▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

Ozempic® (semaglutide) solution for injection

1. NAME OF THE MEDICINE

semaglutide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ozempic 0.25 mg, 0.5 mg/dose

1.5 mL pen:

One mL of solution contains 1.34 mg of semaglutide. One pre-filled pen contains 2 mg semaglutide in 1.5 mL solution.

3 mL pen:

One mL of solution contains 0.68 mg of semaglutide. One pre-filled pen contains 2 mg semaglutide in 3 mL solution.

Ozempic 1 mg/dose

One mL of solution contains 1.34 mg semaglutide. One pre-filled pen contains 4 mg semaglutide in 3 mL solution.

Ozempic 2 mg/dose

One mL of solution contains 2.68 mg semaglutide. One pre-filled pen contains 8 mg semaglutide in 3 mL solution.

Semaglutide is a human glucagon-like-peptide-1 (GLP-1) receptor agonist produced in *Saccharomyces cerevisiae* by recombinant DNA technology followed by protein purification.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Ozempic solution for injection is provided in a pre-filled multidose disposable pen, which contains semaglutide in a 1.5 mL or 3 mL cartridge.

It is a clear and colourless, or almost colourless, isotonic solution with pH = 7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Type 2 diabetes mellitus

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 not tolerated or contraindicated.
- in addition to other medicinal products for the treatment of type 2 diabetes.

Chronic kidney disease

Ozempic is indicated as an adjunct to standard of care therapy to reduce the risk of sustained decline of kidney function and to reduce the risk of cardiovascular death in adults with type 2 diabetes and chronic kidney disease (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

4.2 Dose and Method of Administration

Dosage

Glycaemic control

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. 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.

Type 2 diabetes and chronic kidney disease

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 0.25 mg is not a maintenance dose.

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 therapy of a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see section 4.4 Special Warnings and Precautions for Use).

The use of Ozempic does not require blood glucose self-monitoring. Self-monitoring may be performed when Ozempic is used together with sulfonylurea or insulin in order to allow adjustment of the dose of these medications.

Method of Administration

Ozempic is to be administered once weekly, on the same day each week, 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. For further information on administration, see section 6 Pharmaceutical Particulars.

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.

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.

Dosage Adjustment

Elderly (≥65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited (see section 5.2 Pharmacokinetic Properties).

Gender

No dose adjustment is required based on gender.

Race and Ethnicity

No dose adjustment is required based on race and ethnicity.

Patients with hepatic impairment

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

Patients with 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.

Children and adolescents

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

4.3 Contraindications

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

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.

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 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 may lead to a deterioration of renal function (see section 4.8 Adverse Effects (Undesirable Effects)). 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.

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 (see section 4.8 Adverse Effects (Undesirable Effects)).

Acute Pancreatitis

Acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising 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, Ozempic should be discontinued; if confirmed, Ozempic should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia

Patients treated with Ozempic 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 Ozempic.

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 Adverse Effects (Undesirable Effects)). Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. 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.

Acute kidney injury

There have been post-marketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require haemodialysis, in patients treated with GLP-1 receptor agonists. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Monitor renal function when initiating or escalating doses of Ozempic in patients reporting severe adverse gastrointestinal reactions.

Psychiatric disorders

Suicidal behaviour and ideation have been reported with GLP-1 receptor agonists. Monitor patients for the emergence or worsening of depression, suicidal thoughts or behaviours, and/or any unusual changes in mood or behaviour. Consider the benefits and risks for individual patients prior to initiating or continuing therapy in patients with suicidal thoughts or behaviours or have a history of suicidal attempts.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

It is known that individuals with an anatomical predisposition ('disc at risk'), whether or not they are taking a GLP-1 agonist, are at highest risk of developing non-arteritic anterior ischaemic optic neuropathy (NAION). This pre-existing risk can be assessed by an optometrist or ophthalmologist. Some epidemiological studies indicate an increased risk of NAION during treatment with semaglutide. There is no identified time interval for when NAION may develop following treatment start. Patients reporting a sudden loss of vision (including partial loss) should be urgently referred for ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed (see section 4.8 Adverse Effects (Undesirable Effects)).

Populations not studied

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV and therefore use of semaglutide is not recommended in these patients.

Use in 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.

Use in 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.

Use in elderly

See section 5.2 Pharmacokinetic Properties.

Paediatric Use
The safety and efficacy of semaglutide in children and adolescents aged below 18 years has not been studied.

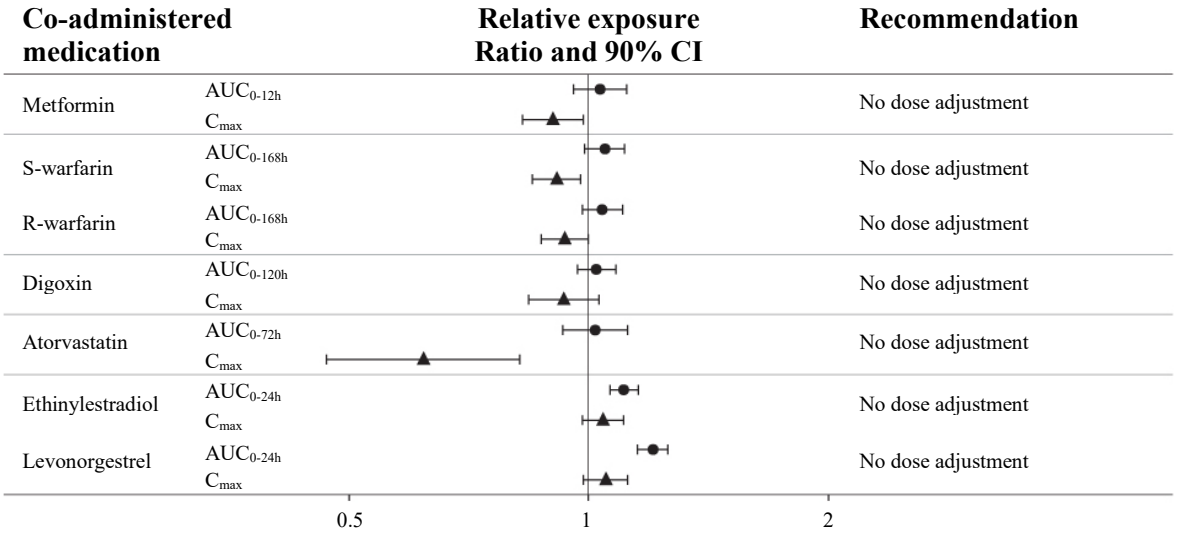
Effects on laboratory tests
No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

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

The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products, therefore semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg steady state exposure.

No clinically relevant drug-drug interaction with semaglutide (Figure 1) was observed based on the evaluated medications. Therefore, no dose adjustment is required when co-administered with semaglutide.



Relative exposure in terms of AUC and C_{max} for each medication when given with semaglutide compared to without semaglutide. Metformin and oral contraceptive drug (ethinylestradiol/levonorgestrel) were assessed at steady state. Warfarin (S-warfarin/R-warfarin), digoxin and atorvastatin were assessed after a single dose. Abbreviations: AUC: area under the curve. C_{max}: maximum concentration. CI: confidence interval.

Figure 1: Impact of semaglutide on the exposure of co-administered oral medications

Oral Contraceptives
Semaglutide is not anticipated to decrease the effectiveness 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 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

Effects on fertility
The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats at daily SC doses of 828 μg/kg, resulting in exposures approximately 13 times the clinical AUC. 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 (≥30 μg/kg/day SC, resulting in subclinical exposures).

Use in pregnancy
Pregnancy Category: D

Semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. 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 5.1 Pharmacodynamic Properties).

Studies in animals have shown reproductive toxicity when semaglutide was administered during organogenesis. In pregnant rats, embryofetal toxicity (lethality, impaired growth and an increased incidence of fetal abnormalities) was observed at subclinical plasma exposures. Mechanistic studies suggest a direct GLP-1 receptor mediated role of semaglutide on some of the effects in rats (species specific). In pregnant rabbits, pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and

skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures. In pregnant cynomolgus monkeys, pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) and with an increase in early pregnancy losses at ≥0.075 mg/kg twice weekly (>2.7 fold clinical exposure at 1 mg/week). Exposures at the NOAEL in all species were subclinical and a direct effect of semaglutide on the fetus cannot be excluded.

Use in lactation

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

4.7 Effects on Ability to Drive and Use Machines

Ozempic 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.

Adverse effects of Ozempic include dizziness which could affect the ability to drive or use machines (see Section 4.8 Adverse Effects (Undesirable Effects).

4.8 Adverse Effects (Undesirable Effects)

Summary of the Safety Profile

In 8 phase 3a trials, 4,792 patients were exposed to Ozempic up to 1 mg alone or in combination with other glucose lowering medicinal products. 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. In general, these reactions were mild or moderate in severity and of short duration.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Tabulated List of Adverse Events

Table 1: Treatment-emergent adverse events with frequency ≥ 5% comparing Ozempic 0.5 mg dose, Ozempic 1.0 mg dose with comparators

Adverse Event Term	Ozempic 0.5 mg dose % (n=1373)	Ozempic 1.0 mg dose % (n=1777)	Comparator % (n=1657)
Nausea	17.0	19.9	6.3
Vomiting	6.4	8.4	3.3
Dyspepsia	4.1	5.2	2.1
Diarrhoea	12.2	13.3	5.7
Constipation	6.9	6.2	2.7
Nasopharyngitis	14.5	10.7	13.8

Lipase increased	8.7	8.5	6.3
Headache	5.3	6.4	5.5
Decreased appetite	6.3	7.2	2.0

Adverse Reactions

Table 2 lists adverse reactions identified in phase 3 clinical trials (including the long-term cardiovascular outcomes study) in patients with type 2 diabetes (further described in section 5.1 Pharmacodynamic Properties). The frequencies of the adverse reactions (except diabetic retinopathy complications, see footnote in Table 2) 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.

Table 2: **Adverse reactions from controlled phase 3a trials**

MedDRA system organ class	Very common	Common	Uncommon	Rare
Immune-system disorders				Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulfonylurea	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	
Hepatobiliary disorders		Cholelithiasis		
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: need for retinal photocoagulation, need for treatment with intravitreal agents, vitreous haemorrhage, onset of diabetes-related blindness. Frequency based on cardiovascular outcomes trial.

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 (described in section 5.1 Pharmacokinetic Properties).

Description of Selected Adverse Reactions
Hypoglycaemia
No episodes of severe hypoglycaemia were observed when Ozempic was used as monotherapy. Severe hypoglycaemia was primarily observed when Ozempic 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 severe episodes (0.1% of subjects, 0.001 events/patient year) were observed with Ozempic in combination with oral antidiabetics other than sulfonylureas.

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. Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide.

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

In a 40-week phase 3b trial, 959 patients were exposed to semaglutide 1 mg or 2 mg. The safety profile of semaglutide 2 mg was consistent with the safety profile of semaglutide seen in the phase 3a trials. Gastrointestinal disorders were reported with a slightly higher frequently in patients exposed to semaglutide 2 mg (34.0%) compared to semaglutide 1 mg (30.8%).

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 Special Warnings and Precautions for Use).

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 complications occurred in more patients treated with Ozempic (3.0%) compared to placebo (1.8%). The treatment difference appeared early and persisted throughout the trial. The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy treated with insulin 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.

In other clinical trials up to 1 year involving 4,807 patients with type 2 diabetes patients, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with Ozempic (1.7%) and comparators (2.0%).

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, versus 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. A similar rate of

injection site reactions was experienced by patients receiving placebo. 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 (1-2%) 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 semaglutide. In a long-term trial in subjects with cardiovascular risk factors, 16% of semaglutide-treated subjects had an increase in heart rate of >10 bpm compared to 11% of subjects on placebo after 2 years of treatment.

Increases in Amylase and Lipase
In placebo-controlled trials, patients exposed to semaglutide had a mean increase from baseline in amylase of 13% and lipase of 22%. These changes were not observed in placebo-treated patients. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Cholelithiasis
In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with semaglutide 0.5 mg and 1 mg respectively. Cholelithiasis was not reported in placebo-treated patients.

Fatigue, Dysgeusia and Dizziness
Other adverse reactions with a frequency of >0.4% associated with semaglutide include fatigue, dysgeusia and dizziness.

<u>Post-Market Adverse Effects</u>

- Renal and urinary disorders: acute kidney injury, urolithiasis
- Skin and subcutaneous tissue disorders: Alopecia, angioedema
- Immune-system disorders: Hypersensitivity – Uncommon (grouped term covering also adverse events related to hypersensitivity such as rash and urticaria)
- Gastrointestinal disorders: Intestinal obstruction*, hiccups.
  *Grouped term covering PTs Intestinal obstruction, Ileus, small intestinal obstruction
- Nervous system disorders: Dysaesthesia
- Hepatobiliary disorders: Cholecystitis
- Eye disorders: Non-arteritic anterior ischaemic optic neuropathy (NAION)*
  *Cases of NAION have been reported with GLP-1 RAs, including semaglutide. A sudden loss of vision should lead to ophthalmological examination.

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 event was nausea. All patients recovered without complications.

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 (see section 5.2 Pharmacokinetic Properties).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

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 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. GLP-1 receptors are also expressed in the heart, vasculature and immune system and kidney from where it may mediate cardiovascular and microvascular effects.

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

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 / mg/dL) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/L / 29 mg/dL; 22%), 2 hour postprandial glucose (4.1mmol/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 (0.6-1.1mmol/L / 11-20 mg/dL) compared to placebo (see Figure 2).

Semaglutide lowered fasting glucose after the first dose.

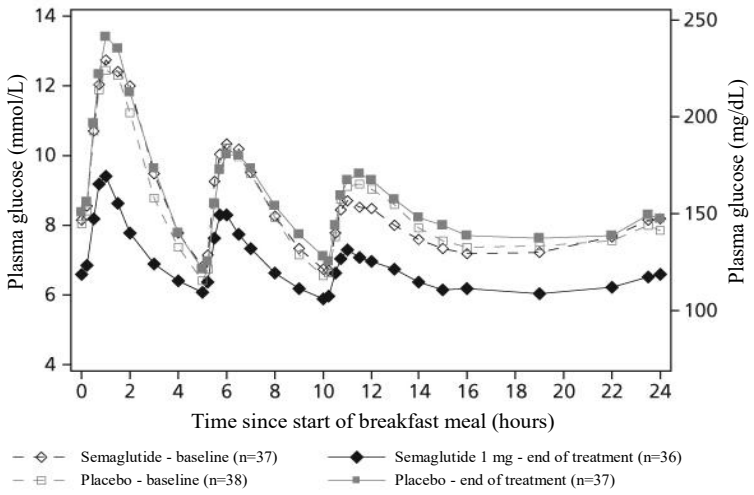


Figure 2: Mean 24 hour plasma glucose profiles (standardised meals) in patients with type 2 diabetes before (baseline) and after 12 weeks of treatment with semaglutide or placebo

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%).

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 3).

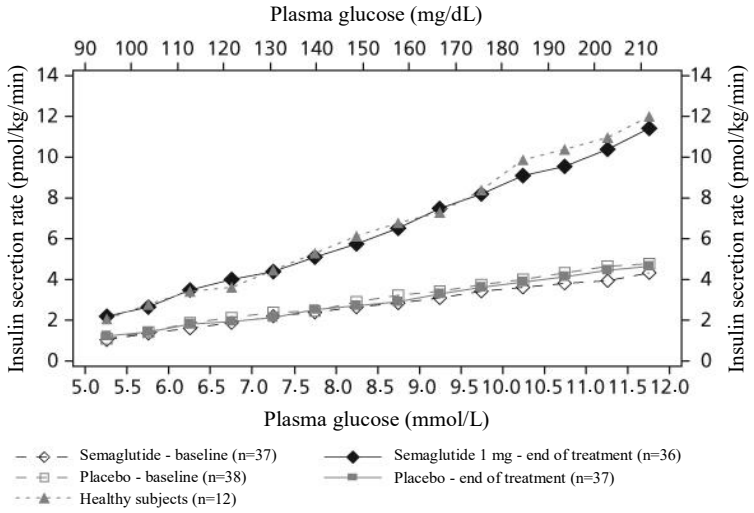


Figure 3: Mean insulin secretion rate versus glucose concentration in patients with type 2 diabetes during graded glucose infusion before (baseline) and after 12 weeks of treatment with semaglutide or placebo and in untreated healthy subjects

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.

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 5.1 Pharmacodynamic Properties). 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 trials
Improvement of glycaemic control, 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 glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective. Additionally, two phase 3 trials were conducted with Ozempic in Japanese patients with safety as the primary objective and efficacy the secondary objective.

The trials included in total 8,124 randomised patients with type 2 diabetes (4,792 treated with semaglutide).

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

An additional trial 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.

Treatment with Ozempic demonstrated statistically significant and clinically meaningful reductions in HbA_{1c} (see Figure 4) and body weight maintained for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide).

SUSTAIN Trials

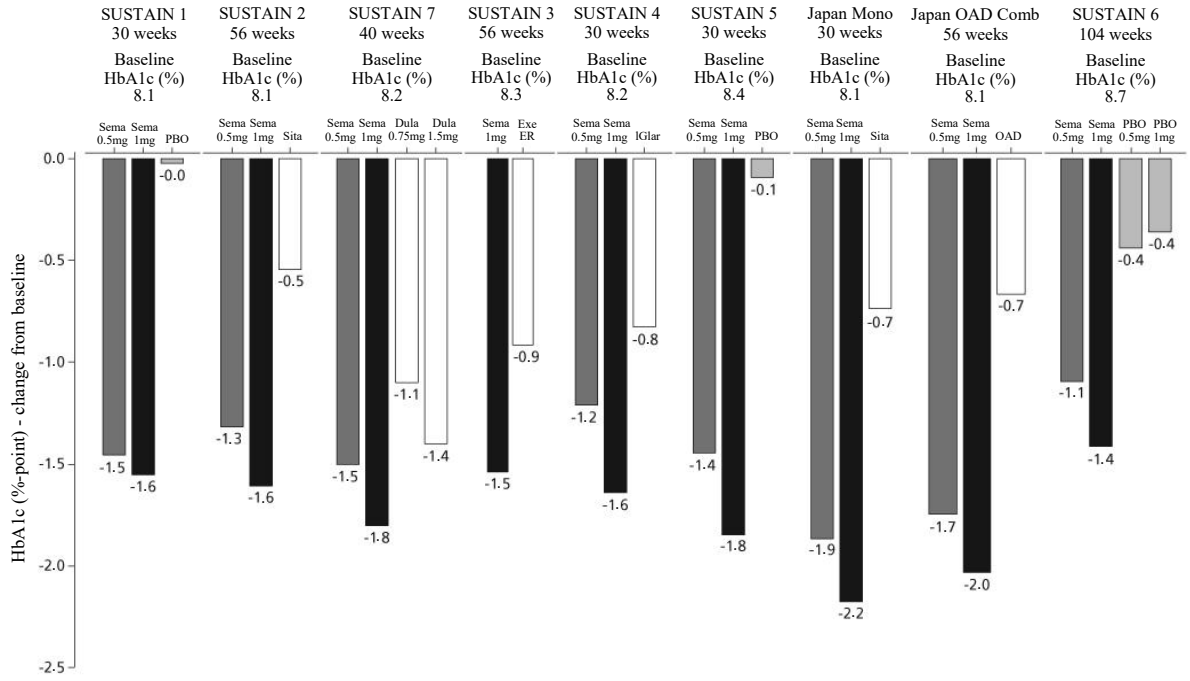


Figure 4: HbA$_{1c}$ (%)-estimated change from baseline to end of treatment in SUSTAIN 1-7, Japan Monotherapy and Japan OAD Combination trials (semaglutide 0.5 mg dark grey, semaglutide 1 mg black, competitors white and placebo light grey)

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.

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.

Table 3: Results at 30 weeks, 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
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 thiazolidinediones (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.

Table 4: **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

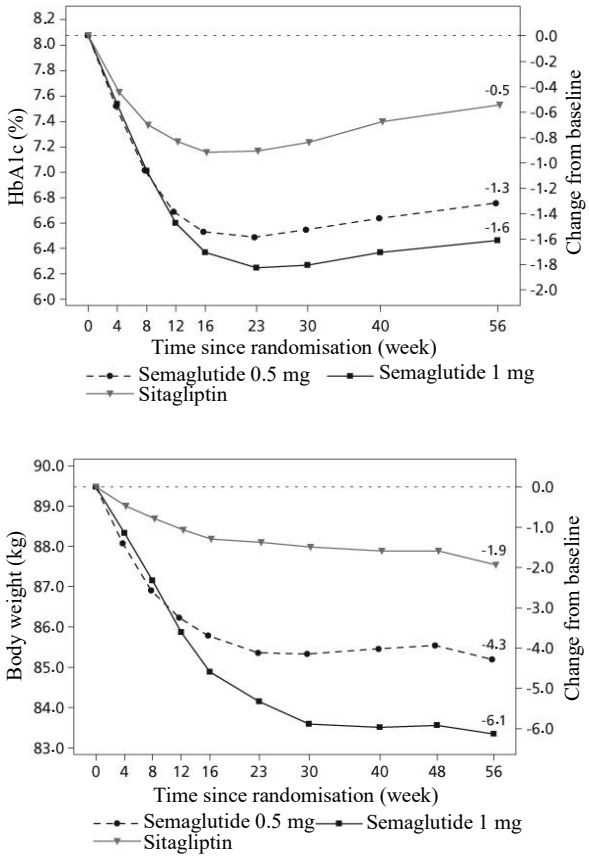


Figure 5: Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 56 (SUSTAIN 2)

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 5: 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	-1.8	-1.1	-1.4
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
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

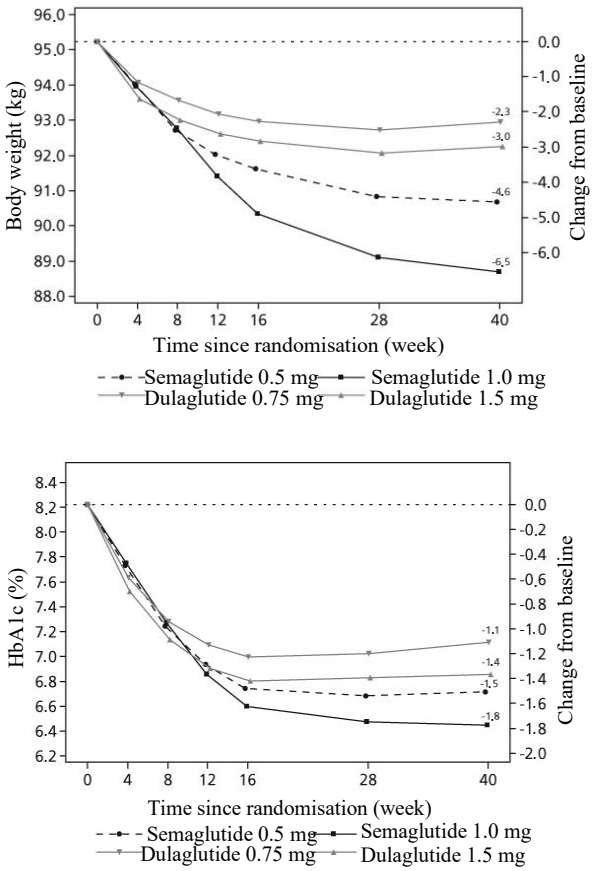


Figure 6: Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 40

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 or exenatide ER 2.0 mg each administered once-weekly. 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.

Table 6: **Results of a 56 week trial of Ozempic versus exenatide ER (SUSTAIN 3)**

	Ozempic 1 mg	**Exenatide ER 2.0 mg**
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.

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.

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 7: **Results of a 30-week 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]	-
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.

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%.

Table 8: 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
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]	-

[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 FORTE – Ozempic 2 mg vs. Ozempic 1 mg

In a 40-week double-blind trial, 961 patients inadequately controlled with metformin with or without sulfonylurea were randomised to Ozempic 1 mg once weekly or Ozempic 2 mg once weekly.
Patients had a mean age of 58 years and a mean duration of type 2 diabetes of 9.5 years, 88.1% were White, 4.5% were Black or African-American and 7.2% were Asian. For ethnicity, 11.6% of patients (n=111) were Hispanic or Latino. Mean BMI was 34.6 kg/m^2.

Treatment with Ozempic 2 mg resulted in a statistically superior reduction in HbA1c after 40 weeks of treatment compared to Ozempic 1 mg.

Table 9: Results at 40 weeks of Ozempic 2 mg with metformin with or without SU (SUSTAIN FORTE)

\	**Ozempic 1 mg**	**Ozempic 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 Ozempic 1 mg [95% CI]	-	-0.2 [-0.4; -0.1][a]
Patients (%) achieving HbA_{1c} <7%	58[b]	68[b]
Patients (%) achieving HbA_{1c} <6.5%	39[c]	52[c]
FPG (mmol/L)		
Baseline (mean)	10.9	10.7

Change from baseline at week 40	-3.1	-3.4
Difference from Ozempic 1 mg [95% CI]	-	-0.3 [-0.6; -0.0][d]
Body weight (kg)		
Baseline (mean)	98.6	100.1
Change from baseline at week 40	-6.0	-6.9
Difference from Ozempic 1 mg [95% CI]	-	-0.9 [-1.7; -0.2][e]
Patients (%) achieving weight loss ≥5%	51[d]	59[d]
Patients (%) achieving weight loss ≥10%	23[d]	28[d]

[a]p<0.001 (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA1c and body weight
[b]p <0.0001 for treatment difference, unadjusted for multiplicity
[c]p <0.0001 for treatment difference, unadjusted for multiplicity
[d]p <0.05 for treatment difference, unadjusted for multiplicity
[e]p<0.05 (2-sided) for superiority, adjusted for multiplicity based on hierarchical testing of HbA1c and body weight

Combination with sulfonylurea monotherapy
In SUSTAIN 6 (see section 5.1 – Pharmacodynamic Properties – Clinical Trials), 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 5.1 Pharmacodynamic Properties – Clinical Trials), 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.

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 (Tables 3 to 7). The reduction in body weight was sustained for up to 2 years (Figure 7).

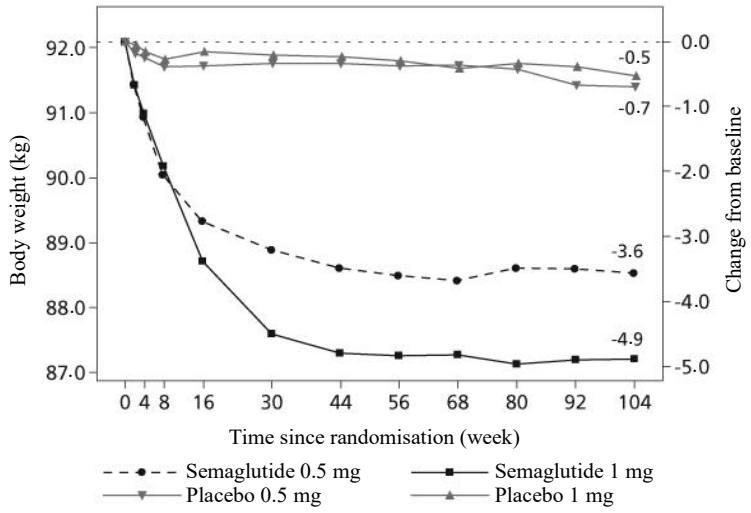


Figure 7: Mean change in body weight (kg) over time in SUSTAIN 6

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 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 (in addition see section 5.1 Pharmacodynamic Properties).

Beta-cell function and insulin resistance
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 (in addition see section 5.1 Pharmacodynamic Properties).

Lipids
Overall, improvements in the fasting blood lipid profile were seen with Ozempic treatment across trials, mostly for the 1 mg group (in addition see section 5.1 Pharmacodynamic Properties).

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 heart failure. The total number of primary component MACE endpoints was 254, including 108 (6.6%) with Ozempic and 146 (8.9%) with placebo.

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 39% decrease in the rate of non-fatal stroke and a 26% decrease in non-fatal myocardial infarction with no difference in cardiovascular death (see Figure 8).

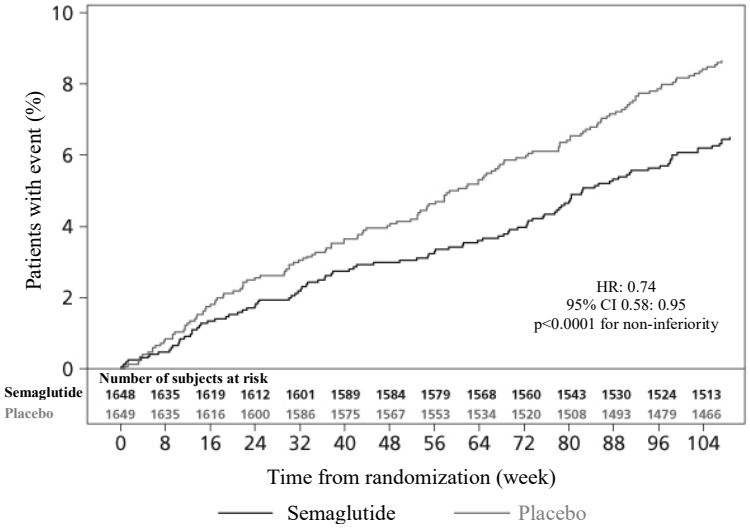


Figure 8: Kaplan-Meier plot of time to first occurrence of the composite outcome: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

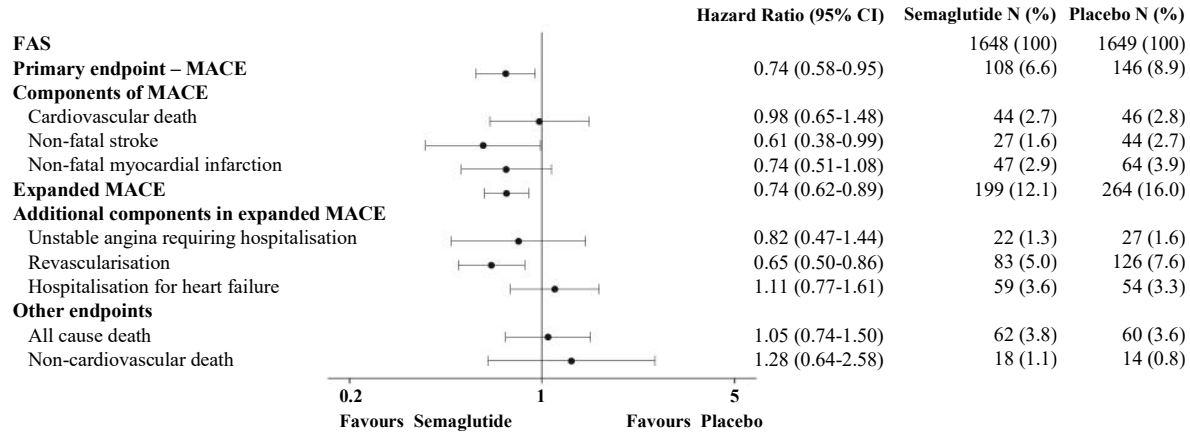


Figure 9: **Forest plot: analyses of each individual cardiovascular event types (SUSTAIN 6)**

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 [0.46; 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.

Patient Reported Outcomes
Patient reported outcomes were assessed by the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs): Ozempic significantly improved total treatment satisfaction and reduced perceived frequency of hyperglycaemia compared to exenatide once weekly, insulin glargine and placebo.

General health status was assessed by the Short Form health survey (SF-36 v2): Ozempic 1 mg once weekly demonstrated significantly greater improvement from baseline in a long-term cardiovascular safety study compared to placebo (SUSTAIN 6) in both mental component summary (MCS) and physical component summary (PCS) scores of the SF-36 v2.

Other Clinical Trials
In an open label monotherapy trial comparing the safety (primary objective) and efficacy (secondary objective) of Ozempic 0.5 mg and 1 mg once weekly with sitagliptin 100 mg once daily in 308 Japanese patients, a significant greater reduction of HbA_{1c} levels from baseline after 30 weeks of treatment were achieved with Ozempic 0.5 mg and 1 mg compared to sitagliptin (-1.9 %, -2.2% vs -0.7%).

Significantly more patients achieved an HbA_{1c} level of 7% with Ozempic 0.5 mg (84%) and 1 mg (95%) compared to sitagliptin (35%). Patients treated with Ozempic 0.5 mg and 1 mg had a significant decrease in body weight compared to that of patients treated with sitagliptin (-2.2 kg and -3.9 kg vs 0.0 kg). The most frequently reported adverse reactions (ARs) in this trial were gastrointestinal disorders. Greater proportions of patients treated with Ozempic 0.5 mg and 1 mg experienced gastrointestinal disorders vs patients treated with sitagliptin (38% and 41% for Ozempic 0.5 mg and 1 mg vs 17% with sitagliptin).

In an open label trial comparing the safety (primary objective) and efficacy (secondary objective) of Ozempic 0.5 mg and 1 mg once weekly with 1-2 OADs in 601 Japanese patients on monotherapy or 1 OAD, a higher reduction in HbA_{1c} was seen with Ozempic 0.5 mg (-1.7%) and 1 mg (-2.0%) compared to additional OAD (-0.7%). Patients treated with Ozempic 0.5 mg and 1 mg had a significant decrease in body weight compared to that of patients treated with additional OAD (-1.4 kg and -3.2 kg vs +0.4 kg). The most frequently reported ARs in this trial were gastrointestinal disorders. Greater proportion of patients treated with Ozempic 0.5 mg and 1 mg experienced gastrointestinal disorders vs patients treated with additional OAD (54% and 54% vs 20%).

FLOW Trial (Chronic Kidney Disease)

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

The phase 3b 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 a baseline eGFR of 50 to 75 mL/min/1.73 m^2 and a UACR of >300 and <5000 mg/g, or eGFR 25 to <50 mL/min/1.73 m^2 and a UACR of >100 and <5000 mg/g. The FLOW trial evaluated the effect of semaglutide 1 mg once weekly compared with the corresponding placebo, in addition to standard-of-care, using 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.

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. 65.8% were White and 23.9% were Asian. 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. The median UACR was 568 mg/g with 68.5% of patients with a 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.

Ozempic 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]; corresponding to a relative risk reduction in kidney disease progression of 24% (see Figure 10).

The individual components of the primary composite contributed to the treatment effect. There were only a small number of kidney deaths in the trial (see Figure 11). The treatment benefit of Ozempic over placebo on the primary composite outcome was generally consistent across the pre-specified subgroups.

Ozempic 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/1.73m^2/year) [0.86; 1.47]95%CI (-2.19 for semaglutide and -3.36 for placebo).

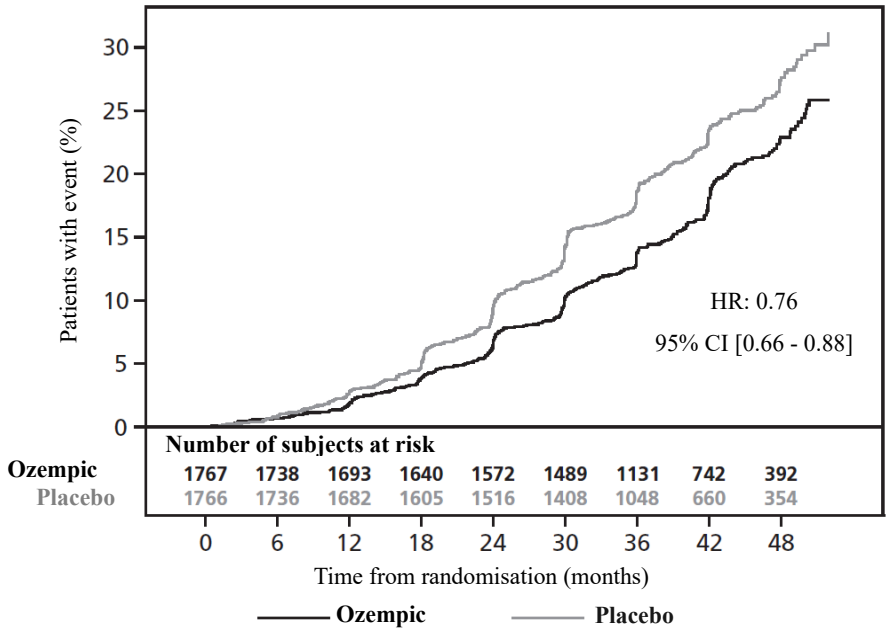


Figure 10: Cumulative incidence function of time to first occurrence of the primary composite outcome: onset of persistent ≥50% reduction in eGFR, onset of persistent eGFR <15 mL/min/1.73 m^2, initiation of chronic kidney replacement therapy, kidney death or cardiovascular death (FLOW)

Ozempic showed superiority over placebo, in addition to standard-of-care, in reducing the risk of MACE (using a composite outcome consisting of: non-fatal myocardial infarction, non-fatal stroke or CV death) with a HR of 0.82 ([0.68; 0.98]95%CI) (see Figure 11).

Treatment with Ozempic, in addition to standard-of-care, reduced all-cause mortality with a HR of 0.80 ([0.67, 0.95]95%CI) and reduced the risk of CV death with a HR of 0.71 ([0.56, 0.89]95%CI) (Figure 11).

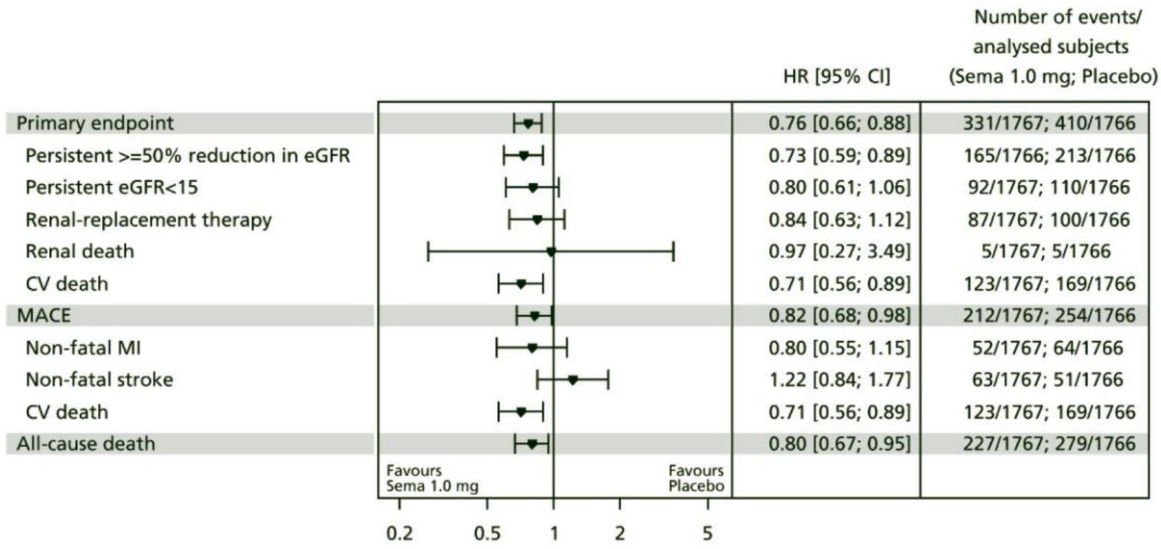


Figure 11: Forest plot: analyses of time to first occurrence of the primary composite outcome and its components, first occurrence of MACE and its components and all cause death (FLOW)

STRIDE Trial (Peripheral Arterial Disease)

In a 52-week randomised, double-blind, placebo-controlled trial (STRIDE, NCT04560998), 792 patients with T2D and peripheral arterial disease (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/m^2 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 metres on constant load treadmill [12 – 41] 95% CI compared to placebo (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 (metres)		
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]+	
Pain-free walking distance (metres), 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]*	
Patients (%) experiencing meaningful within-patient change[d]	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 randomised 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.

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.

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%.

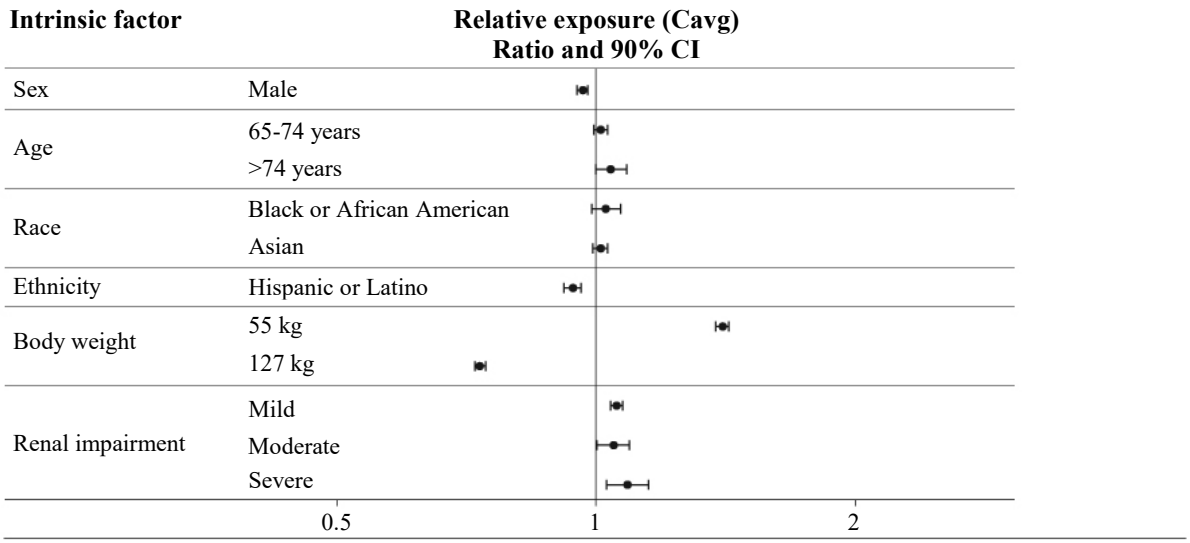
Distribution
The mean volume of distribution of semaglutide following s.c. administration in patients with type 2 diabetes was approximately 12.5 L. Semaglutide was extensively bound to plasma albumin (>99%).

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

Excretion
The primary excretion routes of semaglutide related material were via the urine and faeces. 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. The effects of intrinsic factors on the pharmacokinetics of semaglutide are shown in Figure 12



Semaglutide exposure (Cavg) relative to reference subject profile: non-Hispanic/non-Latino, White, female below 65 years, body weight 85 kg, with normal renal function. Population PK model also included maintenance dose and injection site as covariates. Body weight test categories (55 and 127 kg) represent the 5% and 95% percentiles in the dataset. Abbreviations: Cavg: average semaglutide concentration. CI: Confidence interval.

Figure 12: **Impact of intrinsic factors on semaglutide exposure**

Age
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
Gender had no effect on the pharmacokinetics of semaglutide.

Race
Race (White, Black or African-American, Asian) had no effect on the pharmacokinetics of semaglutide.

Ethnicity
Ethnicity (Hispanic or Latino) had no effect on the pharmacokinetics of semaglutide.

Body Weight
Body weight had an effect on the exposure of semaglutide. Higher body weight results in lower 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 renal impairment based on data from phase 3a studies (Figure 10), 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 study with a single-dose of 0.5 mg semaglutide.

Paediatrics
Semaglutide has not been studied in paediatric patients.

5.3 Preclinical Safety Data

Genotoxicity
Semaglutide was not mutagenic in the bacterial reverse mutation assay, and was not clastogenic *in vitro* (cytogenetic assay in human lymphocytes), or *in vivo* (rat bone marrow micronucleus test).

Carcinogenicity
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 (at ≥ 4x the clinical AUC in mice [based on the plasma AUC at the maximum recommended human dose of 1 mg/week] and subclinical exposures in rats; a no effect level was not established in either species). 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.

Juvenile toxicity
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. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Dibasic sodium phosphate dihydrate
Propylene glycol
Phenol
Hydrochloric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities
Substances added to Ozempic may cause degradation of semaglutide. Ozempic must not be mixed with other medicinal products, e.g. infusion fluids.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Shelf-life for pen in use*:* 42 days (6 weeks).

6.4 Special Precautions for Storage

Before use: Store in a refrigerator (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.

After first use: Store below 30°C or in a refrigerator (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 the Ozempic pen is not in use in order to protect from light.

Ozempic should be protected from excessive heat and light.

The Ozempic pen is for use by one person only.

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

Always remove the injection needle immediately after each injection and store the Ozempic pen without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

6.5 Nature and Contents of Container

The primary packaging is a 1.5 mL or 3 mL glass cartridge (Type I glass) closed at one end with a rubber plunger (Type I/chlorobutyl) and at the other end with an aluminium cap with a rubber disc (Type I/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 three variants of the pre-filled pen for Ozempic:

Ozempic 0.25 mg, 0.5 mg/dose solution for injection in pre-filled pen is able 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 contains either 1.5 mL or 3 mL solution, at either 1.34 mg/mL or 0.68 mg/mL concentration, respectively.

Ozempic 1 mg/dose for injection in pre-filled pen is only able to deliver doses of 1 mg. This pen is to be used for maintenance treatment at the 1 mg dose only. The pen contains 3 mL solution, at 1.34 mg/mL concentration.

Ozempic 2 mg/dose for injection in pre-filled pen is only able to deliver doses of 2 mg. This pen is to be used for maintenance treatment at the 2 mg dose only. The pen contains 3 mL solution.

Ozempic can be administered with needles up to a length of 8 mm. The pen is designed to be used with NovoFine® disposable needles.

Pack sizes of:

Ozempic® 0.25 mg, 0.5 mg/dose (1.5 mL or 3 mL):
1 pre-filled pen including 6 disposable NovoFine Plus needles.
1 pre-filled pen without needles included.

Ozempic® 1 mg/dose (3 mL):
1 pre-filled pen including 4 disposable NovoFine Plus needles.
1 pre-filled pen without needles included.

Ozempic 2 mg/dose:
1 pre-filled pen including 4 disposable NovoFine Plus needles

Not all pack sizes may be marketed.

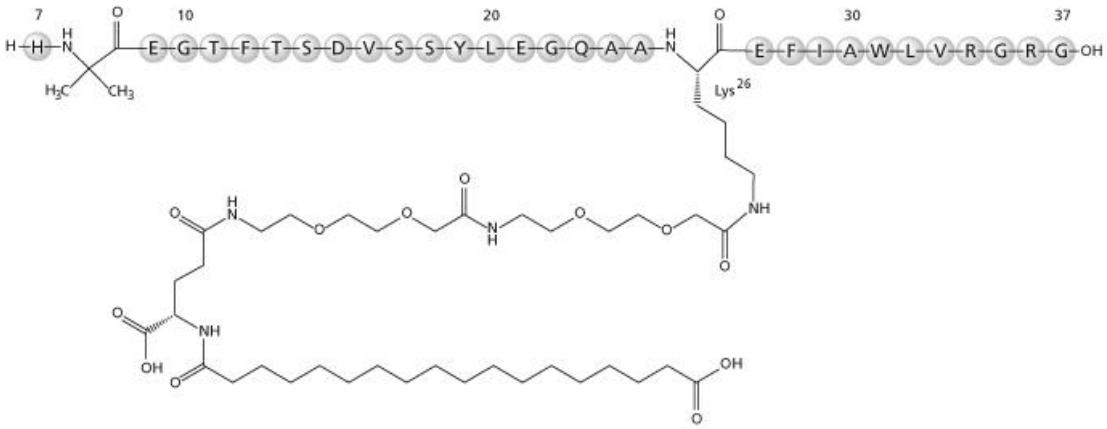
6.6 Special Precautions for Disposal

The patient should be advised to discard the injection needle after each injection in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure
Molecular formula: $C_{187}H_{291}N_{45}O_{59}$

Molecular weight: 4113.6 daltons



CAS number
RN910463-68-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited

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North Sydney NSW 2060,
Australia.

www.novonordisk.com.au

9. DATE OF FIRST APPROVAL

28 August 2019

10. DATE OF REVISION

25 September 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
5.1	Addition of STRIDE clinical trial data

VV-LAB-098353 v16.0