin monotherapy or metformin and sulfonylurea)*

In a 30-week open-label trial, 1 089 patients were randomised to Ozempic® 0,5 mg once weekly, Ozempic® 1 mg once weekly, or insulin glargine once daily on a background of metformin (48 %) or metformin and sulfonylurea (51 %).

Patients on insulin glargine started on 10 U injected once daily. The mean daily insulin dose at the end of the trial was 29 U per day.

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Patients had a mean age of 57 years and a mean duration of type 2 diabetes of 8,6 years. 77 % were White, 9 % were Black or African-Americans and 11 % were Asian. For ethnicity, 20 % of patients (n= 213) were Hispanic or Latino. Mean BMI was 33 kg/m^2.

Treatment with Ozempic® 0,5 mg and 1 mg once weekly for 30 weeks resulted in statistically superior reduction in HbA1c and body weight compared to insulin glargine (see Table 6). The proportion of patients reporting severe or blood glucose confirmed (< 3,1 mmol/l) hypoglycaemic episodes were lower with Ozempic® 0,5 mg (4,4 %), and Ozempic® 1 mg (5,6 %) compared to insulin glargine (10,6 %).

More patients on Ozempic® 0,5 mg (47 %) and Ozempic® 1 mg (64 %) achieved HbA_{1c} < 7 % without severe or blood glucose confirmed symptomatic hypoglycaemia and without weight gain compared to insulin glargine (16 %).

Table 6 Results of a 30-weeks trial of Ozempic® compared to insulin glargine (SUSTAIN 4)

	Ozempic® 0.5 mg	Ozempic® 1 mg		Insulin glargine
Intent-to-Treat (ITT) Population (N)	362	360		360
HbA_{1c} (%)				
Baseline (mean)	8.1	8.2		8.1
Change from baseline at week 30	-1.2	-1.6		-0.8
Difference from insulin glargine [95% CI]	-0.4 [-0.5; -0.2][a]	-0.8 [-1.0 --0.7][a]		-
Patients (%) achieving HbA_{1c} < 7%	57[b]	73[b]		38
Patients (%) achieving HbA_{1c} ≤ 6.5%	37[b]	54[b]		18
FPG (mmol/l)				
Baseline (mean)	9.6	9.9		9.7
Change from baseline at week 30	-2.0	-2.7		-2.1
Difference from insulin glargine [95% CI]	0.1 [-0.2; 0.4]	-0.6 [-0.9; -0.3][b]		-

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Body weight (kg)				
Baseline (mean)	93.7	94.0		92.6
Change from baseline at week 30	-3.5	-5.2		+1.2
Difference from insulin glargine [95% CI]	-4.6 [-5.3; -4.0][a]	-6.3 [-7.0; -5.7][a]		-
Patients (%) achieving weight loss ≥ 5%	37[b]	51[b]		4
Patients (%) achieving weight loss ≥ 10%	7[b]	16[b]		1

[a]p < 0.0001 (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA_{1c} and body weight

[b]p < 0.001 for treatment difference, unadjusted for multiplicity

SUSTAIN 5 – *Ozempic® vs. placebo in combination with basal insulin*

In a 30-week double-blind trial, 397 patients inadequately controlled with basal insulin with or without metformin were randomised to Ozempic® 0,5 mg once weekly, Ozempic® 1 mg once weekly or placebo. Patients with HbA_{1c} ≤ 8,0 % at screening reduced the insulin dose by 20 % at the beginning of trial to reduce the risk of hypoglycaemia.

Patients had a mean age of 59 years and a mean duration of type 2 diabetes of 13 years, 78 % were White, 5 % were Black or African American and 17 % were Asian. For ethnicity, 12 % of patients (n= 46) were Hispanic or Latino. Mean BMI was 32 kg/m^2.

Treatment with Ozempic® 0,5 mg and 1 mg resulted in statistically superior reductions in HbA_{1c} after 30 weeks of treatment compared to placebo. Severe or blood glucose (BG)-confirmed symptomatic episodes of hypoglycaemia were not significantly different between Ozempic® and placebo. The proportion of patients reporting severe or confirmed (< 3,1 mmol) hypoglycaemic symptomatic episodes was higher with Ozempic® compared to placebo with screening HbA_{1c} ≤ 8 %, and comparable for patients with screening HbA_{1c} > 8 %.

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Table 7 Results at 30 weeks of Ozempic® in combination with basal insulin with or without metformin (SUSTAIN 5)

	Ozempic® 0.5 mg	Ozempic® 1 mg		Placebo
Intent-to-Treat (ITT) Population (N)	132	131		133
HbA_{1c} (%)				
Baseline (mean)	8.4	8.3		8.4
Change from baseline at week 30	-1.4	-1.8		-0.1
Difference from placebo [95% CI]	-1.4 [-1.6; -1.1][a]	-1.8 [-2.0; -1.5][a]		-
Patients (%) achieving HbA_{1c} < 7%	61[b]	79[b]		11
Patients (%) achieving HbA_{1c} ≤ 6.5%	41[b]	61[b]		5
FPG (mmol/l)				
Baseline (mean)	8.9	8.5		8.6
Change from baseline at week 30	-1.6	-2.4		-0.5
Difference from placebo [95% CI]	-1.1 [-1.7; -0.5][c]	-1.9 [-2.5; -1.3][b]		-
Body weight (kg)				
Baseline (mean)	92.7	92.5		89.9
Change from baseline at week 30	-3.7	-6.4		-1.4
Difference from placebo [95% CI]	-2.3 [-3.3; -1.3][a]	-5.1 [-6.1; -4.0][a]		-
Patients (%) achieving weight loss ≥ 5%	42[b]	66[b]		11
Patients (%) achieving weight loss ≥ 10%	9[c]	26[b]		3

[a] $p < 0.0001$ (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA_{1c} and body weight

[b] $p < 0.0001$ for treatment difference, unadjusted for multiplicity

[c] $p < 0.05$ for treatment difference, unadjusted for multiplicity

SUSTAIN 9 – *Ozempic® vs. placebo as add-on to SGLT2 inhibitor with or without metformin or SU*

In a 30-week double-blind placebo-controlled trial, 302 patients inadequately controlled with SGLT2 inhibitor with or without metformin or SU were randomised to Ozempic® 1.0 mg once weekly or placebo.

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Patients had a mean age of 57 years and a mean duration of type 2 diabetes of 9.7 years, 69 % were White, 4 % were Black or African-American and 24 % were Asian. For ethnicity, 7 % of patients (n= 22) were Hispanic or Latino. Mean BMI was 32 kg/m^2.

Treatment with Ozempic® 1,0 mg as add-on to SGLT2 inhibitors resulted in statistically superior reductions in HbA_{1c} and body weight after 30 weeks of treatment compared to placebo.

Table 8: Results at 30 weeks of Ozempic® in combination with SGLT2 inhibitor with or without metformin or SU (SUSTAIN 9)

	Ozempic® 1 mg	**Placebo**
Intent-to-Treat (ITT) Population (N)	151	151
HbA_{1c} (%)		
Baseline (mean)	8,0	8,1
Change from baseline week 30	-1,5	-0,1
Difference from placebo [95 % CI]	-1,4 [-1,6, -1,2][a]	-
Patients (%) achieving HbA_{1c} < 7 %	78,7[b]	18,7
Patients (%) achieving HbA_{1c} ≤ 6,5 %	56,1[b]	3,9
FPG (mmol/L)		
Baseline (mean)	9,1	8,9
Change from baseline at week 30	-2,2	0,0
Difference from placebo [95 % CI]	-2,2 [-2,6, -1,8][b]	-
Body weight (kg)		
Baseline (mean)	89,6	93,8
Change from baseline week 30	-4,7	-0,9
Difference from placebo [95 % CI]	-3,8 [-4,7, -2,9][a]	-
Patients (%) achieving weight loss ≥ 5 %	49,9[b]	8,2
Patients (%) achieving weight loss ≥ 10 %	15,1[b]	1,4

[a] $p < 0,0001$ (2-sided) for superiority, adjusted regarding multiplicity based on hierarchical testing of the HbA_{1c} value and body weight

[b] $p < 0,001$ for treatment difference, unadjusted for multiplicity

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Combination with sulfonylurea monotherapy

In SUSTAIN 6 (see section Prevention of cardiovascular disease), a subgroup on sulfonylurea monotherapy was evaluated at week 30. There were 123 patients on sulfonylurea monotherapy at baseline. HbA_{1c} at baseline was 8,2 %, 8,4 % and 8,4 % for Ozempic® 0,5 mg, Ozempic® 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1,6 %, -1,5 % and 0,1 % for Ozempic® 0,5 mg, Ozempic® 1 mg, and placebo, respectively.

Combination with premix insulin ± 1–2 OADs

In SUSTAIN 6 (see section Prevention of cardiovascular disease), a subgroup on premix insulin (with or without 2 OADs) was evaluated at week 30. There were 867 patients on premix insulin at baseline. HbA_{1c} at baseline was 8,8 %, 8,9 % and 8,9 % for Ozempic® 0,5 mg, Ozempic® 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1,3 %, -1,8 % and -0,4 % for Ozempic® 0,5 mg, Ozempic® 1 mg, and placebo, respectively.

Proportion of patients achieving HbA_{1c} targets

Up to 79 % of the patients achieved the treatment targets of an HbA_{1c} < 7 % and the proportion of patients was significantly greater with Ozempic® compared to patients receiving sitagliptin, exenatide ER, insulin glargine, dulaglutide and placebo (please see Table 2 to 6).

The proportion of patients achieving an HbA_{1c} below 7 % without severe or BG confirmed symptomatic hypoglycaemia and no weight gain was significantly greater with Ozempic® 0,5 mg and 1 mg (up to 66 % and 74 %, respectively) compared with patients receiving

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sitagliptin (27 %), exenatide ER (29 %), insulin glargine (16 %) and dulaglutide 0,75 mg (44 %) and 1,5 mg (58 %).

Body Weight

Ozempic® 1 mg used as monotherapy or in combination with 1-2 medicinal products resulted in statistically superior reductions in body weight up to 6,5 kg, compared to patients receiving placebo, sitagliptin, exenatide ER, insulin glargine or dulaglutide (Table 2 to 5). The reduction in body weight was sustained for up to 2 years (Figure 6).

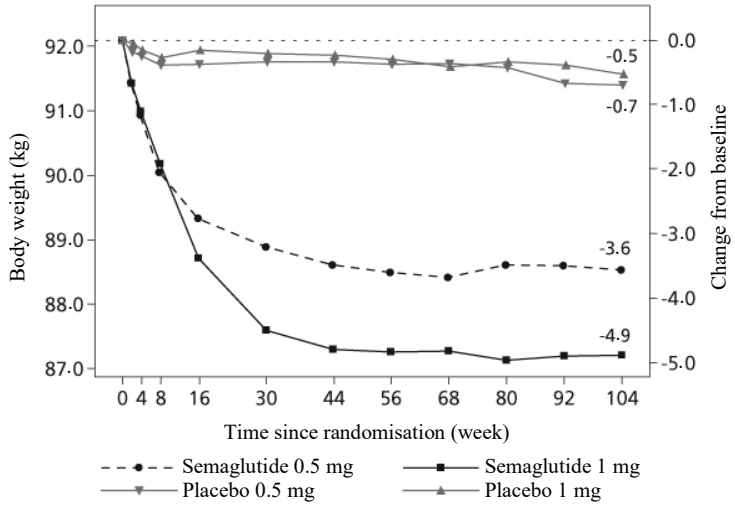

Figure 6 Mean change in body weight (kg) over time in SUSTAIN 6

After one year of treatment, a weight loss of ≥ 5 % and ≥ 10 % was achieved for more subjects with Ozempic® 0,5 mg (46 % and 13 %) and 1 mg (up to 62 % and 24 %) compared with the active comparators sitagliptin and exenatide ER (up to18 % and up to 4 %) (Table 2 to 6).

In the 40-week trial versus dulaglutide a weight loss of ≥ 5 % and ≥ 10 % was achieved for more subjects with Ozempic® 0,5 mg (44 % and 14 %) compared with dulaglutide 0,75 mg

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(23 % and 3 %) and Ozempic 1 mg (up to 63 % and 27 %) compared with dulaglutide 1,5 mg (30 % and 8 %).

In the cardiovascular trial (SUSTAIN 6), a weight loss ≥ 5 % and ≥ 10 % was achieved for more subjects with Ozempic® 0,5 mg (36 % and 13 %) and 1 mg (47 % and 20 %) compared with placebo 0,5 mg (18 % and 6 %) and placebo 1 mg (19 % and 7 %).

In the kidney outcomes trial FLOW, treatment with semaglutide 1 mg resulted in a sustained reduction in body weight at week 104 vs placebo, in addition to standard of care (-5,6 kg for semaglutide vs -1,4 kg for placebo).

Fasting plasma glucose and Postprandial increments

Ozempic® 0,5 mg and 1 mg showed significant reductions in fasting plasma glucose levels of up to 2,8 mmol/L and reductions in postprandial increments across all three daily meals (difference between pre-meal and post-meal values from three meals) of up to 1,2 mmol/L.

Beta-cell function and insulin resistence

Beta-cell function measured by homeostasis model assessment for beta cell function (HOMA-B) and insulin resistance measured by homeostasis model assessment for insulin resistance (HOMA-IR) overall improved with Ozempic® 0,5 mg and 1 mg.

Lipids

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Overall, improvements in the fasting blood lipid profile were seen with Ozempic® treatment across trials, mostly for the 1 mg group

Prevention of cardiovascular disease

In a 104-week double-blind trial (SUSTAIN 6), 3 297 patients with type 2 diabetes at high cardiovascular risk were randomised to Ozempic® 0,5 mg or 1 mg once weekly or placebo 0,5 mg or placebo 1 mg in addition to standard of care hereafter followed for 2 years. In total 98,0 % of the patients completed the trial and the vital status was known at the end of the trial for 99,6 % of the patients.

The trial population was distributed by age as: 1 598 patients (48,5 %) ≥ 65 years, 321 (9,7 %) ≥ 75 years and 20 (0,6 %) ≥ 85 years. There were 2 358 patients with normal or mild renal impairment, 832 with moderate and 107 with severe or end stage renal impairment. There were 61 % males, the mean age was 65 years and mean BMI was 33 kg/m^2. The mean duration of diabetes was 13,9 years.

The primary endpoint was the time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The secondary endpoint was time from randomisation to first occurrence of an expanded composite cardiovascular outcome, defined as MACE, revascularisation (coronary and peripheral), unstable angina requiring hospitalisation or hospitalisation for hearth failure. The total number of primary component MACE endpoints was 254, including 108 (6,6 %) with Ozempic® and 146 (8,9 %) with placebo.

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Treatment with Ozempic® resulted in a 26 % risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. This was mainly driven by a significant (39 %) decrease in the rate of non-fatal stroke and a non-significant (26 %) decrease in non-fatal myocardial infarction with no difference in cardiovascular death (see Figure 7).

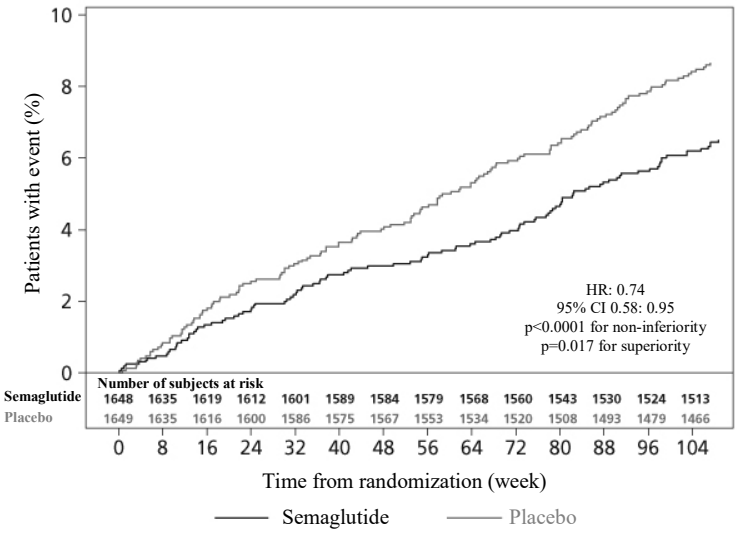

Figure 7 Kaplan-Meier plot of time to first occurrence of the composite outcome: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

The risk of a composite coronary or peripheral revascularisation was significantly reduced, whereas the risk of unstable angina requiring hospitalisation and the risk of hospitalisation for heart failure were not significantly reduced. See Figure 8 for results on primary and secondary cardiovascular endpoints.

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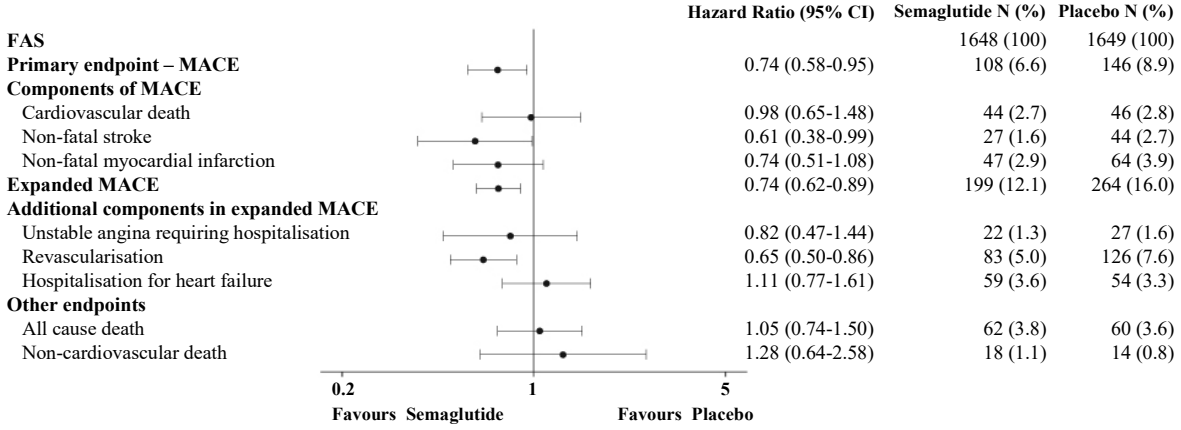

Figure 8 Forest plot: analyses of each individual cardiovascular event types (SUSTAIN 6)

Microvascular outcome comprised 158 new or worsening of nephropathy events. The hazard ratio for time to nephropathy (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, need for continuous renal replacement therapy and death due to renal disease) was 0,64 [046; 0,88] driven by new onset of persistent macroalbuminuria.

A significant and sustained reduction in HbA_{1c} from baseline to week 104 was observed with Ozempic® 0,5 mg and 1 mg vs placebo 0.5 mg and 1 mg, in addition to standard of care (-1,1 and -1,4 vs -0,4 and -0,4, respectively).

Blood pressure

Significant reductions in mean systolic blood pressure were observed when Ozempic® 0,5 mg (3,5 - 5,1 mmHg) and Ozempic® 1 mg (5,4 - 7,3 mmHg) were used in combination with oral antidiabetic medicinal products or basal insulin. For diastolic blood pressure, there were no significant differences between Ozempic® and comparators.

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Immunogenicity

Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of subjects tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1−2 %) and no subjects had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

Kidney outcomes

FLOW – Ozempic® vs placebo on progression of kidney impairment in patients with type 2 diabetes and chronic kidney disease.

The kidney outcomes trial FLOW was a multi-centre, international, randomised, double-blind, parallel-group, placebo-controlled, and event-driven trial in adults with type 2 diabetes and chronic kidney disease with baseline eGFR of 50-75 mL/min/1,73 m^2 and UACR > 300 and < 5 000 mg/g, or eGFR 25-50 mL/min/1,73 m^2 and UACR of > 100 and < 5 000 mg/g. The FLOW trial evaluated the effect of semaglutide 1 mg once weekly compared with corresponding placebo, in addition to standard of care, on the incidence of the primary composite outcome of persistent ≥ 50 % reduction in eGFR, persistent eGFR < 15 mL/min/1,73 m^2, initiation of chronic kidney replacement therapy (dialysis or kidney transplantation), kidney death or cardiovascular death. The study was stopped early for efficacy following the planned interim analysis based on a recommendation by the independent Data Monitoring Committee. The nominal significance level for superiority was 0.01612 accounting for the interim analysis.

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A total of 3 533 patients were randomised 1:1 to receive either semaglutide 1 mg or placebo and followed for a median of 40,9 months. The mean age of the population was 66,6 years and 69,7 % were male. The mean baseline BMI was 32,0 kg/m^2. The mean duration of diabetes at baseline was 17,4 years and mean baseline HbA_{1c} was 7,8 % (61,5 mmol/mol). The mean baseline eGFR was 47 mL/min/1,73 m^2 with 11,3 % of patients having an eGFR < 30 mL/min/1,73 m^2. Median UACR was 568 mg/g with 68,5 % of patients with UACR ≥ 300 mg/g. At baseline, about 95 % of the patients were treated with renin-angiotensin-aldosterone system inhibitors and 16 % with sodium-glucose cotransporter2 (SGLT2) inhibitors.

Semaglutide was superior to placebo, in addition to standard of care, in preventing the primary composite outcome of persistent ≥ 50 % reduction in eGFR, onset of persistent eGFR < 15 mL/min/1,73 m^2, initiation of chronic kidney replacement therapy, kidney death or cardiovascular death. The hazard ratio [95 % CI] for time to first occurrence of the primary composite outcome was 0,76 [0.66; 0.88], one-sided p value: 0.0001; corresponding to a relative risk reduction in kidney disease progression of 24 % (see Figure 9).

The individual components of the primary composite that contributed to the treatment effect were persistent ≥ 50% reduction in eGFR, onset of persistent eGFR < 15 mL/min/1,73 m^2, initiation of chronic kidney replacement therapy and cardiovascular death. There were few kidney deaths in the trial (see Figure 8). The treatment benefit of semaglutide over placebo on the primary composite outcome was overall consistent across subgroups, including eGFR and UACR categories, indicating benefits across chronic kidney disease subgroups.

Semaglutide showed superiority over placebo, in addition to standard of care, in reducing the yearly rate of change in eGFR with an estimated treatment difference of 1,16

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(mL/min/1,73m^2/year) [0.86; 1.47] 95 % CI (-2,19 for semaglutide and -3,36 for placebo; one-sided p value < 0.0001).

At week 104, the estimated treatment ratio for UACR was 0,68 (mg/g) [0.62; 0.75] 95 % CI (0.60 for semaglutide and 0,88 for placebo); corresponding to a clinically relevant reduction of 32 %.

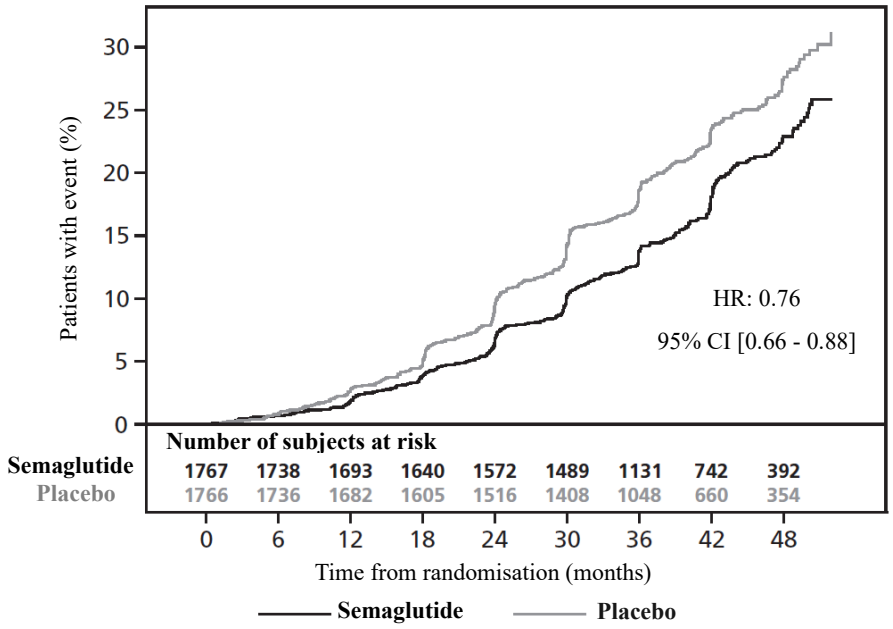

Figure 9: Cumulative incidence function of time to first occurrence of the primary composite outcome: onset of persistent ≥ 50% reduction in eGFR, onset of persistent eGFR < 15 mL/min/1,73 m^2, initiation of chronic kidney replacement therapy, kidney death or cardiovascular death (FLOW)

Semaglutide showed superiority over placebo, in addition to standard of care, in reducing the risk of MACE (non-fatal myocardial infarction, non-fatal stroke or CV death) with a HR of 0.82 ([0.68; 0.98] 95 % CI; one sided p value: 0.0145) (see Figure 10).

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Treatment with semaglutide was superior to placebo, in addition to standard of care, in improving all cause survival in patients with type 2 diabetes and chronic kidney disease with a significant reduction in all-cause death with a HR of 0.80 ([0.67, 0.95] 95 % CI, p-value: 0.0052). A reduction in the risk of CV death was observed for semaglutide versus placebo, in addition to standard of care (HR 0.71, [0.56, 0.89] 95 % CI) (see Figure 10).

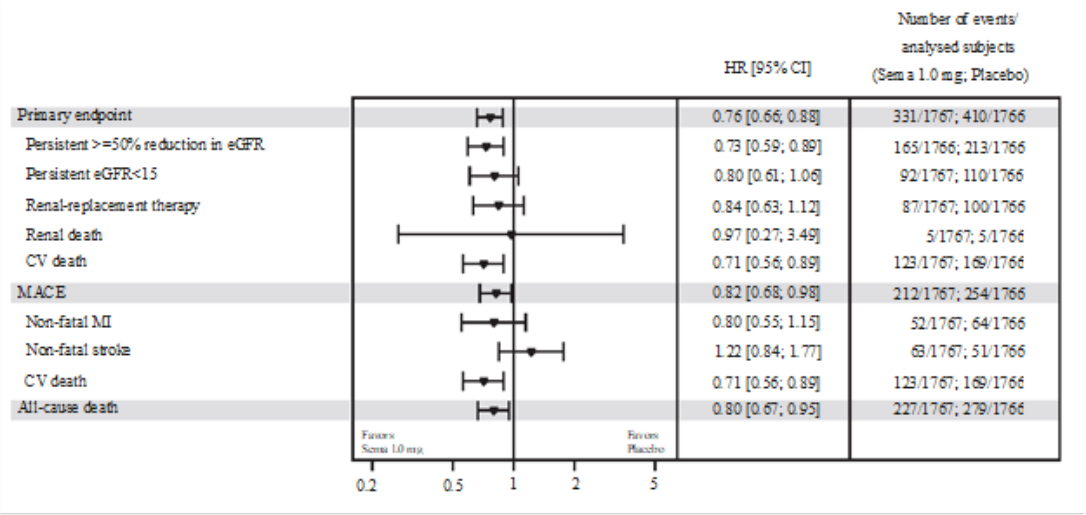

Figure 10: Forest plot: analyses of time to first occurrence of the primary composite outcome and its components, first occurrence of MACE and its components and all cause death (FLOW)

Functional capacity in patients with type 2 diabetes (T2D) and peripheral arterial disease (PAD)

STRIDE (NCT04560998) was a 52-week, randomised, double-blind, placebo-controlled trial comparing Ozempic® 1 mg versus placebo added to standard of care and administered once-weekly in patients with T2D and PAD with intermittent claudication. The treatment duration is 52 weeks including an 8 weeks dose escalation period. The follow up period is 5 weeks. The primary objective was to demonstrate the effect of Ozempic® 1 mg once weekly on walking ability compared with placebo, added to standard of care, in patients with T2D and PAD with intermittent claudication. The primary endpoint was change in maximum

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walking distance on a constant load treadmill test with fixed inclination of 12 % and a fixed speed of 3,2 km/h (2 mph) from baseline to week 52. The confirmatory secondary endpoints were follow up change in maximum walking distance from baseline to week 57, change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score from baseline to week 52 and change in pain-free walking distance from baseline to week 52.

A total of 792 patients were randomised 1:1 to receive either Ozempic® 1 mg or placebo for 52 weeks and followed for an additional 5 weeks off-treatment.

STRIDE included a population of patients with T2D and stable symptomatic PAD with intermittent claudication corresponding to Fontaine stage IIa (Rutherford classification grade I, category 1 and 2) with ankle brachial index (ABI) ≤ 0,90 or toe-brachial index (TBI) ≤ 0,70 (the leg with lowest index was chosen in case of bilateral disease) and MWD ≤ 600 meters on a constant load treadmill test. The mean age of the study population was 67 years, and 75,4 % of patients were male and 24,6 % of patients were female.

The effect of Ozempic® 1 mg once weekly on patient-perceived symptoms and the impact of intermittent claudication for patients living with T2D and PAD was assessed using the VascuQoL-6 questionnaire. The questionnaire comprises 6 items addressing symptoms, pain, social and emotional impact, and activity limitations. Each item is scored on a 4-point numeric response scale (1 = worst; 4 = best), with higher scores indicating a better health status, resulting in a total score ranging from 6 to 24 points.

In STRIDE, treatment with Ozempic® 1 mg once-weekly resulted in a statistically significant improvement in the functional capacity outcomes (maximum walking distance, pain free

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walking distance) and patient reported symptoms and impacts of intermittent claudication (VascuQol-6 total score) at week 52 compared to placebo. For the treatment policy (composite strategy) estimand, the ETR (estimated treatment ratio) between Ozempic® 1 mg and placebo for maximum walking distance on a constant load treadmill test at week 52 was: 1,13 [1.056, 1.211] 95 % CI, indicating a 13 % improvement with Ozempic® 1 mg. The median treatment difference at week 52 was 26,35 meters [11.765, 40.928] 95 % CI. For the hypothetical estimand (on treatment without rescue), the mean difference in maximum walking distance between Ozempic®1 mg and placebo was 39,91 meters [13.850, 65.974] 95 % CI. The statistically significant effect on maximum walking distance was sustained at week 57 compared to placebo (Table 9).

Table 9 Functional capacity outcomes and VascuQoL-6 total score from STRIDE

Intention-to-treat[a]	**Ozempic®** **N = 396**	**Placebo** **N = 396**
Maximum walking distance (meters)		
Week 52		
Baseline[b] median	184.50	185.75
Ratio to baseline median	1.21	1.08
Treatment ratio (HL Estimate) [95% CI][c]	1.13 [1.056, 1.211]*	
Patients (%) experiencing meaningful within-patient change[d]	49.1	35.1
Treatment difference (%) [95% CI][e]	14.0 [6.73, 21.36]+	
Week 57 (5 weeks follow-up Off-treatment)		
Ratio to baseline median	1.16	1.10
Treatment ratio (HL Estimate) [95% CI][c]	1.08 [1.004, 1.156]*	
Pain-free walking distance (meters), week 52		
Baseline[b] median	119.00	109.00
Ratio to baseline median	1.21	1.10
Treatment ratio (HL Estimate) [95% CI][c]	1.11 [1.033, 1.197]*	

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Intention-to-treat[a]	**Ozempic® N = 396**	**Placebo N = 396**
VascuQol-6 total score, week 52		
Baseline median	15.0	15.0
Change from baseline median	2.0	1.0
Treatment difference (HL Estimate) [95% CI][c]	1.00 [0.478, 1.518]*	
Patients (%) experiencing meaningful within-patient changed	37.5	32.4
Treatment difference (%) [95% CI][e]	5.1 [-2.13, 12.30]	

HL = Hodges-Lehmann estimate of location shift (median of all paired differences between Ozempic® and placebo); CI = confidence interval.

[a] The intention-to-treat population includes all randomized patients. Missing data at week 52/57 due to death or physical inability to perform treadmill assessments were handled using composite strategy. Missing data at post-baseline visits for other reasons were imputed using multiple imputation within groups defined by randomised treatment and completion status at week 52.

[b] Baseline was defined as the average of the walking distance measurements taken at baseline visit (week 0).

[c] 95% CIs were estimated with the Hodges-Lehmann method.

[*] $p < 0.05$ (two-sided) for superiority of Ozempic® vs. placebo obtained from Wilcoxon-rank sum test, adjusted for multiplicity.

[+] $p < 0.05$ (two-sided) unadjusted from logistic regression model.

[d] The meaningful within-patient change for maximum walking distance at week 52 is defined as an improvement of at least 1.2 (20%) relative to baseline walking distance and for VascuQoL-6 total score, an improvement of at least +3 points change from baseline score respectively. These estimates were obtained from the anchor-based analysis based on 1-category improvement in the PGI-S (Patient Global Impression of Severity) scale. The binary endpoint was analysed using a logistic regression model with randomised treatment as a fixed factor.

[e] The estimated proportions, treatment difference along with 95% CI were derived from the same logistic model using delta method.

5.2 Pharmacokinetic properties

Semaglutide has pharmacokinetic properties compatible with once weekly administration, with an elimination half-life of approximately 1 week.

Absorption

Maximum concentration was reached 1 to 3 days post dose.

Steady-state exposure was achieved following 4 – 5 weeks of once weekly administration. In patients with type 2 diabetes, the mean steady state concentrations following s.c. administration of 0,5 mg and 1 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively.

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Semaglutide exposure increased in a dose proportional manner for doses of 0,5 mg and 1 mg.

Similar exposure was achieved with s.c. administration of semaglutide in the abdomen, thigh or upper arm. Absolute bioavailability of s.c. semaglutide was 89 %.

Distribution

The mean volume of distribution of semaglutide following s.c. administration in patients with type 2 diabetes was approximately 12,5 L. Semaglutide was extensively bound to plasma albumin (> 99 %).

Metabolism/biotransformation

Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

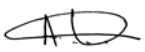
Elimination

The primary excretion routes of semaglutide related material were via the urine (53 %) and faeces (18,6 %). Approximately 3 % of the dose was excreted as intact semaglutide via urine.

Clearance of semaglutide in patients with type 2 diabetes was approximately 0,05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Special populations

No dose adjustment of semaglutide is needed based on age, gender, race, ethnicity, body weight, or renal or hepatic impairment.

Signed: 

Renal impairment:

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The experience in patients with end-stage renal disease was limited.

Hepatic impairment:

Hepatic impairment did not have any impact on the exposure of semaglutide.

Body weight:

Body weight has an effect on the exposure of semaglutide. Higher body weight results in lower exposure; a 20 % difference in body weight between individuals will result in an approximate 16 % difference in exposure. Semaglutide doses of 0,5 mg and 1 mg provide adequate systemic exposure over a body weight range of 40 – 198 kg.

Paediatrics:

Semaglutide has not been studied in paediatric patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate

Propylene glycol

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for injections

Ozempic® contains less than 1 mmol sodium (23 mg (*m/v*)) per dose, i.e. essentially 'sodium-free'.

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6.2 Incompatibilities

Substances added to Ozempic® may cause degradation of semaglutide. Ozempic® must not be mixed with other medicines, e.g. infusion fluids.

6.3 Shelf life

3 years.

In-use shelf life: 6 weeks.

After first use:

Store at or below 30 °C or in a refrigerator (between 2 °C to 8 °C).

Do not freeze Ozempic® and do not use Ozempic® if it has been frozen.

Keep the pen cap on when Ozempic® pen is not in use in order to protect from light.

Ozempic® should be protected from excessive heat and light.

Discard any unused portion after 42 days (6 weeks).

Do not use Ozempic® after the expiry date which is stated on the pen.

label and carton i.e. after 'EXP'. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

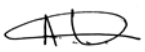
Before use:

Store in a refrigerator (between 2 °C to 8 °C). Keep away from the cooling element. Protect from light.

Do not freeze Ozempic® and do not use Ozempic® if it has been frozen.

For storage conditions after first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

Signed: 

The primary packaging consists of a 1,5 mL or 3 mL glass (Type I glass) cartridge closed at the one end with a grey rubber plunger (chlorobutyl rubber) and at the other end with an aluminium cap with a cream laminate rubber disc (bromobutyl/polyisoprene) inserted.
The cartridge is assembled into a pre-filled multidose disposable pen made of polypropylene, polyoxymethylene polycarbonate and acrylonitrile butadiene styrene.

There are two presentations of the pre-filled pen for Ozempic®:

- Ozempic® 0,25 mg and 0,5 mg/dose pen: Contains 1,5 mL solution for injection. The pen is designed to deliver doses of 0,25 mg or 0,5 mg. This pen is intended to be used for dose escalation and maintenance treatment at the 0,5 mg dose.

  The pen is light blue when capped, with PMS cool grey 6C dose button, on remove of the cap the pen consists of PMS cool grey 6C cartridge holder with light blue housing, labelled with summit red label.
- Ozempic® 1 mg/dose pen: Contains 3 mL solution for injection. The pen is designed to deliver doses of 1 mg only. This pen is to be used for maintenance treatment at the 1 mg dose only.

  The pen is light blue when capped, with PMS cool grey 6C dose button, on remove of the cap the pen consists of PMS cool grey 6C cartridge holder with light blue housing, labelled with petrol blue label.

The pen(s) is/are packed in carton box.

Pack sizes:

Ozempic® 0,25 mg, 0,5 mg/dose pen:

1 x 1,5 mL pre-filled pen including 6 disposable NovoFine® Plus needles.

Ozempic® 1 mg/dose pen:

1 x 3 mL pre-filled pen including 4 disposable NovoFine® Plus needles.

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6.6 Special precautions for disposal and other handling

The patient should be advised to discard the injection needle after each injection and store the pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

Needles and other waste material should be disposed of in accordance with local requirements.

The pen is for use by one person only.

Ozempic® should not be used if it does not appear clear and colourless or almost colourless.

Ozempic® can be administered with needles up to a length of 8 mm. The pen is designed to be used with NovoFine® or NovoTwist® disposable needles. NovoFine® Plus needles are included in the package.

For detailed instructions for use, see the patient information leaflet.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

90 Grayston Drive

Sandown, Sandton

Gauteng

2031

8 REGISTRATION NUMBER

53/21.13/0497

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 July 2020

Signed: 

10 DATE OF REVISION OF THE TEXT

22 May 2026

Signed: