Regulatory Operations

Insert: 2010-508x616-043
LIFT - Current 2

Proffesional

Fixed Dose - 2 mg, 3 ml

Colour: PMS 280C +
PMS 659C +
PMS Cool Gray 6C

1. Name of the medicinal product

Ozempic®

2 mg
Solution for injection in pre-filled pen

2. Qualitative and quantitative composition

One ml of solution contains 2.68 mg of semaglutide*. One pre-filled pen contains 8 mg semaglutide* in 3 ml solution. Each dose contains 2 mg of semaglutide in 0.74 ml solution.

*Human glucagon-like peptide-1 (GLP-1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.

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.

4.1 Therapeutic indications

Ozempic® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For trial results with respect to combinations, effects on glycaemic control, cardiovascular disease and kidney events and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology
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.

Semaglutide 0.25 mg is not a maintenance dose. Weekly doses higher than 2 mg are not recommended.

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

When Ozempic® is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Ozempic®. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Ozempic® is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.

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.

Changing the dosing day
The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (>72 hours). After selecting a new dosing day, once-weekly dosing should be continued.

Special populations
Elderly
No dose adjustment is required based on age.

Renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited.

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide (see section 5.2).

Paediatric population
The safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. No data are available.

Method of administration
Subcutaneous use.

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.

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

For further information on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General
Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Semaglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients whom had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started (see section 4.2).

There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.

Aspiration in association with general anaesthesia or deep sedation
Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Gastrointestinal effects and dehydration
Use of GLP-1 receptor agonists 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 in rare cases can lead to a deterioration of renal function (see section 4.8). Patients treated with semaglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Acute pancreatitis
Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia
Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide (see section 4.8).

Diabetic retinopathy
In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (see section 4.8). Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded.
There is no experience with semaglutide 2 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy and semaglutide 2 mg is therefore not recommended in these patients.

Non-arteritic anterior ischaemic optic neuropathy (NAION)
Data from epidemiological studies indicates an increased risk for non-arteritic anterior ischaemic optic neuropathy (NAION) during treatment with semaglutide. There is no identified time interval for when NAION may develop following treatment start. A sudden loss of vision should lead to ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed (see section 4.8).

Patients with gastroparesis
Semaglutide treated patients with gastroparesis may experience more serious or severe gastrointestinal adverse events. Semaglutide should be used with caution in these patients, and semaglutide is not recommended if gastroparesis is severe (see section 4.8).

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

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. C_{max} 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 C_{max} was decreased by 38%. This was assessed not to be clinically relevant.

Digoxin
Semaglutide did not change the overall exposure or C_{max} 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 the 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

Women of childbearing potential
Women of childbearing potential are recommended to use contraception when treated with semaglutide.

Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding
In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding.

Fertility
The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see section 5.3).

4.7 Effects on ability to drive and use machines

Semaglutide has no or negligible influence on the ability to drive or 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 (see section 4.4).

4.8 Undesirable effects

Summary of safety profile
In 8 phase 3a trials 4 792 patients were exposed to semaglutide up to 1 mg. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration.

Tabulated list of adverse reactions
Table 1 lists adverse reactions identified in all phase 3 trials (including the long-term cardiovascular outcomes trial) and post-marketing reports in patients with type 2 diabetes mellitus (further described in section 5.1). The frequencies of the adverse reactions (except diabetic retinopathy complications, see footnote in Table 1) are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial (see text below the table for additional details).

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); very rare: (<1/10 000) and not known: (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequency of adverse reactions of semaglutide

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very Rare	Not known
Immune system disorders			Hyper-sensitivity[c]	Anaphylactic reaction		
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulfonylurea	Hypoglycaemia[a] when used with other oral antidiabetics (OAD) Decreased appetite				
Nervous system disorders		Dizziness Headache	Dysgeusia			Dysaesthesia[d]
Eye disorders		Diabetic retinopathy complications[b]			Non-arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders			Increased heart rate			
Gastro-intestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Eructation Flatulence	Acute pancreatitis Delayed gastric emptying			Intestinal obstruction[d]
Hepatobiliary disorders		Cholelithiasis				
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.
b) Diabetic retinopathy complications is a composite of: retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage, diabetes-related blindness (uncommon). Frequency based on cardiovascular outcomes trial.
c) Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.
d) From post-marketing reports.

2-year cardiovascular outcomes and safety trial
In cardiovascular high risk population the adverse reaction profile was similar to that seen in the other phase 3a trials (described in section 5.1).

Description of selected adverse reactions
Hypoglycaemia
No episodes of severe hypoglycaemia were observed when semaglutide was used as monotherapy. Severe hypoglycaemia was primarily observed when semaglutide was used with a sulfonylurea (1.2% of subjects, 0.03 events/patient year) or insulin (1.5% of subjects, 0.02 events/patient year). Few episodes (0.1% of subjects, 0.001 events/patient year) were observed with semaglutide in combination with oral antidiabetics other than sulfonylureas.

American Diabetes Association (ADA) classified hypoglycaemia occurred in 11.3% (0.3 events/patient year) of patients when semaglutide 1 mg was added to SGLT2 inhibitor in SUSTAIN 9 compared to 2.0% (0.04 events/patient year) of placebo-treated patients. Severe hypoglycaemia was reported in 0.7% (0.01 events/patient year) and 0% of patients, respectively.

In a 40-week phase 3b trial in patients receiving semaglutide 1 mg and 2 mg, the majority of the hypoglycaemic episodes (45 out of 49 episodes) occurred when semaglutide was used in combination with sulfonylurea or insulin. Overall, there was no increased risk of hypoglycaemia with semaglutide 2 mg.

Gastrointestinal adverse reactions
Nausea occurred in 17% and 19.9% of patients when treated with semaglutide 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% of patients. The events were most frequently reported during the first months on treatment. Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide.

In a 40-week phase 3b trial in patients receiving semaglutide 1 mg and 2 mg, nausea occurred in similar proportions of patients when treated with semaglutide 1 mg and 2 mg, respectively. Diarrhoea and vomiting occurred in higher proportions of patients when treated with semaglutide 2 mg compared to semaglutide 1 mg. The gastrointestinal adverse reactions led to treatment discontinuation in similar proportions in the semaglutide 1 mg and 2 mg treatment groups.

In concomitant use with an SGLT2 inhibitor in SUSTAIN 9, constipation and gastro-oesophageal reflux disease occurred in 6.7% and 4% respectively of patients treated with semaglutide 1 mg compared to no events for placebo-treated patients. The prevalence of these events did not decrease over time.

Patients with gastroparesis may experience more serious or severe gastrointestinal effects when treated with semaglutide.

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 section 4.4).

Diabetic retinopathy complications
A 2-year clinical trial investigated 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial. In clinical trials up to 1 year involving 4 807 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

Non-arteritic anterior ischaemic optic neuropathy (NAION)
Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the relative risk of developing NAION, corresponding to approximately one additional case per 10 000 person-years of treatment.

Discontinuation due to an adverse event
The incidence of discontinuation of treatment due to adverse events was 6.1% and 8.7% for patients treated with semaglutide 0.5 mg and 1 mg, respectively, vs. 1.5% for placebo. The most frequent adverse events leading to discontinuation were gastrointestinal.

Injection site reactions
Injection site reactions (e.g. injection site rash, erythema) have been reported by 0.6% and 0.5% of patients receiving semaglutide 0.5 mg and 1 mg, respectively. These reactions have usually been mild.

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 patients tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1-3%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

Heart rate increase
Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean increases of 1 to 6 beats per minute (bpm) from a baseline of 72 to 76 bpm were observed in subjects treated with Ozempic®. In a long-term trial in subjects with cardiovascular risk factors, 16% of Ozempic®-treated subjects had an increase in heart rate of >10 bpm compared to 11% of subjects on placebo after 2 years of treatment.

4.9 Overdose

Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications.

There is no specific antidote for overdose with semaglutide. 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 semaglutide of approximately 1 week (see section 5.2).

5.1 Pharmacodynamic properties

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

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, in the cardiovascular system and in the kidneys. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. 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, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.

GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys. The mechanism of action of semaglutide is likely multifactorial. Indirect effects are indicated by the beneficial effect of semaglutide on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies but direct effects are likely also involved. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

Clinical data showed that semaglutide lowered albuminuria in patients with kidney disease.

Pharmacodynamic effects
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) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/L; 22% reduction), 2 hour postprandial glucose (4.1 mmol/L; 37% reduction), mean 24 hour glucose concentration (1.7 mmol/L; 22% reduction) and postprandial glucose excursions over 3 meals (0.6-1.1 mmol/L) compared with placebo. Semaglutide lowered fasting glucose after the first dose.

Beta-cell function and insulin secretion
Semaglutide improves beta-cell function. Compared to placebo, semaglutide improved first- and second-phase insulin response with a 3- and 2-fold increase, respectively, and increased maximal beta-cell secretory capacity 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%).

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.

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.

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 very low density lipoproteins (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
Improvement of glycaemic control, reduction of cardiovascular morbidity and mortality, weight loss and risk reduction of chronic kidney disease progression are integral parts of the treatment of type 2 diabetes.

The efficacy and safety of semaglutide 0.5 mg and 1 mg once weekly were evaluated in six randomised controlled phase 3a trials that included 7 215 patients with type 2 diabetes mellitus (4 107 treated with semaglutide). 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.

The efficacy and safety of semaglutide 2 mg once weekly was evaluated in a phase 3b trial (SUSTAIN FORTE) including 961 patients.

In addition, a phase 3b trial (SUSTAIN 7) including 1 201 patients was conducted to compare the efficacy and safety of semaglutide 0.5 mg and 1 mg once weekly to dulaglutide 0.75 mg and 1.5 mg once weekly, respectively. A phase 3b trial (SUSTAIN 9), was conducted to investigate the efficacy and safety of semaglutide as add-on to SGLT2 inhibitor treatment.

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

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

Results target the on-treatment period in all randomised subjects (analyses based on mixed models for repeated measurements or multiple imputation).

In addition, a phase 3b trial (SUSTAIN 11), was conducted to investigate the effect of semaglutide vs. insulin aspart, both as add-on to metformin and optimised insulin glargine (U100).

A phase 3b kidney outcomes trial (FLOW) including 3 533 patients was conducted to investigate the effects of semaglutide 1 mg once weekly vs. 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 vs. placebo in patients with type 2 diabetes and peripheral arterial disease.

Detailed information is provided below.

SUSTAIN 1 – Monotherapy
In a 30-week double-blind placebo-controlled trial, 388 patients inadequately controlled with diet and exercise, were randomised to semaglutide 0.5 mg or semaglutide 1 mg once weekly or placebo.

Table 2 SUSTAIN 1: Results at week 30

	Semaglutide 0.5 mg	Semaglutide 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	72	25
FPG (mmol/L)			
Baseline (mean)	9.7	9.9	9.7
Change from baseline at week 30	-2.5	-2.3	-0.6
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]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 2 – Semaglutide vs. sitagliptin both in combination with 1–2 oral antidiabetic medicinal products (metformin and/or thiazolidinediones)
In a 56-week active-controlled double-blind trial, 1 231 patients were randomised to semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly or sitagliptin 100 mg once daily, all in combination with metformin (94%) and/or thiazolidinediones (6%).

Table 3 SUSTAIN 2: Results at week 56

	Semaglutide 0.5 mg	Semaglutide 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	78	36
FPG (mmol/L)			
Baseline (mean)	9.3	9.3	9.6
Change from baseline at week 56	-2.1	-2.6	-1.1
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]	-

[a]p <0.0001 (2-sided) for superiority

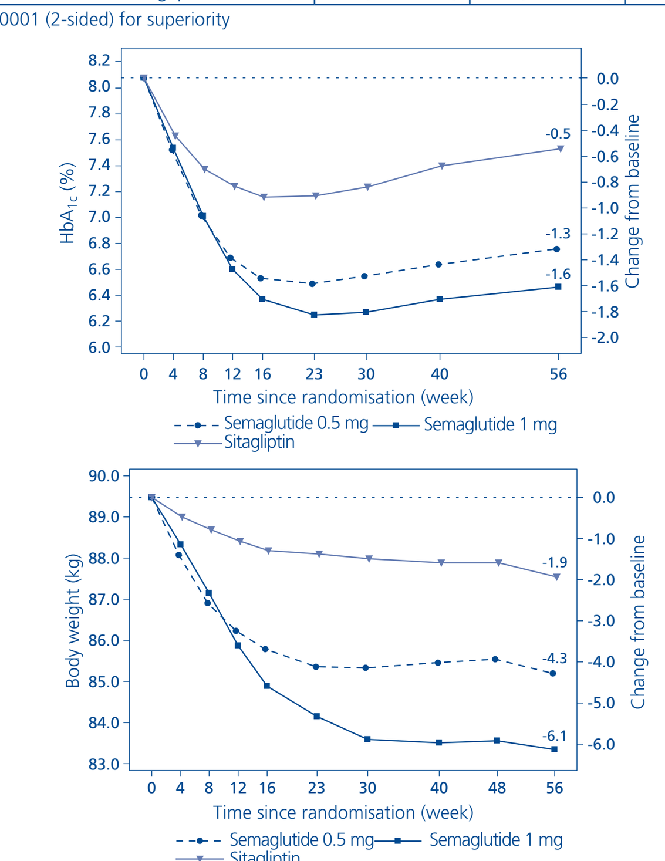

Figure 1 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 56

SUSTAIN 7 – Semaglutide vs. dulaglutide both in combination with metformin
In a 40-week, open-label trial, 1 201 patients on metformin were randomised 1:1:1:1 to once weekly semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1 mg or dulaglutide 1.5 mg, respectively. 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.

Gastrointestinal disorders were the most frequent adverse events, and occurred in similar proportion of patients receiving semaglutide 0.5 mg (129 patients [43%]), semaglutide 1 mg (133 [44%]), and dulaglutide 1.5 mg (143 [48%]); fewer patients had gastrointestinal disorders with dulaglutide 0.75 mg (100 [33%]).
At week 40, the increase in pulse rate for semaglutide (0.5 mg and 1 mg) and dulaglutide (0.75 mg and 1.5 mg) was 2.4, 4.0, and 1.6, 2.1, beats/min, respectively.

Table 4 SUSTAIN 7: Results at week 40

	Semaglutide 0.5 mg	Semaglutide 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	-1.8	-1.1	-1.4
Difference from dulaglutide [95% CI]	-0.4[b] [-0.6, -0.2][a]	-0.4[c] [-0.6, -0.3][a]	-	-
Patients (%) achieving HbA_{1c} <7%	68	79	52	67
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
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[b] [-3.0, -1.5][a]	-3.6[c] [-4.3, -2.8][a]	-	-

[a]p <0.0001 (2-sided) for superiority
[b]Semaglutide 0.5 mg vs. dulaglutide 0.75 mg
[c]Semaglutide 1 mg vs. dulaglutide 1.5 mg

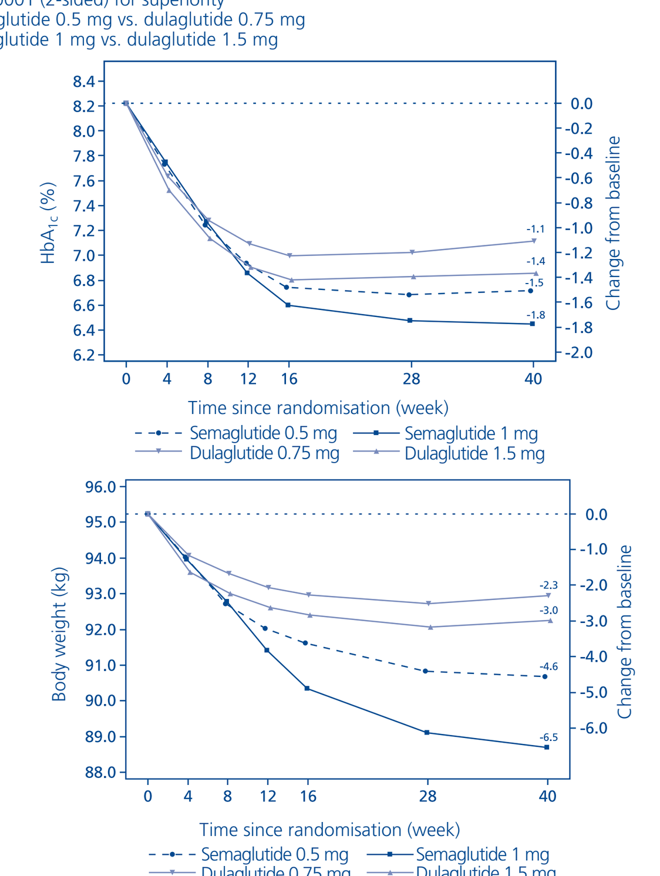

Figure 2 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 40

SUSTAIN 3 – Semaglutide 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 semaglutide 1 mg or exenatide ER 2 mg once weekly.

Table 5 SUSTAIN 3: Results at week 56

	Semaglutide 1 mg	Exenatide ER 2 mg
Intent-to-Treat (ITT) Population (N)	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change from baseline at week 56	-1.5	-0.9
Difference from exenatide [95% CI]	-0.6 [-0.8, -0.4][a]	-
Patients (%) achieving HbA_{1c} <7%	67	40
FPG (mmol/L)		
Baseline (mean)	10.6	10.4
Change from baseline at week 56	-2.8	-2.0
Body weight (kg)		
Baseline (mean)	96.2	95.4
Change from baseline at week 56	-5.6	-1.9
Difference from exenatide [95% CI]	-3.8 [-4.6, -3.0][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 4 – Semaglutide vs. insulin glargine both in combination with 1–2 oral antidiabetic medicinal products (metformin or metformin and sulfonylurea)
In a 30-week open-label comparator trial 1 089 patients were randomised to semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly, or insulin glargine once-daily on a background of metformin (48%) or metformin and sulfonylurea (51%).

Table 6 SUSTAIN 4: Results at week 30

	Semaglutide 0.5 mg	Semaglutide 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	73	38
FPG (mmol/L)			
Baseline (mean)	9.6	9.9	9.7
Change from baseline at week 30	-2.0	-2.7	-2.1
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]	-6.34 [-7.0, -5.7][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 5 – Semaglutide vs. placebo both in combination with basal insulin
In a 30-week double-blind placebo-controlled trial, 397 patients inadequately controlled with basal insulin with or without metformin were randomised to semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly or placebo.

Table 7 SUSTAIN 5: Results at week 30

	Semaglutide 0.5 mg	Semaglutide 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	79	11
FPG (mmol/L)			
Baseline (mean)	8.9	8.5	8.6
Change from baseline at week 30	-1.6	-2.4	-0.5
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]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN FORTE – Semaglutide 2 mg vs. semaglutide 1 mg
In a 40-week double-blind trial, 961 patients inadequately controlled with metformin with or without sulfonylurea were randomised to semaglutide 2 mg once weekly or semaglutide 1 mg once weekly.

Treatment with semaglutide 2 mg resulted in a statistically superior reduction in HbA_{1c} after 40 weeks of treatment compared to semaglutide 1 mg.

Table 8 SUSTAIN FORTE: Results at week 40

	Semaglutide 1 mg	Semaglutide 2 mg
Intent-to-Treat (ITT) Population (N)	481	480
HbA_{1c} (%)		
Baseline (mean)	8.8	8.9
Change from baseline at week 40	-1.9	-2.2
Difference from semaglutide 1 mg [95% CI]	-	-0.2 [-0.4, -0.1][a]
Patients (%) achieving HbA_{1c} <7%	58	68
FPG (mmol/L)		
Baseline (mean)	10.9	10.7
Change from baseline at week 40	-3.1	-3.4
Body weight (kg)		
Baseline (mean)	98.6	100.1
Change from baseline at week 40	-6.0	-6.9
Difference from semaglutide 1 mg [95% CI]		-0.9 [-1.7, -0.2][b]

[a]p<0.001 (2-sided) for superiority
[b]p<0.05 (2-sided) for superiority

SUSTAIN 9 – Semaglutide vs. placebo as add-on to SGLT2 inhibitor ± metformin or sulfonylurea
In a 30-week double-blind placebo-controlled trial, 302 patients inadequately controlled with SGLT2 inhibitor with or without metformin or sulfonylurea were randomised to semaglutide 1 mg once weekly or placebo.

Table 9 SUSTAIN 9: Results at week 30

	Semaglutide 1 mg	Placebo
Intent-to-Treat (ITT) Population (N)	151	151
HbA_{1c} (%)		
Baseline (mean)	8.0	8.1
Change from baseline at 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	18.7
FPG (mmol/L)		
Baseline (mean)	9.1	8.9
Change from baseline at week 30	-2.2	0.0
Body weight (kg)		
Baseline (mean)	89.6	93.8
Change from baseline at week 30	-4.7	-0.9
Difference from placebo [95% CI]	-3.8 [-4.7, -2.9][a]	-

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

SUSTAIN 11 - Semaglutide vs. insulin aspart as add-on to insulin glargine + metformin
In a 52-week open-label trial, 1748 subjects with inadequately controlled T2D after a 12-week run-in period on insulin glargine and metformin were randomised to 1:1 to receive either semaglutide once-weekly (0.5 mg or 1.0 mg) or insulin aspart three times daily. The included population had a mean diabetes duration of 13.4 years and a mean HbA_{1c} of 8.6%, with a target HbA_{1c} of 6.5-7.5%.

Treatment with semaglutide resulted in reduction in HbA_{1c} at week 52 (-1.5% for semaglutide vs. -1.2% for insulin aspart).

The number of severe hypoglycaemic episodes in both treatment arms was low (4 episodes with semaglutide vs. 7 episodes with insulin aspart).

Mean baseline body weight decreased with semaglutide (-4.1 kg) and increased with insulin aspart (+2.8 kg) and the estimated treatment difference was -6.99 kg (95%CI -7.41 to -6.57) at week 52.

Combination with sulfonylurea monotherapy
In SUSTAIN 6 (see subsection "Cardiovascular disease") 123 patients were on sulfonylurea monotherapy at baseline. HbA_{1c} at baseline was 8.2%, 8.4% and 8.4% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.6%, -1.5% and 0.1% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively.

Combination with premix insulin ± 1–2 OADs
In SUSTAIN 6 (see subsection "Cardiovascular disease") 867 patients were on premix insulin (with or without OAD(s)) at baseline. HbA_{1c} at baseline was 8.8%, 8.9% and 8.9% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.3%, -1.8% and -0.4% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively.

Cardiovascular disease
In a 104-week double-blind trial (SUSTAIN 6), 3 297 patients with type 2 diabetes mellitus at high cardiovascular risk were randomised to either semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly or corresponding placebo in addition to standard-of-care hereafter followed for 2 years. In total 98% of the patients completed the trial and the vital status was known at the end of the trial for 99.6% of the patients.

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Length: Max. 29 mm (100%)
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OZEMPIC®
2 mg
solution for injection in pre-filled pen
semaglutide

novo nordisk®

8 mm
1 mm

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/m². The mean duration of diabetes was 13.9 years.

The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The total number of primary component MACE endpoints was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo. See figure 4 for results on primary and secondary cardiovascular endpoints. Treatment with semaglutide resulted in a 26% risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. The total numbers of cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes were 90, 111, and 71, respectively, including 44 (2.7%), 47 (2.9%), and 27 (1.6%), respectively, with semaglutide (figure 4). The risk reduction in the primary composite outcome was mainly driven by decreases in the rate of non-fatal stroke (39%) and non-fatal myocardial infarction (26%) (figure 3).

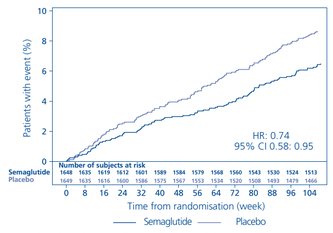


Figure 3 Kaplan-Meier plot of time to first occurrence of the composite outcome: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

	Hazard Ratio (95% CI)	Semaglutide N (%)	Placebo N (%)
FAS		1648 (100)	1649 (100)
Primary endpoint – MACE	0.74 (0.58- 0.95)	108 (6.6)	146 (8.9)
Components of MACE			
Cardiovascular death	0.98 (0.65-1.48)	44 (2.7)	46 (2.8)
Non-fatal stroke	0.61 (0.38-0.99)	27 (1.6)	44 (2.7)
Non-fatal myocardial infarction	0.74 (0.51-1.08)	47 (2.9)	64 (3.9)
Other secondary endpoints			
All cause death	1.05 (0.74-1.50)	62 (3.8)	60 (3.6)

0.2 Favours Semaglutide — 1 — 5 Favours placebo

Figure 4 Forest plot: analyses of time to first occurrence of the composite outcome, its components and all cause death (SUSTAIN 6)

There were 158 events of new or worsening nephropathy. The hazard ratio [95% CI] 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 [0.46, 0.88] driven by new onset of persistent macroalbuminuria.

In a 52-week double blind trial (STRIDE, NCT04560998), 792 patients with T2D and PAD with intermittent claudication Fontaine stage IIa were randomised to either semaglutide 1 mg once weekly or placebo on top of standard of care. The primary endpoint was change in maximum walking distance on a constant load treadmill test from baseline to week 52. The confirmatory secondary endpoints were 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. VascuQoL-6 is a questionnaire which includes the domains pain, social and emotional impact, and activity limitations. The score ranges from 6 to 24, with higher scores indicating better health status. The mean age of the study population was 67 years, and 75.4% of patients were male. Mean BMI was 29.6 kg/m² and mean diabetes duration was 13.3 years.

In STRIDE, treatment with semaglutide 1 mg once-weekly resulted in a statistically significant improvement in the functional capacity outcomes (maximum walking distance, pain-free walking distance) and patient reported symptoms and impacts of intermittent claudication (VascuQoL-6 total score) at week 52 compared to placebo. The 13% relative improvement represents a median change in maximum walking distance of 26 meters on constant load treadmill [12 – 41] 95% CI (Table 10).

Table 10: 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
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]*	
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]*	

HL = Hodges-Lehmann estimate of location shift (median of all paired differences between semaglutide and placebo); CI = confidence interval; PAD = Peripheral arterial disease.

[a] The intention-to-treat population includes all randomized patients. Missing data at week 52 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 semaglutide vs. placebo obtained from Wilcoxon-rank sum test, adjusted for multiplicity.

[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. 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.

Kidney outcomes

In a double-blind kidney outcomes trial (FLOW), 3 533 patients with type 2 diabetes mellitus and chronic kidney disease with eGFR of 50-75 ml/min/1.73 m² and UACR >300 and <5000 mg/g, or eGFR 25–<50 ml/min/1.73 m² and UACR of >100 and <5000 mg/g were randomised to either semaglutide 1 mg once weekly or corresponding placebo in addition to standard-of-care.
The study was stopped early for efficacy following the planned interim analysis based on a recommendation by the independent Data Monitoring Committee. The median follow-up time was 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/m². 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 m² and the median UACR was 568 mg/g. At baseline, about 95% of the patients were treated with renin-angiotensin-aldosterone system inhibitors and 16% with 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 m², initiation of chronic kidney replacement therapy, kidney death or cardiovascular death with a hazard ratio of 0.76 [0.66; 0.88]$_{95\%\ CI}$, corresponding to a relative risk reduction in kidney disease progression of 24% (see Figure 5). The individual components of the primary composite contributed to the treatment effect but there were few kidney deaths (see Figure 6).
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 (ml/min/1.73m²/year) [0.86; 1.47]$_{95\%\ CI}$. Treatment with semaglutide improved overall survival with a significant reduction in all-cause mortality (see Figure 6).

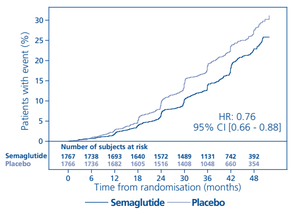


Figure 5 Cumulative incidence function of time to first occurrence of the primary composite outcome: onset of persistent ≥50% reduction in eGFR, onset of persistent eGFR <15 ml/min/1.73 m², initiation of chronic kidney replacement therapy, kidney death or cardiovascular death (FLOW)

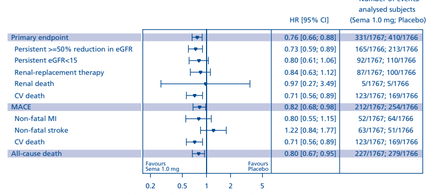


Figure 6 Forest plot: analyses of time to first occurrence of the primary composite outcome and its components, first occurrence of MACE and its components and all cause death (FLOW)

Body weight

After one year of treatment, a weight loss of ≥5% and ≥10% was achieved for more subjects with semaglutide 0.5 mg (46% and 13%) and 1 mg (52–62% and 21–24%) compared with the active comparators sitagliptin (18% and 3%) and exenatide ER (17% and 4%).

In the 40-week trial vs. dulaglutide a weight loss of ≥5% and ≥10% was achieved for more subjects with semaglutide 0.5 mg (44% and 14%) compared with dulaglutide 0.75 mg (23% and 3%) and semaglutide 1 mg (up to 63% and 27%) compared with dulaglutide 1.5 mg (30% and 8%).

A significant and sustained reduction in body weight from baseline to week 104 was observed with semaglutide 0.5 mg and 1 mg vs. placebo 0.5 mg and 1 mg, in addition to standard-of-care (-3.6 kg and -4.9 kg vs. -0.7 kg and -0.5 kg , respectively) in SUSTAIN 6.

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 and -1.4 kg for placebo).

Blood pressure

Significant reductions in mean systolic blood pressure were observed when semaglutide 0.5 mg (3.5-5.1 mmHg) and 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 semaglutide and comparators. The observed reductions in systolic blood pressure for semaglutide 2 mg and 1 mg at week 40 were 5.3 mmHg and 4.5 mmHg, respectively.

5.2 Pharmacokinetic properties

Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once weekly subcutaneous 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.

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 subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively. In the trial comparing semaglutide 1 mg and 2 mg, the mean steady state concentrations were 27 nmol/L and 54 nmol/L, respectively. Semaglutide exposure increased in a dose proportional manner for doses of 0.5 mg, 1 mg and 2 mg. Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. Absolute bioavailability of subcutaneous semaglutide was 89%.

Distribution

The mean volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes was approximately 12.5 L. Semaglutide was extensively bound to plasma albumin (>99%).

Biotransformation

Prior to excretion, semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

Elimination

In a trial with a single subcutaneous dose of radiolabelled semaglutide, it was found that the primary excretion routes of semaglutide-related material were via urine and faeces; approximately 2/3 of semaglutide-related material were excreted in urine and approximately 1/3 in faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine. In patients with type 2 diabetes clearance of semaglutide 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 population

Elderly

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a studies including patients of 20–86 years of age.

Gender, race and ethnicity

Gender, race (White, Black or African-American, Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) had no effect on the pharmacokinetics 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.

Renal impairment

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with subjects with normal renal function. This was also shown for subjects with type 2 diabetes and with renal impairment based on data from phase 3a studies, although 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. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function in a trial with a single-dose of 0.5 mg semaglutide.

Paediatric population

Semaglutide has not been studied in paediatric patients.

Immunogenicity

Development of anti-semaglutide antibodies when treated with semaglutide 1 mg and 2.4 mg occurred infrequently (see section 4.8) and the response did not appear to influence semaglutide pharmacokinetics.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. No other treatment-related tumours were observed. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded.

In fertility studies in rats, semaglutide did not affect mating performance or male fertility. In female rats, an increase in oestrous cycle length and a small reduction in *corpora lutea* (ovulations) were observed at doses associated with maternal body weight loss.

In embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to lack of GLP-1 receptor expression in the yolk sac of non-human primates, this mechanism is considered unlikely to be of relevance to humans. However, a direct effect of semaglutide on the foetus cannot be excluded.

In developmental toxicity studies in rabbits and *cynomolgus* monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16%. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.

Postnatal growth and development were evaluated in *cynomolgus* monkeys. Infants were slightly smaller at delivery, but recovered during the lactation period.

In juvenile rats, semaglutide caused delayed sexual maturation in both males and females. These delays had no impact upon fertility and reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

6.1 List of excipients

Disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before first use

Expiry date is stated on the pen label and carton after 'Expiry'.

After first opening

In-use shelf life: 6 weeks.

Store below 30 °C or in a refrigerator (2 °C – 8 °C). Do not freeze Ozempic®. Keep the pen cap on when the pen is not in use in order to protect it from light.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep away from the cooling element.
Do not freeze Ozempic®.

Keep the pen cap on in order to protect from light.

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

6.5 Nature and contents of container

3 ml glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

Pack size

1 pre-filled pen and 4 disposable NovoFine® Plus needles.
Each pre-filled pen contains 3 ml of solution, delivering 4 doses of 2 mg.

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.

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® should not be used if it has been frozen.

Ozempic® can be administered with 30G, 31G, and 32G disposable needles up to a length of 8 mm.

Any unused medicinal product and other waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Instructions on how to use Ozempic® 2 mg solution for injection in pre-filled pen

Please read these instructions carefully before using your Ozempic® pre-filled pen.
Talk to your doctor, nurse or pharmacist about how to inject Ozempic® correctly.

Start by checking your pen to **make sure that it contains Ozempic® 2 mg,** then look at the illustrations below to get to know the different parts of your pen and needle.
If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who knows how to use the Ozempic® pre-filled pen.
Your pen is a pre-filled dial-a-dose pen. It contains 8 mg of semaglutide, and you can only select doses of 2 mg. One unused pen contains four doses of 2 mg.

Use the table inside the lid of the carton to keep track of how many injections you have taken and when you took the injections.

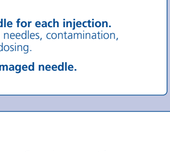
Your pen is designed to be used with 30G, 31G, and 32G disposable needles up to a length of 8 mm.
NovoFine® Plus needles are included in the pack.

⚠ **Important information**
Pay special attention to these notes, as they are important for safe use of the pen.

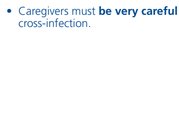
Ozempic® pre-filled pen and needle (example)

1. Prepare your pen with a new needle

- **Check the name and coloured label** of your pen, to make sure that it contains Ozempic® 2 mg. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could be harmful to your health.
- **Pull off the pen cap.**



- **Check that the solution in your pen is clear** and colourless. Look through the pen window. If the solution looks cloudy or coloured, do not use the pen.



- **Take a new needle.** Check the paper tab and the outer needle cap for damages that could affect sterility. If any damage is seen use a new needle.
- **Tear off the paper tab.**

Make sure to attach the needle correctly.

- Push the needle **straight** onto the pen.
- Turn until it is on **tight.**

The needle is covered by two caps. You must remove both caps. If you forget to remove both caps, you will **not** inject any solution.

- **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.

- **Pull off the inner needle cap and throw it away.** If you try to put it back on, you may accidentally stick yourself with the needle.

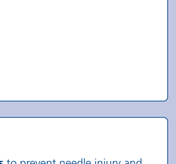
A drop of solution may appear at the needle tip. This is normal, but you must still check the flow, if you use a new pen for the first time. See step 2 'Check the flow with each new pen'.
Do not attach a new needle to your pen until you are ready to take your injection.

⚠ **Always use a new needle for each injection.**
This may prevent blocked needles, contamination, infection and inaccurate dosing.

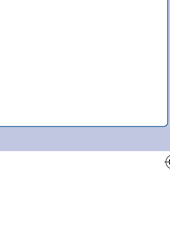
⚠ **Never use a bent or damaged needle.**

2. Check the flow with each new pen

- If your pen is already in use, go to step 3 'Select your dose'. Only check the flow before your **first injection with each new pen.**
- Turn the dose selector to **the flow check symbol** (• •) right past '0'. Make sure the flow check symbol lines up with the pointer.



- Hold the pen with the needle pointing up. **Press and hold in the dose button** until the dose counter returns to '0'. The '0' must line up with the dose pointer. A drop of solution should appear at the needle tip.

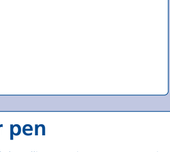


A small drop may remain at the needle tip, but it will not be injected.
If no drop appears, repeat step 2 'Check the flow with each new pen' up to 6 times. If there is still no drop, change the needle and repeat step 2 'Check the flow with each new pen' once more.
Dispose of the pen and use a new one if a drop of solution still does not appear.

⚠ **Always make sure that a drop appears** at the needle tip before you use a new pen for the first time. This makes sure that the solution flows.
If no drop appears, you will **not** inject any medicine, even though the dose counter may move. **This may indicate a blocked or damaged needle.**
If you do not check the flow before your first injection with each new pen, you may not get the prescribed dose and the intended effect of Ozempic®.

3. Select your dose

- **Turn the dose selector to select 2 mg.** Keep turning until the dose counter stops and shows 2 mg.



Only the dose counter and dose pointer will show that 2 mg has been selected.
You can only select 2 mg per dose. When your pen contains less than 2 mg, the dose counter stops before 2 is shown.
The dose selector clicks differently when turned forwards, backwards or past 2 mg. Do not count the pen clicks.

⚠ **Always use the dose counter and the dose pointer to see that 2 mg has been selected before injecting this medicine.**
Do not count the pen clicks.
Only doses of 2 mg must be selected with the dose selector. 2 mg must line up precisely with the dose pointer to ensure that you get a correct dose.

How much solution is left

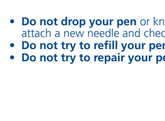
- **To see how much solution is left,** use the dose counter: Turn the dose selector until the **dose counter stops.**
If it shows 2, **at least 2 mg** is left in your pen.
If the **dose counter stops before 2 mg,** there is not enough solution left for a full dose of 2 mg.

⚠ If there is not enough solution left in your pen for a full dose, do not use it. Use a new Ozempic® pen.

4. Inject your dose

- **Insert the needle into your skin** as your doctor or nurse has shown you.
- **Make sure you can see the dose counter.** Do not cover it with your fingers. This could interrupt the injection.

- **Press and hold down the dose button. Watch as the dose counter returns to '0'.** The '0' must line up with the dose pointer. You may then hear or feel a click.
- **Continue pressing the dose button while keeping the needle in your skin.**



- **Count slowly to 6, while keeping the dose button pressed.**
- If the needle is removed earlier, you may see a stream of solution coming from the needle tip. If so, the full dose will not be delivered.

- **Remove the needle from your skin.** You can then release the dose button. If blood appears at the injection site, press lightly.

You may see a drop of solution at the needle tip after injecting. This is normal and does not affect your dose.

⚠ **Always watch the dose counter to know how many mg you inject.** Hold the dose button down until the dose counter returns to '0'.

How to identify a blocked or damaged needle
– If '0' does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
– In this case, you have **not** received any medicine – even though the dose counter has moved from the original dose that you have set.

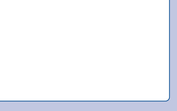
How to handle a blocked needle
Change the needle as described in step 5 'After your injection' and repeat all steps starting with step 1 'Prepare your pen with a new needle'. Make sure you select the full dose you need.

Never touch the dose counter when you inject. This can interrupt the injection.

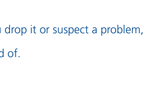
5. After your injection

Always dispose of the needle after each injection to ensure convenient injections and prevent blocked needles. If the needle is blocked, you will **not** inject any medicine.

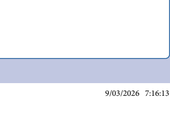
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer needle cap.



- Once the needle is covered, **carefully push the outer needle cap completely on.**
- **Unscrew the needle** and dispose of it carefully as instructed by your doctor, nurse, pharmacist or local authorities.



- **Put the pen cap on** your pen after each use to protect the solution from light.



When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

⚠ **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle.

⚠ **Always remove the needle from your pen immediately after each injection.**
This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

⚠ Further important information

- Always keep your pen and needles **out of the sight and reach of others,** especially children.
- **Never share** your pen or your needles with other people.
- Caregivers must **be very careful when handling used needles** to prevent needle injury and cross-infection.

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing. If this happens you might not get the intended effect of this medicine.

- **Do not leave the pen in a car** or another place where it can get too hot or too cold.
- **Do not inject Ozempic® which has been frozen.** If you do that, you might not get the intended effect of this medicine.
- **Do not inject Ozempic® which has been exposed to direct sunlight.** If you do that, you might not get the intended effect of this medicine.
- **Do not expose your pen to dust, dirt or liquid.**
- **Do not wash, soak or lubricate your pen.** It may be cleaned with a mild detergent on a moistened cloth.
- **Do not drop your pen** or knock it against hard surfaces. If you drop it or suspect a problem, attach a new needle and check the flow before you inject.
- **Do not try to refill your pen.** Once empty, it must be disposed of.
- **Do not try to repair your pen** or pull it apart.

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