▼ 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

Wegovy® (semaglutide) solution for injection in Single-dose pen

Wegovy® FlexTouch® (semaglutide) solution for injection

Wegovy® (semaglutide) solution for injection in Pre-filled syringe

Wegovy® (semaglutide) tablet for oral administration

1 NAME OF THE MEDICINE

semaglutide (rys)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Single-dose pen
0.25 mg dose pen: One mL of solution contains 0.5 mg of semaglutide. One pre-filled pen contains 0.25 mg semaglutide in 0.5 mL

0.5 mg dose pen: One mL of solution contains 1 mg of semaglutide. One pre-filled pen contains 0.5 mg semaglutide in 0.5 mL

1 mg dose pen: One mL of solution contains 2 mg of semaglutide. One pre-filled pen contains 1.0 mg semaglutide in 0.5 mL

1.7 mg dose pen: One mL of solution contains 2.27 mg of semaglutide. One pre-filled pen contains 1.7 mg semaglutide in 0.75 mL

2.4 mg dose pen: One mL of solution contains 3.2 mg of semaglutide. One pre-filled pen contains 2.4 mg of semaglutide in 0.75 mL

FlexTouch pen
Each pen contains four doses.

0.25 mg dose pen: One mL of solution contains 0.68 mg of semaglutide. One pre-filled pen contains 1.0 mg semaglutide in 1.5 mL solution.

0.5 mg dose pen: One mL of solution contains 1.34 mg of semaglutide. One pre-filled pen contains 2.0 mg semaglutide in 1.5 mL solution.

1 mg dose pen: One mL of solution contains 1.34 mg of semaglutide. One pre-filled pen contains 4.0 mg semaglutide in 3 mL solution.

1.7 mg dose pen: One mL of solution contains 2.27 mg of semaglutide. One pre-filled pen contains 6.8 mg semaglutide in 3 mL solution.

2.4 mg dose pen: One mL of solution contains 3.2 mg of semaglutide. One pre-filled pen contains 9.6 mg semaglutide in 3 mL solution.

Pre-filled syringe

0.25 mg dose syringe: One mL of solution contains 0.5 mg of semaglutide. One pre-filled syringe contains 0.25 mg semaglutide in 0.5 mL.

0.5 mg dose syringe: One mL of solution contains 1 mg of semaglutide. One pre-filled syringe contains 0.5 mg semaglutide in 0.5 mL.

1 mg dose syringe: One mL of solution contains 2 mg of semaglutide. One pre-filled syringe contains 1.0 mg semaglutide in 0.5 mL.

1.7 mg dose syringe: One mL of solution contains 2.27 mg of semaglutide. One pre-filled syringe contains 1.7 mg semaglutide in 0.75 mL.

2.4 mg dose syringe: One mL of solution contains 3.2 mg of semaglutide. One pre-filled syringe contains 2.4 mg of semaglutide in 0.75 mL.

Tablet

Tablet for oral administration.

One tablet contains 1.5 mg, 4 mg, 9 mg or 25 mg of semaglutide.

Semaglutide is a human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in a Saccharomyces cerevisiae strain followed by purification.

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

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen and pre-filled syringe

Clear and colourless isotonic solution; pH=7.4.

Tablet

The 1.5 mg, 4 mg and 9 mg tablets are white to light yellow, round, debossed with ‘1.5’, ‘4’ or ‘9’ on one side and ‘novo’ on the other side.

The 25 mg tablet is white to light yellow, oval shaped, debossed with ‘25’ on one side and ‘novo’ on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Weight Management

Adults (solution for injection and tablet)

Wegovy is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obesity), or

- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

Adolescents (solution for injection)
Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with initial:

- obesity* and
- body weight above 60 kg

Treatment with Wegovy should be re-evaluated and discontinued if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.

*Obesity (BMI ≥ 95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see **Table 1**).

Table 1 BMI cut-off points for obesity (≥95th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m^2) at 95th Percentile	
	Males	**Females**
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30.0

Reduction in risk of major adverse cardiovascular events (solution for injection and tablet)

Wegovy is indicated as an adjunct to standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with established cardiovascular disease, with a Body Mass Index (BMI) ≥27 kg/m^2, and without established Type 1 or Type 2 diabetes (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

Metabolic dysfunction-associated steatohepatitis (MASH) (solution for injection)

Wegovy is indicated for the treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) in adults with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). This indication was approved via the **provisional approval** pathway based on resolution of steatohepatitis and improvement in liver fibrosis. Continued approval of this indication depends on verification and description of clinical benefit in confirmatory trials.[1]

[1] Module 2.5, Clinical Overview, Section 1.1, p.6

Concomitant use with other GLP-1 receptor agonists

Concomitant use of WEGOVY (semaglutide) tablets or WEGOVY (semaglutide) injection with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Solution for injection

Weight management in adults

The recommended maintenance dose is 2.4 mg once weekly.

The maintenance dose of 2.4 mg once weekly is reached by starting with a weekly dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see Table 2).

If needed, in adults with BMI ≥ 30 kg/m^2 at treatment initiation, dose increases can be made to the next maintenance dose of 7.2 mg once weekly (administered as 3 injections of 2.4 mg) after a minimum of 4 weeks on the 2.4 mg dose. If no additional clinical improvement in body weight is observed with the 7.2 mg dose, lower the dose to 2.4 mg once weekly.

In case of significant gastrointestinal symptoms, consider delaying dose escalation until symptoms have improved. If patients do not tolerate the 2.4 mg dose, the dose can be decreased to a 1.7 mg weekly dose for maintenance. Patients should re-escalate the dose to 2.4 mg weekly, if tolerated.

Table 2 Dose escalation schedule

Dose escalation	Weekly dose
Week 1-4	0.25 mg
Week 5-8	0.5 mg
Week 9-12	1 mg
Week 13-16	1.7 mg
Maintenance dose	2.4 mg
Maintenance dose	7.2 mg (3 injections of 2.4 mg)

Weight management in adolescents

For adolescents aged 12 to 17 years, the same dose escalation schedule as for adults should be applied (see Table 2). The dose should be increased until 2.4 mg (maintenance dose) or until the maximum tolerated dose has been reached. Weekly doses higher than 2.4 mg are not recommended.

Reduction in risk of major adverse cardiovascular events (MACE) in adults or treatment of metabolic dysfunction-associated steatohepatitis (MASH) in adults

The same dose escalation schedule as for weight management in adults (see above) can be applied up to a maximum maintenance dose of 2.4 mg weekly.

Tablet

The starting dose for orally administered semaglutide is 1.5 mg once daily. After one month at this dose, the dose escalation steps for orally administered semaglutide once daily are 4 mg, 9 mg and 25 mg with a minimum duration of 1 month at each dose level. The dose should be escalated until 25 mg (maintenance dose).

The maximum recommended single daily dose of orally administered semaglutide is 25 mg.

Orally administered semaglutide should always be used as only one tablet per day. Taking more than one tablet a day should not be done to achieve the effect of a higher dose.

Method of administration

Solution for injection

Wegovy is administered once weekly at any time of the day, with or without meals.

Wegovy 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. Wegovy should not be administered intravenously or intramuscularly.

For the 7.2 mg dose inject three doses of 2.4 mg one after each other. The injections can be given in the same body area but should be at least 5 cm apart.

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.

Patients should be advised to read the instruction for use included in the package leaflet carefully before administering Wegovy.

Single-dose pen

The single-dose pen is for single use in one patient only. The single-dose pen should be discarded after use. When administering semaglutide, the pen should be pressed firmly against the skin until the yellow bar has stopped moving. The injection takes about 5-10 seconds.

FlexTouch pen

The Wegovy FlexTouch pen is for use by one patient only. It contains 4 doses. A new needle should be attached for each use. The needle should be discarded after each use.

Pre-filled syringe

When using the pre-filled syringe, abdominal injections must be at least 5 centimetres from the belly button and upper arm injections must be in the back of the arm and only with help from someone else.

Tablet

Wegovy tablet is for once daily oral use.

Wegovy tablets should be taken on an empty stomach, after a recommended fasting period of at least 8 hours. Wegovy tablets should be swallowed whole with up to half a glass of water equivalent

to 120 mL. Do not split, crush or chew the tablet. Wait at least 30 minutes before eating or drinking or taking other oral medicinal products.

Waiting less than 30 minutes may decrease the absorption of semaglutide.

Missed Dose

Solution for injection

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 of the week. In each case, patients can then resume their regular once weekly dosing schedule. If more doses are missed, reducing the starting dose for re-initiation should be considered.

Tablet

If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

Switching from Wegovy Injection to Wegovy Tablets

Patients treated with once weekly Wegovy injection 2.4 mg can be transitioned to once daily Wegovy tablet 25 mg. Patients can start Wegovy tablet one week after their last Wegovy injection.

Switching from Wegovy Tablets to Wegovy Injection

Patients treated with once daily Wegovy tablet 25 mg can be transitioned to once weekly Wegovy injection 2.4 mg. Patients can start Wegovy injection the day after their last dose of Wegovy tablet.

For patients who do not tolerate Wegovy 25 mg tablets, consider switching to Wegovy 1.7 mg injection.

If additional weight reduction is needed in patients with type 2 diabetes mellitus treated with Wegovy 25 mg tablets, consider switching to Wegovy 1.7 mg injection and follow the recommended dosage escalation for Wegovy injection.

Special Populations

Patients with Type 2 diabetes:

Wegovy should not be used in combination with other GLP-1 receptor agonist products.

When initiating Wegovy, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia.

Elderly (≥ 65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥85 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 renal impairment
No dose adjustment is required for patients with renal impairment. Experience with the use of semaglutide in patients with severe (CrCL <30 mL/min) renal impairment is limited. Semaglutide is not recommended for use in patients with end-stage renal disease (see section 5.2 Pharmacokinetic Properties).

Patients with hepatic impairment (Child-Pugh A, B or C)
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 (Child-Pugh C) is limited. Caution should be exercised when treating these patients with semaglutide. In a trial in adult patients with MASH and compensated liver cirrhosis (F4c), no safety signals were identified (n=47 on active treatment).[2]

Children and adolescents: weight management
Solution for injection

Safety and efficacy of Wegovy in children below 12 years have not been studied.

For adolescents aged 12 to 17 years, the same dose escalation schedule as for adults should be applied up until 2.4 mg once weekly (see Table 2). The dose should be increased until the maintenance dose of 2.4 mg weekly or a lower maximum tolerated dose has been reached. Weekly doses higher than 2.4 mg are not recommended.

It is recommended to regularly review the goals of treatment with Wegovy, particularly once the target weight (e.g. BMI <85th percentile) has been achieved.

Tablet

The safety and efficacy of Wegovy tablet in children and adolescents below 18 years have not been established. No data are available

Children and adolescents: metabolic dysfunction-associated steatohepatitis (MASH)

The safety and efficacy of Wegovy in children and adolescents with MASH below 18 years have not been established. No data are available.

4.3 CONTRAINDICATIONS

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

Wegovy is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of Wegovy and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

[2] Module 5.3.5.1 - NN9931-4492 Clinical Trial Report, Section 13, p. 166

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 can 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. There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which have in some cases required haemodialysis, in patients treated with semaglutide.

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, including semaglutide. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Wegovy should be discontinued; if confirmed, Wegovy should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

The clinical significance of elevations in lipase or amylase with Wegovy is unknown in the absence of other signs and symptoms of pancreatitis.

Acute Gallbladder Disease

Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in WEGOVY-treated patients than in placebo-treated patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

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

The safety and efficacy of Wegovy have not been investigated in patients:

- treated with other products for weight management,
- with type 1 diabetes,
- with congestive heart failure New York Heart Association (NYHA) class IV.

The use of semaglutide is not recommended in these patients.

There is limited experience with Wegovy in patients:

- aged 85 years or more,
- with inflammatory bowel disease,
- with diabetic gastroparesis,
- with MASH and BMI<25 kg/m^2 (or BMI<23 kg/m^2 for Asian population)[3].

Use with caution in these patients.

Patients with type 2 diabetes

Wegovy must not be used as a substitute for insulin in patients with diabetes.

Semaglutide should not be used in combination with other GLP-1 receptor agonist products. It has not been evaluated and an increased risk of adverse reactions related to overdose is considered likely.

Hypoglycaemia in patients with overweight or obesity and type 2 diabetes

Insulin and sulfonylurea are known to cause hypoglycaemia. Patients treated with Wegovy 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 a GLP-1 receptor agonists.

The addition of Wegovy in patients treated with insulin has not been evaluated.

Diabetic retinopathy in patients with overweight or obesity and type 2 diabetes

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 local clinical guidelines. There is no experience with Wegovy in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy. In these patients, treatment with Wegovy is not recommended.

Use in the elderly

See section 5.2 Pharmacokinetic Properties.

Paediatric use

Safety and efficacy of Wegovy in children with overweight or obesity below 12 years have not been studied. Semaglutide has not been studied in paediatric patients with MASH.

Use in renal impairment

Experience with the use of semaglutide in patients with severe (CrCL <30 mL/min) renal impairment is limited. Semaglutide is not recommended for use in patients with end-stage renal disease (see sections 5.1 Pharmacodynamic Properties and 5.2 Pharmacokinetic Properties).

[3] ESSENCE interim, Summary 2.7.4, Section 5.1.1.4

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.

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. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg.

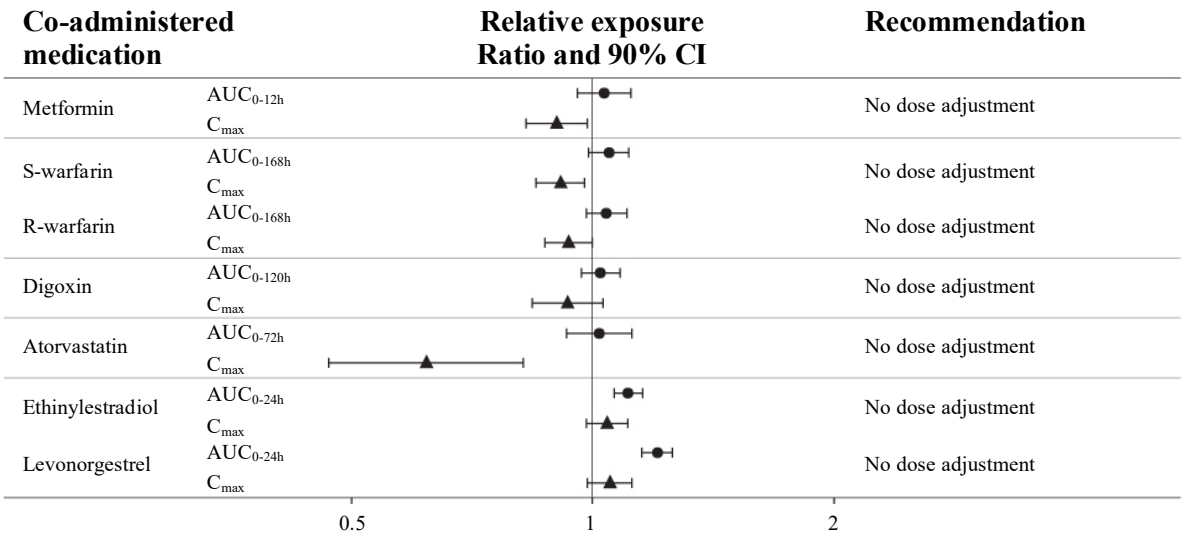
Wegovy can potentially cause a delay of gastric emptying and thereby can also impact the absorption of concomitantly administered oral medications which can pose safety risks especially for medications that have a narrow therapeutic index or that require clinical monitoring.

Monitor the effects of oral medications concomitantly administered with Wegovy. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring.

Solution for injection

In clinical pharmacology trials assessing the effect of semaglutide 1.0 mg on the absorption of co-administered oral medications at steady state no clinically relevant drug-drug interactions with semaglutide (Figure 1) was observed based on the evaluated medications. Therefore, no dose adjustment is required when co-administered with semaglutide.

Figure 1 (Forest Plot) - Impact of semaglutide on the pharmacokinetics of co-administered medications



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

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.

Thyroxine

Total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single dose of levothyroxine. Maximum exposure (C_{max}) was unchanged. Monitoring of thyroid parameters should be considered when treating patients with Wegovy at the same time as levothyroxine.

Warfarin

Semaglutide did not change the AUC or C_{max} of R- and S-warfarin following a single dose of warfarin, and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

Rosuvastatin

AUC of rosuvastatin was increased by 41% [90% CI: 24; 60] when co-administered with semaglutide. Based on the wide therapeutic index of rosuvastatin the magnitude of changes in the exposure in not considered clinically relevant.

Digoxin, oral contraceptives, metformin, furosemide

No clinically relevant change in AUC or C_{max} of digoxin, oral contraceptives (containing ethinylestradiol and levonorgestrel), metformin or furosemide was observed when concurrently administered with semaglutide.

Interactions with medicinal products with very low bioavailability (F: 1%) have not been evaluated.

Effects of other medicinal products on Wegovy tablet

Omeprazole

No clinically relevant change in AUC or C_{max} of semaglutide was observed when taken with omeprazole.

In a trial investigating the pharmacokinetics of semaglutide co-administered with five other tablets, the AUC of semaglutide decreased by 34% and C_{max} by 32%. This suggests that the presence of multiple tablets in the stomach influences the absorption of semaglutide if co-administered at the same time. After administering semaglutide, the patients should wait 30 minutes before taking other oral medicinal products.

Interaction of Wegovy tablet with food

Concomitant intake of food reduces the exposure of semaglutide.

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 subcutaneous (s.c.) doses of 828 µg/kg, resulting in exposures approximately 4.5 times the clinical AUC at 2.4 mg/week and 1.7 times the clinical AUC at 7.2 mg/week. 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 5.2 Pharmacokinetic 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 (>1.4-fold clinical exposure at 2.4 mg/week and subclinical exposure at 7.2 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.

In lactating women, no measurable concentrations of semaglutide were found in breastmilk. Salcaprozate sodium was present in breastmilk and some of its metabolites were excreted in breastmilk at low concentrations. As a risk to a breast-fed child cannot be excluded, Wegovy should not be used during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Wegovy has no or negligible influence on the ability to drive or use machines. However, dizziness can be experienced mainly during the dose escalation period. Driving or use of machines should be done cautiously if dizziness occurs.

Effect on the ability to drive and use machines for patients with overweight or obesity and type 2 diabetes

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

Weight management:

In four phase 3a trials with a trial duration of 68 weeks, 2,650 adult patients were exposed to Wegovy with a maximum weekly maintenance dose of 2.4 mg. In two phase 3b trials with a trial duration of 72 weeks, 1,311 adult patients were exposed to Wegovy with a maximum weekly maintenance dose of 7.2 mg. Similar to other GLP-1 receptor agonists, the most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhoea, constipation and vomiting.

In a 64-week phase 3b trial, 204 adult patients were exposed to Wegovy tablet. The safety profile of Wegovy tablet was consistent with the safety profile of semaglutide seen in the phase 3a trials with semaglutide s.c.

MASH:

In an ongoing 240-week phase 3 trial (ESSENCE), 800 adult patients were exposed to Wegovy at the time of interim analysis. Median duration of exposure was 95 weeks. Similar to other GLP-1 receptor agonists, the most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhoea, constipation and vomiting.

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 3 Adverse events in placebo-controlled trials (excluding SELECT), with maximum maintenance dose of 2.4 mg, reported in ≥1% of Wegovy-treated adult patients

System organ class/Preferred term	Treatment of overweight/obesity with Wegovy		Treatment of MASH with Wegovy	
	Wegovy N = 2650 %	Placebo N = 1529 %	Wegovy N=800 %	Placebo N=395 %
Nervous system disorders				
Headache	12.8	8.7	8.0	6.3
Dizziness	6.8	3.3	5.3	6.3
Dysaesthesia[a]	2.1	1.2	2.9	1.5
Dysgeusia[b]	1.7	0.5	0.9	0.8
Gastrointestinal Disorders				
Nausea	38.3	14.0	36.1	12.4
Diarrhea	26.8	14.3	26.8	12.2
Constipation	21.8	10.2	22.1	7.8
Vomiting	21.8	5.7	18.5	5.6
Abdominal pain[c]	18.1	9.0	18.5	16.5
Dyspepsia	7.6	2.7	7.6	2.8
Eructation	6.5	0.4	5.3	0.8
Abdominal distension	6.3	4.3	7.5	3.5
Flatulence	5.3	3.7	3.6	2.5
Gastroesophageal reflux disease	4.6	2.1	7.4	1.5
Gastritis[d]	3.2	1.5	2.5	2.5
Dry mouth	1.6	0.7	0.6	1.5
Metabolism and nutrition disorders				
Decreased appetite	7.8	2.8	14.0	2.5
Hepatobiliary disorders				
Cholelithiasis	1.6	1.1	1.4	0.8
Vascular disorders				
Hypotension	0.8	0.2	1.6	0.8
Eye disorders				
Diabetic retinopathy in patients with type 2 diabetes	4.0	0.7	1.1	1.4
Skin and subcutaneous tissue disorders				
Hair loss	2.5	1.0	1.6	0.5
General disorders and administration site conditions				
Fatigue[e]	9.6	4.7	11.4	7.3
Injection site reactions[f]	4.2	4.9	4.0	4.3
Investigations				
Increased lipase[g]	0.9	0.3	2.5	1.3

[a]Includes hyperaesthesia, paraesthesia, dysaesthesia, pain of skin, skin burning sensation, burning sensation, sensitive skin, skin sensitization, skin discomfort, allodynia and hyperpathia

[b]Includes dysgeusia and taste disorder

[c]Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, abdominal tenderness, abdominal discomfort and epigastric discomfort
[d]Includes chronic gastritis, gastritis, gastritis erosive, and reflux gastritis
[e]Includes fatigue and asthenia
[f]Includes preferred terms within high level terms: administration site reactions, application and instillation site reactions, infusion site reactions, injection site reactions
[g]Includes lipase increased, lipase abnormal, hyperlipasaemia, lipase

Table 4 Adverse events in placebo-controlled trials (STEP-UP and STEP-UP T2D), with maximum maintenance dose of 7.2 mg, reported in ≥5% of Wegovy-treated adult patients

System organ class/Preferred term	Treatment of overweight/obesity with Wegovy		
	Wegovy 7.2mg N = 1311 %	Wegovy 2.4 mg N = 304 %	Placebo N=303 %
Nervous system disorders			
Headache	9.2	7.9	6.6
Dizziness	5.9	5.3	1.0
Gastrointestinal Disorders			
Nausea	40.3	34.9	12.5
Diarrhea	25.0	25.3	11.6
Constipation	21.2	19.1	7.6
Vomiting	22.9	15.5	5.6
Dyspepsia	9.8	5.3	3.0
Eructation	7.9	7.9	0.7
Abdominal pain	5.9	4.9	3.0
Abdominal pain upper	5.6	2.0	3.6
Gastroesophageal reflux disease	4.8	5.6	1.7
Metabolism and nutrition disorders			
Decreased appetite	7.2	5.9	4.6
Vascular disorders			
Hypertension	1.7	2.6	5.3
Skin and subcutaneous tissue disorders			
Hair loss	6.2	3.3	1.0
Sensitive skin	6.8	0.7	0
Respiratory disorders			
Upper respiratory track infection	5.9	7.2	6.3
Nasopharyngitis	6.7	5.9	10.6
Sinusitis	3.0	5.3	2.6
General disorders and administration site conditions			
Fatigue	10.1	6.9	4.0
COVID 19	9.9	8.6	9.6
Back pain	5.2	6.6	2.3
Hyperaesthesia	5.3	0.7	0
Arthralgia	4.4	5.9	4.0

Tabulated list of adverse reactions

Solution for injection

Table 5 lists adverse reactions identified in phase 3a clinical trials in adult patients. The frequencies are based on a pool of the phase 3a trials.

Adverse reactions associated with Wegovy are listed by body system and frequency. Frequency categories 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).

Table 5 Adverse reactions from controlled phase 3 studies in weight management and MASH (excluding SELECT) in adults

MedDRA system organ class	Very common	Common	Uncommon	Rare
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders		Hypoglycaemia in patients with type 2 diabetes[a]		
Nervous system disorders	Headache[b,d]	Dizziness[b] Dysgeusia[b,c,d] Dysaesthesia[a,c,f] Headache[e]	Dysgeusia[e]	
Eye disorders		Diabetic retinopathy in patients with type 2 diabetes[a]		
Cardiac disorders			Increased heart rate[a,c]	
Vascular disorders		Hypotension[e]	Hypotension[d] Orthostatic hypotension	
Gastrointestinal disorders	Vomiting[a,b] Diarrhoea[a,b] Constipation[a,b] Nausea[a,b] Abdominal pain[b,c]	Gastritis[b,c] Gastrooesophageal reflux disease[b] Dyspepsia[b] Eructation[b] Flatulence[b] Abdominal distension[b] Dry mouth Delayed gastric emptying[e]	Acute pancreatitis[a] Delayed gastric emptying[d]	
Hepatobiliary disorders		Cholelithiasis[a]		
Skin and subcutaneous disorders		Hair loss[a]		
General disorders and administration site conditions	Fatigue[b,c]	Injection site reactions[c]		
Investigations		Increased lipase[e]	Increased amylase[c] Increased lipase[c,d]	

a) See description of selected adverse reactions below

b) Mainly seen in the dose-escalation period

c) Grouped preferred terms

d) Frequency observed in weight loss phase 3a trials only

e) Frequency observed in MASH phase 3a trial only

f) Frequency is based on the 3a program. An increased frequency has been observed with the 7.2 mg dose. Please refer to dysaesthesia subheading below for more information

Tablet

Table 6 lists adverse reactions identified in phase 3 clinical trials in adult patients. The frequencies are based, unless otherwise specified on a pool of the phase 3a trials with Wegovy injection. Events not relevant with oral administration are omitted in the following overview.
Adverse reactions associated with Wegovy® are listed by system organ class and frequency. Frequency categories 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).

Table 6 Frequency of adverse reactions of Wegovy

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders[276]				Anaphylactic reaction		
Metabolism and nutrition disorders[277]		Hypoglycaemia in patients with type 2 diabetes[a]				
Nervous system disorders[278]	Headache[b]	Dizziness[b] Dysgeusia[b] Dysaesthesia[a,c]				
Eye disorders[279]		Diabetic retinopathy in patients with type 2 diabetes[a]			Non-arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders			Increased heart rate[a,c]			
Vascular disorders			Hypotension Orthostatic hypotension			
Gastrointestinal disorders[280]	Vomiting[a,b] Diarrhoea[a,b] Constipation[a,b] Nausea[a,b] Abdominal pain[b,c] Dyspepsia[b, d]	Gastritis[b,c] Gastroesophageal reflux disease[b] Eructation[b] Flatulence[b] Abdominal distension[b]	Acute pancreatitis[a] Delayed gastric emptying			Intestinal obstruction[c,e, f]
Hepatobiliary disorders		Cholelithiasis[a]				
Skin and subcutaneous disorders		Hair loss[a]		Angioedema		
General disorders and administration site conditions[433]	Fatigue[b,c]					
Investigations			Increased amylase[c] Increased lipase[c] Increased bilirubin[g]			

[a)] See description of selected adverse reactions below
[b)] Mainly seen in the dose-escalation period
[c)] Grouped preferred terms
[d)] The frequency is based on the OASIS 4 phase 3b trial with Wegovy® tablet

[e)] From post-marketing reports
[f)] Grouped term covering PTs Intestinal obstruction, Ileus, small intestinal obstruction
[g)] The frequency is based on CV outcomes trials in adults with Wegovy® s.c.

Description of selected adverse reactions

Gastrointestinal adverse reactions

The events were most frequently reported during dose escalation. Over 68 weeks, nausea occurred in 43.9% of patients when treated with Wegovy (16.1% for placebo), diarrhoea in 29.7% (15.9% for placebo) and vomiting in 24.5% (6.3% for placebo). Most events were mild to moderate in severity and of short duration. Constipation occurred in 24.2% of patients treated with Wegovy (11.1% for placebo) and were mild to moderate in severity and of longer duration. In patients treated with semaglutide, the median duration of nausea was 8 days, 2 days for vomiting, 3 days for diarrhoea, and 47 days for constipation.

Other events that occurred at a higher incidence among WEGOVY-treated adult patients included dyspepsia, abdominal pain, abdominal distension, eructation, flatulence, gastroesophageal reflux disease, gastritis, haemorrhoids, and hiccups.

Patients with moderate renal impairment (eGFR ≥30 mL/min/1.73m^2) may experience more gastrointestinal effects when treated with semaglutide.

The gastrointestinal events led to permanent treatment discontinuation in 4.3% of patients.

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 0.2% for Wegovy and <0.1% for placebo, respectively.

In SELECT, the cardiovascular outcome trial, the frequency of acute pancreatitis confirmed by adjudication was 0.2% for Wegovy and 0.3% for placebo.

Acute gallstone disease /cholelithiasis / cholecystitis

Cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with Wegovy. Cholelithiasis and cholecystitis were reported in 1.1% and 0.3%, respectively, of patients treated with placebo.

Hair loss

Hair loss was reported in 2.5% of patients treated with Wegovy and in 1.0% of patients treated with placebo. In STEP UP trials, hair loss was reported in 5.3% of patients treated with semaglutide 7.2 mg and in 1.0% of patients on placebo. The events were mainly of mild severity and most patients recovered while on continued treatment. Hair loss was reported more frequently in patients with a greater weight loss (≥ 20%).

Increased heart rate

In the phase 3a trials, a mean increase of 3 beats per minute (bpm) from a baseline mean of 72 bpm was observed in patients treated with Wegovy. The proportions of patients with a maximum increase from baseline ≥20 bpm at any timepoint during the on-treatment period were 26.0% in the Wegovy group vs 15.6% in the placebo group.

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 testing positive for anti-semaglutide antibodies at any time post-baseline was 2.9 – 10.9% for semaglutide 2.4 mg and 15.3% for semaglutide 7.2 mg. No patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

During treatment, high semaglutide concentrations might have lowered the sensitivity of the assays, hence the risk of false negatives cannot be excluded. However, in subjects testing positive for antibodies during and after treatment, the presence of antibodies was transient and with no apparent impact on efficacy and safety.

Dysaesthesia
Events related to a clinical picture of altered skin sensation such as dysaesthesia, paraesthesia, hyperaesthesia, burning sensation, allodynia and sensitive skin were reported in 2.1% of patients treated with Wegovy injection and 1.2% of patients treated with placebo. The events were mild to moderate in severity and most patients recovered while on continued treatment.

In STEP-UP, dysaesthesia-related events were reported by 21.6% of patients treated with semaglutide 7.2 mg and 0.3% of patients on placebo. Most events in the 7.2 mg group were mild to moderate and 85% (368 out of 434 events) recovered while on treatment. 28% (123 of all 434 events) in the semaglutide 7.2 mg s.c. group recovered after changes in the dose of the trial product.

Events related to a clinical picture of altered skin sensation such as sensitive skin, hyperaesthesia, paraesthesia, skin burning sensation and allodynia were reported in 4.9% of patients treated with Wegovy® tablet. No events were reported in patients treated with placebo. The events were mild to moderate in severity and most patients recovered while on continued treatment.

Fractures
In SELECT, the cardiovascular outcomes trial in adults, more fractures of the hip and pelvis were reported on semaglutide than on placebo in female patients: 1.0% (24/2448) vs. 0.2% (5/2424), and in patients aged 75 years and older: 2.4% (17/703) vs. 0.6% (4/663), respectively.

Urolithiasis
In SELECT, the cardiovascular outcomes trial, 1.2% of semaglutide-treated patients and 0.8% of patients receiving placebo reported urolithiasis, including serious reactions that were reported more frequently among patients receiving semaglutide (0.6%) than placebo (0.4%).

Patients with type 2 diabetes
Hypoglycaemia in patients with overweight or obesity, MASH and type 2 diabetes
In STEP 2, clinically significant hypoglycaemia was observed in 6.2% (0.1 events/patient year) of subjects treated with Wegovy compared with 2.5% (0.03 events/patient year) of subjects treated with placebo. One episode (0.2% of subjects, 0.002 events/patient year) was reported as severe. The risk of hypoglycaemia was increased when Wegovy was used with a sulfonylurea.

In ESSENCE, severe hypoglycaemia was reported in 2.2% of patients (0.015 events/patient year) treated with Wegovy compared to 0.5% of patients (0.003 event /patient year) treated with placebo.[4]

Diabetic retinopathy in patients with overweight or obesity and type 2 diabetes
Few episodes of diabetic retinopathy (4.0 % vs 2.7% of patients treated with Wegovy vs placebo, respectively) were observed in STEP 2.

[4] ESSENCE interim, Summary 2.7.4, Section 2.2.11

Long-term glycaemic control decreases the risk of diabetic retinopathy. A 2-year clinical trial investigated semaglutide 0.5 mg and 1 mg vs placebo in 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 (3.0%) 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.

In STEP 2, retinal disorders were reported by 6.9% of patients treated with Wegovy, 6.2% of patients treated with semaglutide 1 mg, and 4.2% of patients treated with placebo. The majority of events were reported as diabetic retinopathy (4.0%, 2.7%, and 2.7%, respectively) and non-proliferative retinopathy (0.7%, 0%, and 0%, respectively).

Paediatric population
In a clinical trial conducted in adolescents of 12 years to below 18 years with obesity or overweight with at least one weight-related comorbidity, 133 patients were exposed to Wegovy. The trial duration was 68 weeks.

Overall, the frequency, type and severity of adverse reactions in the adolescents were comparable to that observed in the adult population. Cholelithiasis was reported in 3.8% of patients treated with Wegovy.

Semaglutide did not appear to affect growth or pubertal development during the trial period.

To date, there are no long-term (beyond 68 weeks) clinical trial data on safety or efficacy in adolescents.

Wegovy has not been studied in children and adolescents below 18 years with MASH.

Cardiovascular outcomes trial
In SELECT, the cardiovascular outcomes trial, the adverse event profile of systematically collected adverse events was similar to that seen in the phase 3a trials (described in Section 5.1 Pharmacodynamic Properties – Clinical trials). Additional adverse events included urolithiasis and hip fractures. For non-systematically collected adverse events, no definite conclusions can be made.

Trial in adults with MASH
In ESSENCE, in adults with MASH, the adverse reaction profile was similar to that seen in the weight management phase 3a trials (described in Section 5.1 Pharmacodynamic Properties – Clinical trials).5 Due to the low number of patients with 'lean-MASH' (MASH with BMI <25 kg/m2 or BMI<23 kg/m2 for Asian population) included in the ESSENCE trial, safety data for this sub-group is limited.

Post-market adverse effects

The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of WEGOVY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Skin and subcutaneous tissue disorders: Alopecia
- Eye disorders: Non-arteritic anterior ischaemic optic neuropathy (NAION)*

[5] ESSENCE interim, Summary 2.7.4, Section 2.1.3.4

*Cases of NAION have been reported with GLP-1 RAs, including semaglutide. A sudden loss of vision should lead to ophthalmological examination.

- Gastrointestinal Disorders: acute pancreatitis and necrotizing pancreatitis, sometimes resulting in death; ileus, intestinal obstruction, severe constipation including faecal impaction
- Hypersensitivity: anaphylaxis, angioedema, rash, urticaria
- Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anaesthesia or deep sedation Renal and Urinary Disorders: acute kidney injury.

4.9 OVERDOSE

Overdose with semaglutide may be associated with gastrointestinal disorders which could lead to dehydration. In the event of overdose the patient should be observed for clinical signs and appropriate supportive treatment initiated. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of Wegovy 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

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 regulator and has multiple actions in glucose and appetite regulation. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fullness and control of eating, and reduces feelings of hunger, and frequency and intensity of cravings.

Animal studies show that semaglutide works in the brain through the GLP-1 receptor. Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem. Semaglutide affects the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala. Semaglutide has shown an effect to change food intake in animals away from more rewarding high fat, sweet items.

Semaglutide orchestrates the homeostatic and hedonic contributions with executive function to regulate caloric intake, appetite, reward and food choice.

In addition, in clinical studies semaglutide have shown to reduce blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. 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.

The mechanism of action of semaglutide for cardiovascular risk reduction has not been established.

MASH pathogenesis is characterised by accumulation of fat in the liver leading to lipotoxicity, cellular damage and upregulation of proinflammatory cytokines, activating the immune system and pathways leading to hepatic collagen deposition (fibrosis).[6]

The liver-specific mechanism of action of semaglutide is multifactorial and thought to be mediated through improvement in metabolic factors, including weight loss, improved glucose and lipid metabolism, and reduced inflammation. Semaglutide affects gene pathways of both inflammation and fibrosis, consequently positively changing the proteomic pattern of an individual with MASH. Moreover, semaglutide lowers liver fat deposition.

Pharmacodynamic effects

Weight loss distribution

In a sub-study in STEP 1 (N = 140), body composition was measured using dual energy X-ray absorptiometry (DEXA). The results of the DEXA assessment showed that treatment with Wegovy was accompanied by greater reduction in fat mass than in lean body mass leading to an improvement in body composition compared to placebo after 68 weeks. Furthermore, this reduction in total fat mass was accompanied by a reduction in visceral fat. In the semaglutide group, there was a mean (SD) decrease in total fat mass proportion of 3.9%-points (5.4%-points), an increase in lean body mass proportion of 3.4% (5.1%) and a decrease in regional visceral fat mass proportion of 2.2%-points (4.4%). These results suggest that most of the total weight loss was attributable to a reduction in fat tissue, including visceral fat.

In a sub-study in STEP UP (N=55), body composition was measured using magnetic resonance imaging (MRI). The results of the MRI assessment showed that treatment with Wegovy injection in the pooled Wegovy group (consisting of participants on the 7.2 mg weekly dose (n=43) and on the 2.4 mg weekly dose (n=6)) was accompanied by a greater reduction in fat mass/volume than in lean body mass/volume leading to an improvement in body composition compared to placebo (n=6) after 72 weeks.

Appetite regulation, energy intake and food choice

Solution for injection

Wegovy reduces appetite by increasing feelings of fullness and satiety, while lowering hunger and prospective food consumption. In a phase 1 trial, energy intake during an ad libitum meal was 35% lower with Wegovy compared to placebo after 20 weeks of dosing. This was supported by improved control of eating, less food cravings (for dairy and savoury foods), less desire for sweet food and a relatively lower preference for high fat food.

Tablet

Wegovy reduces appetite by increasing feelings of fullness and satiety, while lowering hunger and prospective food consumption. In two phase 1 trials, energy intake during an ad libitum meal was 35% and 39% lower with Wegovy injection and Wegovy tablet, respectively, compared to placebo after 20 weeks of dosing. This was supported in both trials by improved control of eating and less food cravings.

Cardiac electrophysiology (QTc)

The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at doses up to 1.5 mg at steady state.

The semaglutide exposure for subjects with overweight or obesity treated with Wegovy is comparable to the exposure evaluated in the semaglutide QTc study in healthy volunteers.

[6] Clinical Overview 2.5, Section 1.3.1, p. 8

Similar results have been shown by 12-lead ECG for QTc assessments for patients with obesity treated with semaglutide 7.2 mg.

MASH disease activity

*Liver steatosis**

A higher proportion of patients with MASH and F2 or F3 achieved an improvement in histology-assessed liver steatosis with semaglutide (70.0%) compared to placebo (42.3%) at week 72 in ESSENCE. Additionally, in ESSENCE semaglutide reduced liver steatosis assessed by TE using Controlled Attenuation Parameter (CAP) (dB/m) (43.4) compared to placebo (13.1) at 72 weeks.[7]

*Hepatocyte ballooning and lobular inflammation**

A higher proportion of patients with MASH and F2 or F3 achieved an improvement in histology-assessed hepatocyte ballooning with semaglutide (58.3%) compared to placebo (40.1%) at 72 weeks in ESSENCE. Additionally, in ESSENCE 36.0% of patients treated with semaglutide had an improvement in histology-assessed lobular inflammation compared to 20.6% in the placebo group at week 72.[8]

*Plasma liver enzymes (ALT, AST) and FAST score**

Semaglutide reduced the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST)in ESSENCE and in Trial NN9931-4296. Moreover, treatment with semaglutide resulted in a reduction in FAST score in ESSENCE.[9]

*Liver fibrosis**

Semaglutide decreased liver stiffness assessed by transient elastography (TE) and the levels of the pro-peptide of type III collagen biomarker (Pro-C3) in ESSENCE. [10] Semaglutide also reduced the Enhanced Liver Fibrosis (ELF) score in ESSENCE and in Trial NN9931-4296.

*Secondary endpoints not under multiplicity control

Clinical trials

Clinical programme for weight management (STEP & OASIS)

The efficacy and safety of Wegovy injection for weight management in combination with a reduced calorie intake and increased physical activity were evaluated in four 68-week double-blinded randomised placebo-controlled phase 3a trials (STEP 1-4). A total of 4684 patients (2652 randomised to treatment with Wegovy) were included in these trials. Furthermore, the two-year efficacy and safety of Wegovy compared to placebo were evaluated in a double-blinded randomised placebo-controlled phase 3b trial (STEP 5) including 304 patients (152 on treatment with Wegovy injection).

The efficacy and safety of semaglutide 7.2 mg was evaluated in two 72-week double-blinded randomised placebo-controlled 3-armed phase 3b trials (STEP UP and STEP UP T2D) including 1919 patients (1312 randomised to treatment with semaglutide 7.2 mg).

[7] Module 5.3.5.1: N9931-4553 CTR (interim) redacted, Section 5.1.4.6, p. 70; TFL 8.2.36 and Section 5.1.4.14, p. 82; TFL 8.2.78

[8] Module 5.3.5.1: N9931-4553 CTR (interim) redacted, Section 5.1.4.4, p. 68; TFL 8.2.32 and Section 5.1.4.5, p. 69; TFL 8.2.34

[9] Module 5.3.5.1: N9931-4553 CTR (interim) redacted, Section 5.1.4.12, p. 78; 5.1.4.13, p. 81; 5.1.4.15, p. 84

[10] Module 5.3.5.1: N9931-4553 CTR (interim) redacted, Section 5.1.4.10, p. 74; 5.1.4.11, p. 77; 5.1.4.16, p. 85

The efficacy and safety of 25 mg orally administered semaglutide once daily for weight management in combination with a reduced calorie intake and increased physical activity have been evaluated in a 64-week double-blinded randomised placebo-controlled phase 3b trial (OASIS 4) including 307 patients (205 randomised to treatment with orally administered semaglutide).

The OASIS 4 trial with 25 mg orally administered semaglutide once daily showed exposure levels overall comparable to the exposure levels shown in STEP 1 (semaglutide s.c. 2.4 mg once weekly).

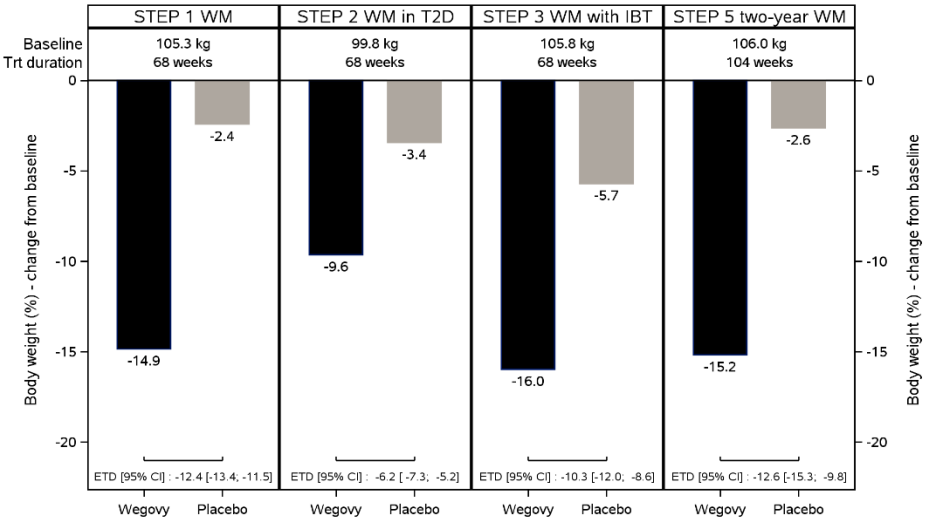
Treatment with Wegovy demonstrated superior, clinically meaningful, and sustained weight loss compared with placebo in patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) and at least one weight-related comorbidity (Figure 2). Furthermore, across the trials, a higher proportion of patients achieved ≥5%, ≥10% and ≥15% weight loss with Wegovy compared with placebo.

Treatment with Wegovy also showed statistically significant improvements in waist circumference and systolic blood pressure compared to placebo. Wegovy also showed statistically significant improvements in physical functioning compared to placebo, except for STEP 3 where the improvement was not statistically significant.

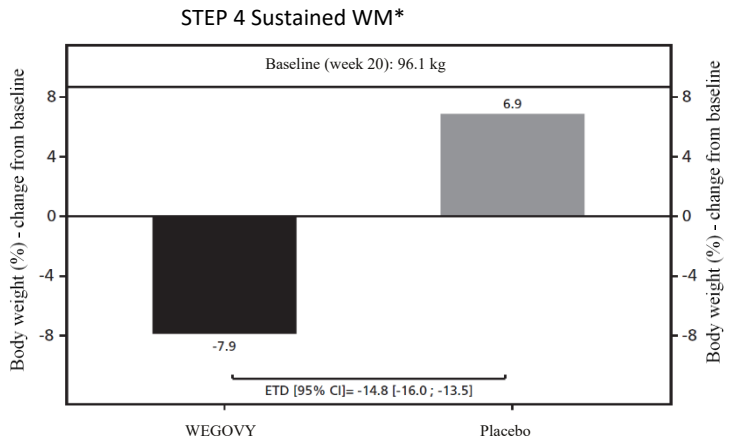
Wegovy demonstrated efficacy in weight loss regardless of age, sex, race, ethnicity, baseline body weight, BMI, presence of type 2 diabetes and level of renal function.

The efficacy of Wegovy tablet was not impacted by baseline upper gastrointestinal disease.

Figure 2 Body weight (%) change from baseline to week 68 and 104



Trt: Treatment, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment difference and corresponding confidence interval are from the primary analysis.
nn9536/nn9536-exploratory/lueu001
25JAN2022:12:58:17 - fbarploteff.sas/fbarbwchbitpct.png



*baseline for STEP 4 was defined as the start of the randomisation period at week 20

SELECT: Cardiovascular outcomes trial in patients with overweight or obesity

A dedicated cardiovascular outcomes trial, SELECT, has been conducted with semaglutide 2.4 mg once weekly against placebo in patients with established cardiovascular disease, BMI ≥27 kg/m^2 and without a history of type 1 and type 2 diabetes. Treatment with semaglutide in SELECT resulted in a significant risk reduction (20%) in 3-component MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) compared with placebo.

Clinical programme for MASH (ESSENCE & NN9931-4296)

The efficacy and safety of Wegovy for MASH have been evaluated in one phase 3 trial (ESSENCE, semaglutide s.c. 2.4 mg once weekly) in adult patients with MASH and fibrosis stage 2 (F2) or 3 (F3) and in one phase 2 trial (NN9931-4296, semaglutide s.c. 0.1, 0.2, or 0.4 mg once daily) in adult patients with MASH and F1 to F3. Treatment with Wegovy in ESSENCE demonstrated superior and clinically meaningful differences relative to placebo in the proportion of patients achieving resolution of steatohepatitis with no worsening of liver fibrosis, improvement in liver fibrosis with no worsening of steatohepatitis, as well as in the proportion of patients achieving resolution of steatohepatitis with improvement in liver fibrosis. [11]

Weight management

STEP 1: Weight management

In a 68-week double-blind trial, 1961 patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity were randomised to Wegovy or placebo. All patients received counselling with regards to diet (500 kcal/2092 kJ deficit per day) relative to the estimated total energy expenditure (TEE) (calculated once at randomisation), and physical activity (150 min of physical activity per week was encouraged).

At baseline, patients had a mean BMI of 37.9 kg/m^2 and a mean body weight of 105.3 kg. The mean age of patients was 46 years. There were 75.1% Caucasian/White, 5.7% Black/African American, and 13.3% Asian. A total of 12.0% were Hispanic or Latino. The majority of patients had at least one weight-related comorbidity. These included, but were not limited to, pre-diabetes (43.7%), dyslipidaemia (37.0%), hypertension (36.0%), knee or hip osteoarthritis (15.9%), obstructive sleep apnoea (11.7%), asthma/chronic obstructive pulmonary disease (COPD) (11.6%), liver disease

[11] NN9931 Summary 2.7.3 interim (redacted), Section 3, p. 36-97

(metabolic dysfunction-associated steatotic liver disease (MASLD) or MASH) (8.6%) and polycystic ovary syndrome (PCOS) (6.6%).

Weight loss with Wegovy occurred early and continued throughout the trial. At end of treatment (week 68), the weight loss with Wegovy was superior and clinically meaningful compared with placebo (see Table 7 and

Figure ***3***). Furthermore, a higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with Wegovy compared with placebo (see Table 8 and Figure 4). Among patients with pre-diabetes at baseline, 84.1% and 47.8% achieved a normo-glycaemic status at end of treatment with Wegovy and placebo, respectively.

Following the 68-week trial, a 52-week off-treatment extension was conducted including 327 patients who had completed the main trial period on the maintenance dose of Wegovy or placebo. The trial extension consisted of four clinic visits and did not include structured lifestyle intervention. In the off-treatment period from week 68 to week 120, mean body weight increased in both treatment groups. However, for patients that had been treated with semaglutide for the main trial period the weight remained 5.6% below baseline compared to 0.1% for the placebo group.

Table 7 Results of a 68-week trial comparing Wegovy with placebo in patients with obesity, or overweight and at least one weight-related comorbidity (STEP 1)

	Wegovy	**Placebo**
Full analysis set (N)	1306	655
Body weight		
Baseline (kg)	105.4	105.2
Change (%) from baseline[1,2]	-14.9	−2.4
Difference (%) from placebo[1] [95% CI]	-12.4 [-13.4;-11.5]*	-
Change (kg) from baseline	-15.3	-2.6
Difference (kg) from placebo[1] [95% CI]	-12.7 [-13.7;-11.7]	-
Patients (%) achieving weight loss ≥5%[3]	83.5*	31.1
Patients (%) achieving weight loss ≥10%[3]	66.1*	12.0
Patients (%) achieving weight loss ≥15%[3]	47.9*	4.8
Patients (%) achieving weight loss ≥20%[3]	30.2	1.7
Waist circumference (cm)		
Baseline	114.6	114.8
Change from baseline[1]	−13.5	−4.1
Difference from placebo[1] [95% CI]	-9.4 [−10.3; −8.5]*	-
Cardiometabolic factors		
Systolic blood pressure (mmHg)		
Baseline	126	127
Change from baseline[1]	-6.2	−1.1
Difference from placebo[1] [95% CI]	-5.1 [-6.3; -3.9]*	-
Diastolic blood pressure (mmHg)		
Baseline	80	80
Change from baseline[1]	-2.8	−0.4
Difference from placebo[1] [95% CI]	-2.4 [-3.3; -1.6]	-
Lipids		
Total cholesterol		
Baseline (mmol/L)[4]	4.9	5.0
Change (%) from baseline[1]	−3.3	0.1
Relative Difference (%) from placebo[1] [95% CI]	−3.3 [−4.8; −1.8]	-
LDL cholesterol		
Baseline (mmol/L)[4]	2.9	2.9
Change (%) from baseline[1]	−2.5	1.3
Relative Difference (%) from placebo[1] [95% CI]	−3.8 [−5.9; −1.5]	-
HDL cholesterol		

Baseline (mmol/L)[4]	1.3	1.3
Change (%) from baseline[1]	5.2	1.4
Relative Difference (%) from placebo[1] [95% CI]	3.8 [2.2; 5.4]	-
Triglycerides		
Baseline (mmol/L)[4]	1.4	1.4
Change (%) from baseline[1]	−21.9	−7.3
Relative Difference (%) from placebo[1] [95% CI]	−15.8 [−18.8; −12.7]	-
CRP		
Baseline (mg/L)[4]	3.9	3.9
Change (%) from baseline[1]	−52.6	−15.0
Relative Difference (%) from placebo[1] [95% CI]	-44.3 [−49.5; −38.5]	-
Glycaemic factors		
HbA_{1c} (%)		
Baseline	5.7	5.7
Change from baseline[1,2]	−0.5	−0.2
Difference from placebo[1] [95% CI]	−0.3 [−0.3; −0.3]	-
FPG (mmol/L)		
Baseline	5.3	5.3
Change from baseline[1]	−0.5	−0.03
Difference from placebo[1] [95% CI]	−0.4 [−0.5; −0.4]	-
Glycaemic status[5]		
Patients (%) with pre-diabetes at baseline	43.7	
Patients (%) achieving normo-glycaemic status at end of treatment	84.1	47.8

[*] p<0.0001 (unadjusted 2-sided) for superiority.

[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

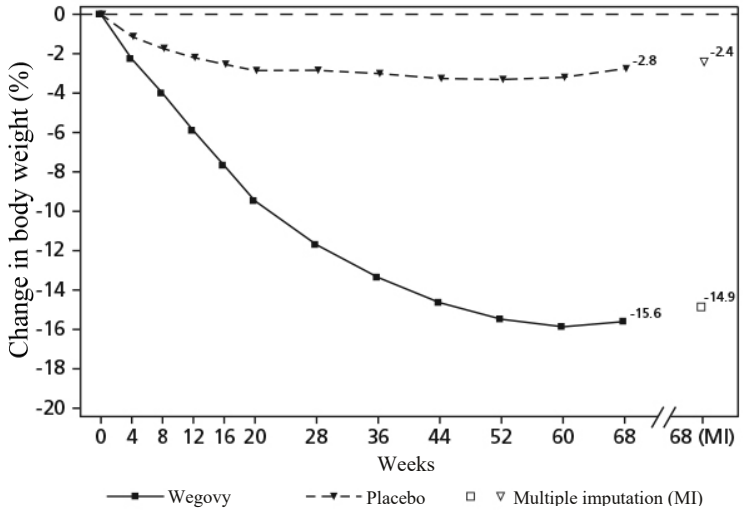
[2] During the trial, randomised treatment was permanently discontinued by 17.1% and 22.4% of patients randomised to Wegovy and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -16.9% and -2.4% for Wegovy and placebo, respectively.

[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

[4] Geometric mean

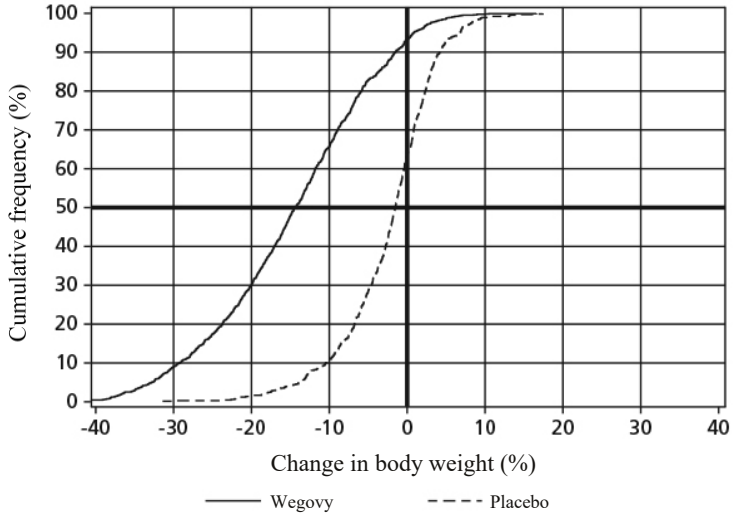
[5] exploratory endpoint

Figure 3 STEP 1 - Mean change in body weight (%) from baseline to week 68



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Figure 4 STEP 1 - Cumulative distribution of change (%) in body weight after 68 weeks of treatment



Observed data from in-trial period including imputed data from retrieved dropouts for missing observations.

STEP 2: Weight Management in patients with type 2 diabetes

In a 68-week, double-blind and double-dummy trial, 1210 patients with overweight or obesity (BMI ≥27 kg/m^2) and type 2 diabetes were randomised to either Wegovy, semaglutide 1 mg once-weekly or placebo. Patients included in the trial had insufficiently controlled diabetes (HbA_{1c} 7–10%) and were treated with either diet and exercise alone or 1–3 oral anti-diabetic drugs. All patients received counselling with regards to diet (500 kcal/2092 kJ deficit per day) relative to the estimated total energy expenditure (TEE) (calculated once at randomisation), and physical activity (150 min of physical activity per week was encouraged).

At baseline, patients had a mean BMI of 35.7 kg/m^2, a mean body weight of 99.8 kg and a mean HbA_{1C} of 8.1%. The mean age was 55 years. There were 62.1% Caucasian/White, 8.3% Black/African American, and 26.2% Asian. A total of 12.8% were Hispanic or Latino. The majority of patients had at least two weight-related comorbidities. Besides type 2 diabetes these included, but were not limited

to, hypertension (69.8%), dyslipidaemia (68.0%), liver disease (NAFLD or NASH) (22.6%), knee or hip osteoarthritis (19.6%), obstructive sleep apnoea (15.1%), asthma/COPD (8.4%) and PCOS (4.1%).

Treatment with Wegovy for 68 weeks resulted in superior and clinically meaningful reductions in body weight and in HbA_{1c} compared to placebo (see Table 8 and Figure 5).

Table 8 Results of a 68-week trial comparing Wegovy with placebo in patients with obesity or overweight, and type 2 diabetes (STEP 2)

	Wegovy	**Placebo**
Full analysis set (N)	404	403
Body weight		
Baseline (kg)	99.9	100.5
Change (%) from baseline[1,2]	-9.6	−3.4
Difference (%) from placebo[1] [95% CI]	-6.2 [-7.3;-5.2]*	-
Change (kg) from baseline	-9.7	-3.5
Difference (kg) from placebo[1] [95% CI]	-6.1 [-7.2;-5.0]	-
Patients (%) achieving weight loss ≥5%[3]	67.4*	30.2
Patients (%) achieving weight loss ≥10%[3]	44.5*	10.2
Patients (%) achieving weight loss ≥15%[3]	25.0*	4.3
Patients (%) achieving weight loss ≥20%[3]	12.8	2.3
Waist circumference (cm)		
Baseline	114.5	115.5
Change from baseline[1]	-9.4	-4.5
Difference from placebo[1] [95% CI]	-4.9 [-6.0; -3.8]*	-
Cardiometabolic factors		
Systolic blood pressure (mmHg)		
Baseline	130	130
Change from baseline[1]	-3.9	-0.5
Difference from placebo[1] [95% CI]	-3.4 [-5.6; -1.3]**	-
Diastolic blood pressure (mmHg)		
Baseline	80	80
Change from baseline[1]	-1.6	-0.9
Difference from placebo[1] [95% CI]	-0.7 [-2.0; 0.6]	-
Lipids		
Total cholesterol		
Baseline (mmol/L)[4]	4.4	4.4
Change (%) from baseline[1]	-1.4	-0.5
Relative Difference (%) from placebo[1] [95% CI]	-0.9 [-3.6; 2.0]	-
LDL cholesterol		
Baseline (mmol/L)[4]	2.3	2.3
Change (%) from baseline[1]	0.5	0.1
Relative Difference (%) from placebo[1] [95% CI]	0.4 [-4.0; 4.9]	-
HDL cholesterol		
Baseline (mmol/L)[4]	1.2	1.1
Change (%) from baseline[1]	6.9	4.1
Relative Difference (%) from placebo[1] [95% CI]	2.7 [0.3; 5.1]	-
Triglycerides		
Baseline (mmol/L)[4]	1.7	1.8
Change (%) from baseline[1]	-22.0	-9.4

Relative Difference (%) from placebo[1] [95% CI]	-13.9 [-19.0; -8.4]	-
CRP		
Baseline (mg/L)[4]	3.5	3.4
Change (%) from baseline[1]	-48.9	-16.7
Relative Difference (%) from placebo[1] [95% CI]	-38.7 [-46.5; -29.8]	-
Glycaemic factors		
HbA_{1c} (%)		
Baseline	8.1	8.1
Change from baseline[1,2]	-1.6	-0.4
Difference from placebo[1] [95% CI]	-1.2 [-1.4; -1.1]*	-
Patients (%) achieving HbA1c <7%[3]	77.4	26.0
Patients (%) achieving HbA1c ≤6.5%[3]	65.9	15.1
FPG (mmol/L)		
Baseline	8.5	8.8
Change from baseline[1]	-2.1	-0.1
Difference from placebo[1] [95% CI]	-2.0 [-2.4; -1.7]	-

* p<0.0001 (unadjusted 2-sided) for superiority; **p<0.05 (unadjusted 2-sided) for superiority

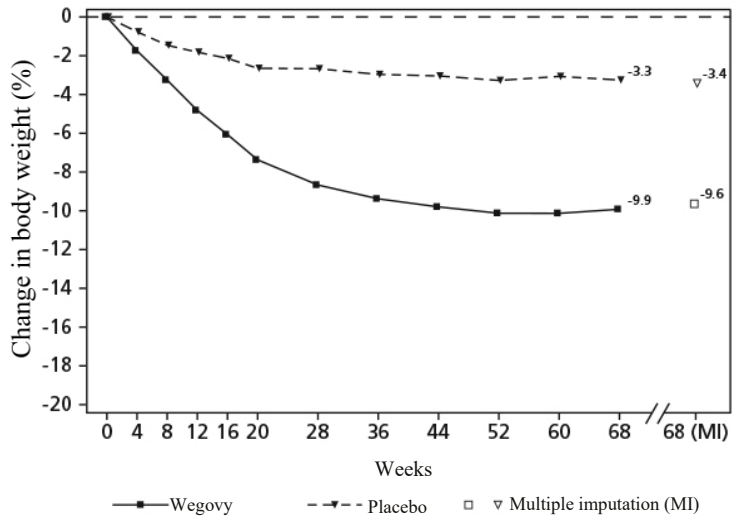
[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[2] During the trial, randomised treatment was permanently discontinued by 11.6% and 13.9% of patients randomised to Wegovy and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -10.6% and -3.1% for Wegovy and placebo, respectively.

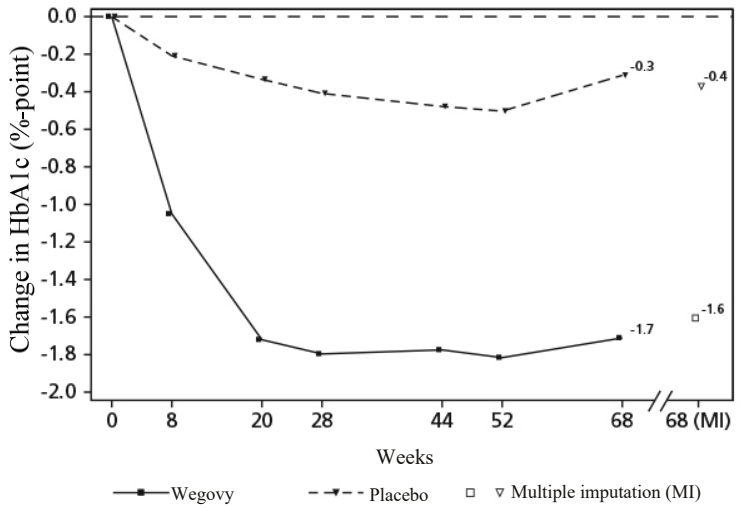
[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

[4] Geometric mean.

Figure 5 STEP 2 - Mean change in body weight (%) and HbA1c (%) from baseline to week 68



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts



HbA1c: Haemoglobin A1c
Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

STEP 3: Weight Management with Intensive Behavioural Therapy

In a 68-week double-blind trial, 611 patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity were randomised to Wegovy or placebo. During the trial, all patients received intensive behavioural therapy (IBT) consisting of an initial 8 weeks low calorie diet followed by a 60 weeks hypo-caloric diet, increased physical activity and behavioural counselling. The first 8 weeks included a 1000-1200 kcal/day (4184-5020.8 kJ/day) low-calorie diet provided as meal replacements and portion-controlled meals. From week 8 and onwards, daily caloric targets were defined based on baseline body weight and ranged from 1200 to 1800 kcal/day (5020.8-7531.2 kJ/day). Physical activity was prescribed with a target of 100 minutes physical activity per week, progressing gradually by 25 minutes every 4 weeks and up to 200 minutes/week.

At baseline, patients had a mean BMI of 38.0 kg/m^2 and a mean body weight of 105.8 kg. The mean age was 46 years. There were 76.1% Caucasian/White, 19.0% Black/African American, and 1.8% Asian. A total of 19.8% were Hispanic or Latino. The majority of patients had at least one weight-related comorbidity. These included, but were not limited to, pre-diabetes (49.8%), hypertension (34.7%), dyslipidaemia (34.7%), knee or hip osteoarthritis (18.7%), asthma/COPD (15.1%), obstructive sleep apnoea (12.6%), liver disease (NAFLD or NASH) (6.1%) and PCOS (5.5%).

Treatment with Wegovy and IBT for 68 weeks resulted in superior and clinically meaningful reduction in body weight compared to placebo (see Table 9 and Figure 6). Among patients with pre-diabetes at baseline, 89.5% and 55.0% of patients achieved normo-glycaemic status at end of treatment with Wegovy and placebo, respectively.

Table 9 Results of a 68-week trial comparing Wegovy with placebo in patients with obesity, or overweight and at least one weight-related comorbidity, on IBT (STEP 3)

	Wegovy	Placebo
Full analysis set (N)	407	204
Body weight		
Baseline (kg)	106.9	103.7
Change (%) from baseline[1,2]	-16.0	-5.7

Difference (%) from placebo[1] [95% CI]	-10.3 [-12.0;-8.6]*	-
Change (kg) from baseline	-16.8	-6.2
Difference (kg) from placebo[1] [95% CI]	-10.6 [-12.5;-8.8]	-
Patients (%) achieving weight loss ≥5%[3]	84.8*	47.8
Patients (%) achieving weight loss ≥10%[3]	73.0*	27.1
Patients (%) achieving weight loss ≥15%[3]	53.5*	13.2
Patients (%) achieving weight loss ≥20%[3]	33.9	3.5
Waist circumference (cm)		
Baseline	113.6	111.8
Change from baseline[1]	-14.6	-6.3
Difference from placebo[1] [95% CI]	-8.3 [-10.1; -6.6]*	-

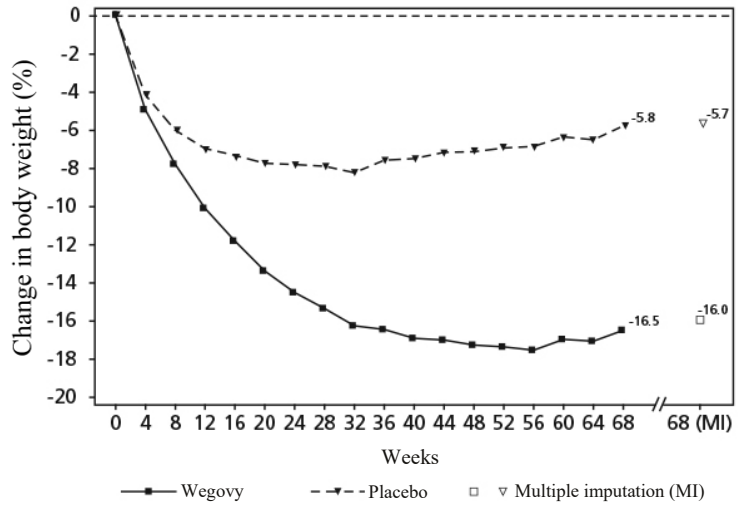
* p<0.0001 (unadjusted 2-sided) for superiority[1]

Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[2] During the trial, randomised treatment was permanently discontinued by 16.7% and 18.6% of patients randomised to Wegovy and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -17.6% and -5.0% for Wegovy and placebo, respectively

[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

Figure 6 STEP 3 - Mean change in body weight (%) from baseline to week 68



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

STEP 4: Sustained Weight Management

In a 68-week double-blind withdrawal trial, 902 patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity were included. All patients received counselling with regards to diet (500 kcal/2092 kJ deficit per day) relative to the estimated total energy expenditure (TEE) (calculated once at randomisation), and physical activity (150 min of physical activity per week was encouraged). From week 0 to week 20 (run-in), all patients received Wegovy. At week 20 (baseline), 803 patients who had reached the maintenance dose of Wegovy were randomised to continue Wegovy or switch to placebo for the remaining 48 weeks.

At the beginning of the run-in period (week 0), patients had a mean BMI of 38.4 kg/m^2, a mean body weight of 107.2 kg and a mean age of 46 years. At baseline (week 20), patients had a mean BMI of 34.4 kg/m^2 and a mean body weight of 96.1 kg. There were 83.7% Caucasian/White, 13.0% Black/African American, and 2.4% Asian. A total of 7.8% were Hispanic or Latino. The majority of patients had at least one weight-related comorbidity. These included, but were not limited to, pre-diabetes (46.8%), hypertension (37.1%), dyslipidaemia (35.9%), knee or hip osteoarthritis (13.3%), obstructive sleep apnoea (11.7%), asthma/COPD (11.5%), liver disease (MASLD and MASH) (7.3%) and PCOS (3.9%).

Patients who had reached the maintenance dose of Wegovy (2.4 mg) at week 20 (baseline) and continued treatment with Wegovy for 48 weeks continued losing weight and had a superior and clinically meaningful reduction in body weight compared to those switched to placebo (see Table 10 and

Figure ***7***). On the other hand, in patients switching to placebo at week 20 (baseline), body weight increased steadily from week 20 to week 68. However, the observed mean body weight was lower at week 68 than at start of the run-in period (week 0) (see

Figure ***7***). Patients treated with Wegovy from week 0 (run-in) to week 68 (end of treatment) achieved a mean change in body weight of 17.4%, with weight loss ≥5% achieved by 87.8%, ≥10% achieved by 78.0%, ≥15% achieved by 62.2% and ≥20% achieved by 38.6% of these patients.

Table 10 Results from the 48-week (week 20 to week 68) randomised period of the trial comparing Wegovy with placebo in patients with obesity, or overweight and a least one weight-related comorbidity (STEP 4)

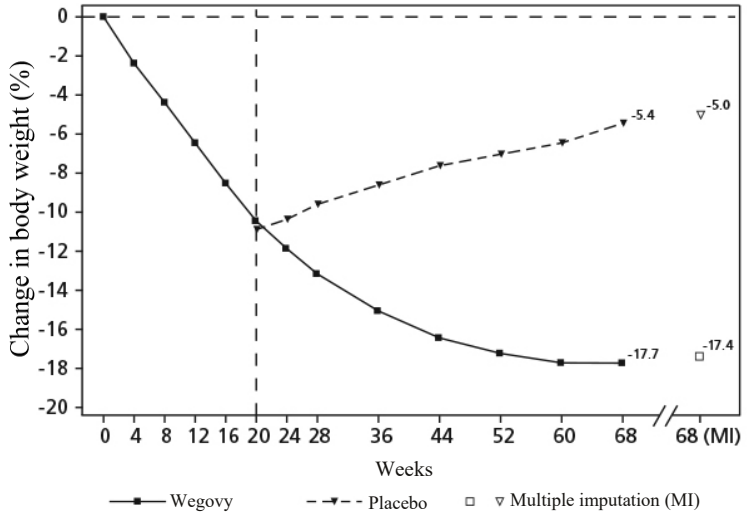
	Wegovy	Placebo
Full analysis set (N)	535	268
Body weight		
Baseline[1] (kg)	96.5	95.4
Change (%) from baseline[1,2,3]	-7.9	6.9
Difference (%) from placebo[2] [95% CI]	-14.8 [-16.0;-13.5]*	-
Change (kg) from baseline[1]	-7.1	6.1
Difference (kg) from placebo[2] [95% CI]	-13.2 [-14.3;-12.0]	-
Waist circumference (cm)		
Baseline[1]	105.5	104.7
Change from baseline[1,2]	-6.4	3.3
Difference from placebo[2] [95% CI]	-9.7 [-10.9; -8.5]*	-

* p<0.0001 (unadjusted 2-sided) for superiority, [1]Baseline = week 20

[2] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[3] During the trial, randomised treatment was permanently discontinued by 5.8% and 11.6% of patients randomized to Wegovy and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -8.1% and 6.5% for Wegovy and placebo, respectively.

Figure 7 STEP 4 - Mean change in body weight (%) from week 0 to week 68



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

STEP 5: long term efficacy

In a 104-week double-blind trial, 304 patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity, were randomised to Wegovy or placebo. All patients were counselled on healthy nutrition and physical activity with the goal of obtaining weight loss.

At baseline, patients had a mean BMI of 38.5 kg/m^2, a mean body weight of 106.0 kg. The mean age was 47 years. There were 93.1% Caucasian/White, 3.9% Black/African American, and 0.7% Asian. A total of 12.8% were Hispanic or Latino. The majority of patients had at least one weight-related comorbidity. These included, but were not limited to, hypertension (38.8%), dyslipidaemia (35.2%), obstructive sleep apnoea (16.8%) and knee osteoarthritis (15.1%).

Treatment with Wegovy for 104 weeks resulted in a superior and clinically meaningful reduction in body weight compared to placebo (see Table 11 and Figure 8). Mean body weight decreased from baseline through to week 68 with Wegovy after which a plateau was reached. With placebo, mean body weight decreased less, and a plateau was reached after approximately 20 weeks of treatment. A higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with Wegovy compared with placebo. Among patients with pre-diabetes at baseline, 80% and 37% achieved a normo-glycaemic status at end of treatment with Wegovy and placebo, respectively.

Table 11 Results of a 104-week trial comparing Wegovy with placebo in patients with obesity or overweight and at least one weight-related comorbidity (STEP 5)

	Wegovy	**Placebo**
Full analysis set (N)	152	152
Body weight		
Baseline (kg)	105.6	106.5
Change (%) from baseline[1, 2]	-15.2	-2.6
Difference (%) from placebo[1] [95% CI]	-12.6 [-15.3; -9.8]*	-
Change (kg) from baseline	-16.1	-3.2

Difference (kg) from placebo[1] [95% CI]	12.9[-16.1;-9.8]	-
Patients (%) achieving weight loss ≥5%[3]	74.7*	37.3
Patients (%) achieving weight loss ≥10%[3]	59.2*	16.8
Patients (%) achieving weight loss ≥15%[3]	49.7*	9.2
Patients (%) achieving weight loss ≥20%[3]	34.5*	4.0
Waist circumference (cm)		
Baseline	115.8	115.7
Change from baseline[1]	-14.4	5.2
Difference from placebo[1] [95% CI]	-9.2 [-12.2; -6.2]*	-
Systolic blood pressure (mmHg)		
Baseline	126	125
Change from baseline[1]	-5.7	-1.6
Difference from placebo[1] [95% CI]	-4.2 [-7.3; -1.0]*	-

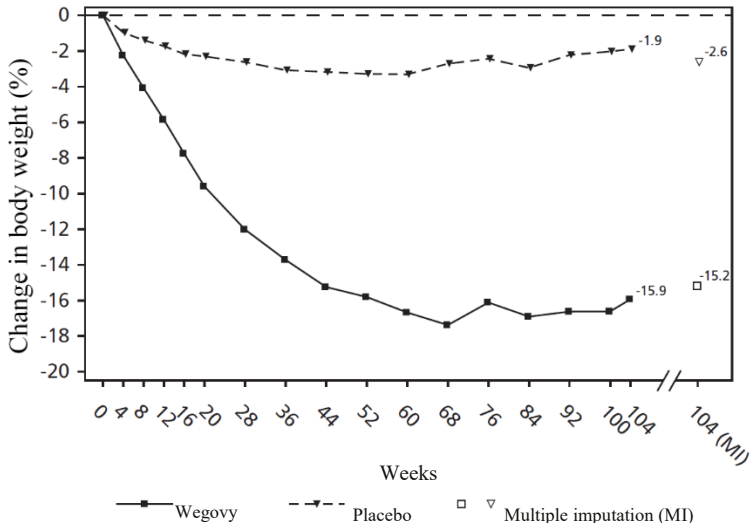
* p<0.0001 (unadjusted 2-sided) for superiority.

[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[2] During the trial, randomised treatment was permanently discontinued by 13.2% and 27.0% of patients randomized to Wegovy® and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -16.7% and -0.6% for Wegovy® and placebo, respectively.

[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

Figure 8 Mean body weight change from baseline to week 104



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Step 8: Semaglutide vs liraglutide

In a 68-week, randomised, open-label, pairwise placebo-controlled trial, 338 patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity, were randomised to Wegovy once weekly, liraglutide 3.0 mg once daily or placebo. Wegovy once weekly and liraglutide 3 mg were open-label, but each active treatment group was double-blinded against placebo administered at the same dosing frequency. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

At baseline, patients had a mean BMI of 37.5 kg/m^2, a mean body weight of 104.5 kg. The mean age was 49 years. There were 73.7% Caucasian/White, 18.9% Black/African American, and 3.8% Asian. A

total of 11.5% were Hispanic or Latino. The majority of patients had at least one weight-related comorbidity. These included, but were not limited to, dyslipidaemia (47.6%), hypertension (42.0%), knee osteoarthritis (18.3%) and obstructive sleep apnoea (18.0%).

Treatment with Wegovy once weekly for 68 weeks resulted in superior and clinically meaningful reduction in body weight compared to liraglutide. Mean body weight decreased from baseline through to week 68 with Wegovy, with liraglutide, mean body weight decreased less, and with placebo less yet. 37.4% of the patients treated with semaglutide lost ≥20%, compared to 7.0% treated with liraglutide. Table 12 shows the results of the confirmatory endpoints ≥10%, ≥15% and ≥20% weight loss.

Table 12 Results of a 68-week trial comparing Wegovy with liraglutide in patients with obesity or overweight (STEP 8)

	Wegovy	Liraglutide 3 mg
Full analysis set (N)	126	127
Body weight		
Baseline (kg)	102.5	103.7
Change (%) from baseline[1, 2]	-15.8	-6.4
Difference (%) from liraglutide[1] [95% CI]	-9.4 [-12.0;-6.8]*	-
Change (kg) from baseline	-15.3	-6.8
Difference (kg) from liraglutide[1] [95% CI]	-8.5 [-11.2;-5.7]	-
Patients (%) achieving weight loss ≥10%[3]	69.4*	27.2
Patients (%) achieving weight loss ≥15%[3]	54.0*	13.4
Patients (%) achieving weight loss ≥20%[3]	37.4*	7.0

* p<0.0001 (unadjusted 2-sided) for superiority.

[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[2] During the trial, randomised treatment was permanently discontinued by 13.5% and 27.6% of patients randomised to Wegovy and liraglutide, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -16.7% and -6.7% for Wegovy and liraglutide, respectively.

[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

MASH

ESSENCE (NN9931-4553)

ESSENCE is an on-going, randomised, multicentre, double-blind, parallel-group trial. The primary endpoints were resolution of steatohepatitis (defined as a NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (According to NASH CRN)) with no worsening of liver fibrosis (fibrosis is graded on the NASH CRN fibrosis scale from 0 to 4) and on at least one stage improvement in liver fibrosis (defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale) with no worsening of steatohepatitis (defined as no increase from baseline in NAS score for ballooning, inflammation, or steatosis), on post-baseline liver biopsies collected at 72 weeks. A total of 800 patients randomised to Wegovy (534 patients) or placebo (266 patients) in a 2 to 1 ratio were included in the interim analysis at week 72. Of these, 31.3 % had MASH and fibrosis stage 2 (F2) and 68.8% had MASH and fibrosis stage 3 (F3) as assessed at baseline. The mean age was 56.0 years. There were 67.5 % Caucasian/White, 0.6% Black/African American, and 27.0% Asian. A total of

18.3% were Hispanic or Latino. The mean BMI was 34.6 kg/m2, 6.6% had BMI<25, 72.8% had BMI≥30 and 55.9% had type 2 diabetes. [12]

At week 72, Wegovy was superior to placebo in inducing resolution of steatohepatitis with no worsening of liver fibrosis and improvement in liver fibrosis with no worsening of steatohepatitis (primary endpoints). As for the confirmatory secondary endpoints, Wegovy was superior to placebo in inducing resolution of steatohepatitis with improvement in liver fibrosis . Treatment with Wegovy resulted in a greater and sustained weight loss. These treatment effects were clinically meaningful. Wegovy did not meet the pre-specified significance level for the confirmatory secondary endpoint SF-36 Bodily pain. See Table 13,

[12] Module 5.3.5.1: NN9931-4553 CTR (interim) redacted, Section 4.4.1, p.49; TFL 8.1.14 and NN9931-4553 CTR (interim) redacted; TFL 8.1.16

Figure ***9***, Figure 10 and Figure 11.

Treatment with Wegovy also resulted in improvements in ALT, AST, liver stiffness assessed by TE, ELF score, Pro-C3 and FAST score compared with placebo at week 72 (see Table 14). These treatment effects were clinically meaningful. Wegovy increased the levels of high-density lipoprotein (HDL) cholesterol and decreased the levels of total cholesterol and triglycerides compared with placebo at week 72 (see Table 14).

Wegovy demonstrated efficacy in improving liver histology regardless of age, sex, race and ethnicity, as well as baseline fibrosis stage, hepatic function, BMI (≥ 25 kg/m^2 or ≥ 23 kg/m^2 for Asian populations), presence of type 2 diabetes and renal function.[13]

Table 13 Results for the primary and confirmatory secondary endpoints of a 72-week interim analysis comparing Wegovy with placebo in patients with MASH and F2 or F3 - ESSENCE [14]

	Wegovy	**Placebo**
Full analysis set (N)	534	266
Primary endpoints		
Resolution of steatohepatitis and no worsening of liver fibrosis[1]		
Proportion (%) of responders[2]	62.9	34.3
Difference (%-point) from placebo[3] [95% CI]	28.6 [21.1; 36.2]*	-
Improvement in liver fibrosis and no worsening of steatohepatitis[4]		
Proportion (%) of responders[2]	36.8	22.4
Difference (%-point) from placebo[3] [95% CI]	14.4 [7.5; 21.3]*	-
Confirmatory secondary endpoints		
Resolution of steatohepatitis and improvement in liver fibrosis[5]		
Proportion (%) of responders[2]	32.7	16.1
Difference (%-point) from placebo[3] [95% CI]	16.5 [10.2; 22.8]*	-
Body weight		
Baseline (kg)	95.4	97.6
Change (%) from baseline[6]	-10.5	-2.0
Difference (%-point) from placebo[6] [95% CI]	-8.5 [-9.5; -7.4]*	-
SF-36v2 Bodily pain		
Baseline	48.2	47.6
Change from baseline[7]	0.9	-0.5
Difference from placebo[7]	1.3 [0.01; 2.7]#	-
Patients (%) achieving clinically relevant improvement[8,9]	28.4	25.4

* p<0.0001 (unadjusted 2-sided) for superiority.

# p<0.05 (two-sided)

[1]Resolution of steatohepatitis is defined as a NAFLD Activity Score (NAS) of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (According to NASH CRN). Fibrosis is graded on the NASH CRN fibrosis scale from 0 to 4.

[2] Missing observations were imputed with multiple imputation (MI) based on unconditional reference.

[13] NN9931 Summary 2.7.3 interim (redacted), Section 3, p. 36-97

[14] Module 5.3.5.1: NN9931-4553 CTR (interim) redacted, Section 5.1

[3] Estimated with a Cochran-Mantel-Haenszel test stratified by baseline diabetes status and baseline fibrosis status.
[4] Improvement in fibrosis is defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation, or steatosis.
[5] Resolution of steatohepatitis is defined as an NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (According to NASH CRN). Improvement in fibrosis is defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale.
[6] Estimated using an ANCOVA model using multiple imputation based on unconditional reference.
[7] Norm-based score
[8] The patient perspective is used as foundation for evaluating clinical relevance. This is also denoted meaningful-within patient change (MWPC).
[9] The MWPC threshold of ≥ 5.0-point improvement in SF-36v2 Acute Bodily Pain norm based score was derived using an anchor-based method based on a one-category improvement in Patient Global Impression of Status (PGI-S)

Table 14 Results for the supportive secondary analyses of a 72-week interim analysis comparing Wegovy with placebo in patients with MASH and F2 or F3 - ESSENCE

	Wegovy	**Placebo**
Full analysis set (N)	534	266
Liver stiffness assessed by TE		
Number of patients at baseline[1]	417	216
Baseline (kPa)[2]	11.5	11.6
Change (%) from baseline[3]	-31.1	-13.5
Relative difference (%) from placebo[3] [95% CI]	-20.4 [-25.9; -14.4]	-
ELF score		
Baseline	10.0	10.0
Change from baseline[3]	-0.57	0.01
Difference from placebo[3] [95% CI]	-0.57 [-0.68; -0.47]	-
Pro-C3		
Baseline (ng/mL)[2]	49.1	48.8
Change (%) from baseline[3]	-16.2	1.0
Relative difference (%) from placebo[3] [95% CI]	-17.0 [-21.7; -12.1]	-
ALT		
Baseline (units/L)[2]	57.1	56.4
Change (%) from baseline[3]	-52.1	-22.2
Relative difference (%) from placebo[3] [95% CI]	-38.5 [-43.4; -33.1]	-
AST		
Baseline (units/L)[2]	46.9	45.9
Change (%) from baseline[3]	-44.9	-17.1
Relative difference (%) from placebo[3] [95% CI]	-33.5 [-37.9; -28.9]	-
FAST score		
Number of patients at baseline	383	197
Baseline	0.59	0.58
Change from baseline[3]	-0.28	-0.10
Difference from placebo[3] [95% CI]	-0.18 [-0.22; -0.14]	-
HbA1c[4]		
Number of patients with type 2 diabetes at baseline	296	151
Baseline (%)	7.2	6.9
Change (%-point) from baseline[3]	-1.1	-0.0

Difference (%-point) from placebo[3] [95% CI]	-1.1 [-1.3; -0.9]	-
Total cholesterol		
Baseline (mmol/L)[2]	4.7	4.5
Change (%) from baseline[3]	-6.0	-3.2
Relative difference (%) from placebo[3] [95% CI]	-2.9 [-5.6; -0.19]	-
LDL cholesterol		
Baseline (mmol/L)[2]	2.6	2.4
Change (%) from baseline[3]	-6.1	-4.1
Relative difference (%) from placebo[3] [95% CI]	-2.0 [-6.3; 2.5]	-
HDL cholesterol		
Baseline (mmol/L)[2]	1.2	1.1
Change (%) from baseline[3]	2.6	-1.9
Relative difference (%) from placebo[3] [95% CI]	4.7 [2.1; 7.3]	-
Triglycerides		
Baseline (mmol/L)[2]	1.7	1.7
Change (%) from baseline[3]	-16.8	-0.3
Relative difference (%) from placebo[3] [95% CI]	-16.5 [-21.0; -11.8]	-

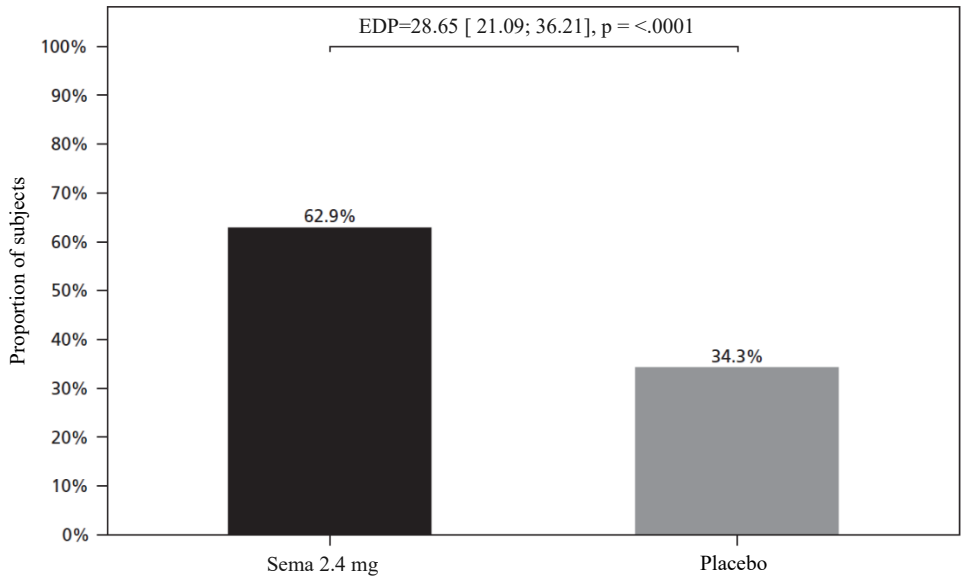
[1] Patients from sites with available equipment [2] Geometric mean

[3] Estimated using an ANCOVA model using multiple imputation based on unconditional reference.

[4] For patients with type 2 diabetes

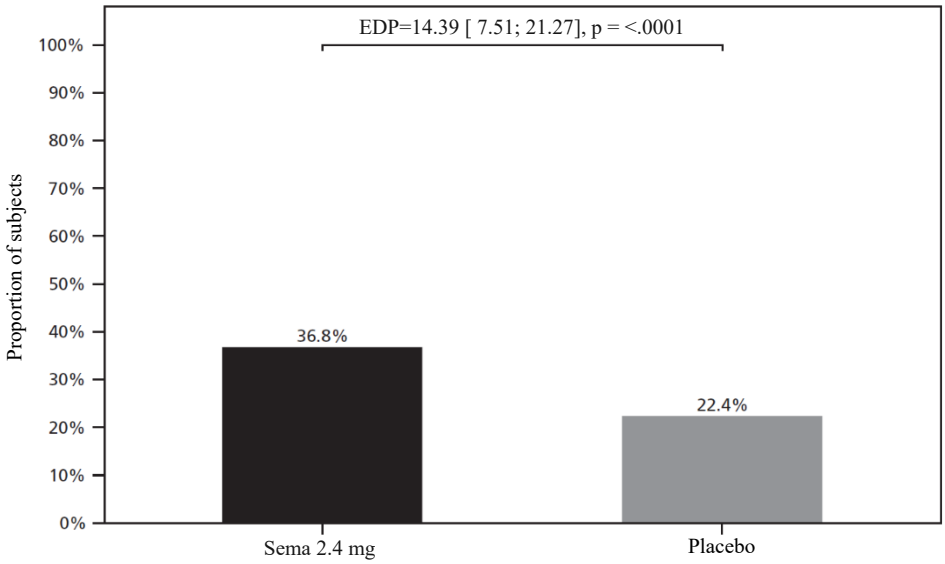
Secondary endpoints are not under multiplicity control.

Figure 9 ESSENCE – Resolution of steatohepatitis and no worsening of liver fibrosis[15]



CMH: Cochran-Mantel-Haenszel, EDP: Estimated difference in responder proportions, FAS: Full analysis set for interim, MI: Multiple imputation, NAFLD: Non-alcoholic fatty liver disease, NAS: NAFLD activity score, NASH CRN: Non-Alcoholic Steatohepatitis Clinical Research Network. CMH test stratified by baseline diabetes status and baseline fibrosis stage. Missing data in any treatment group will be handled by MI that is informed by data from placebo subjects. Subjects who experience a liver-related clinical event, including death, before the week 72 visit will be handled as non-responders. No worsening of liver fibrosis is defined as no increase in fibrosis score. Fibrosis is graded on the NASH CRN fibrosis scale from 0-4. Resolution of steatohepatitis is defined as a NAS of 0-1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN.

Figure 10 ESSENCE – Improvement in liver fibrosis and no worsening of steatohepatitis[16]

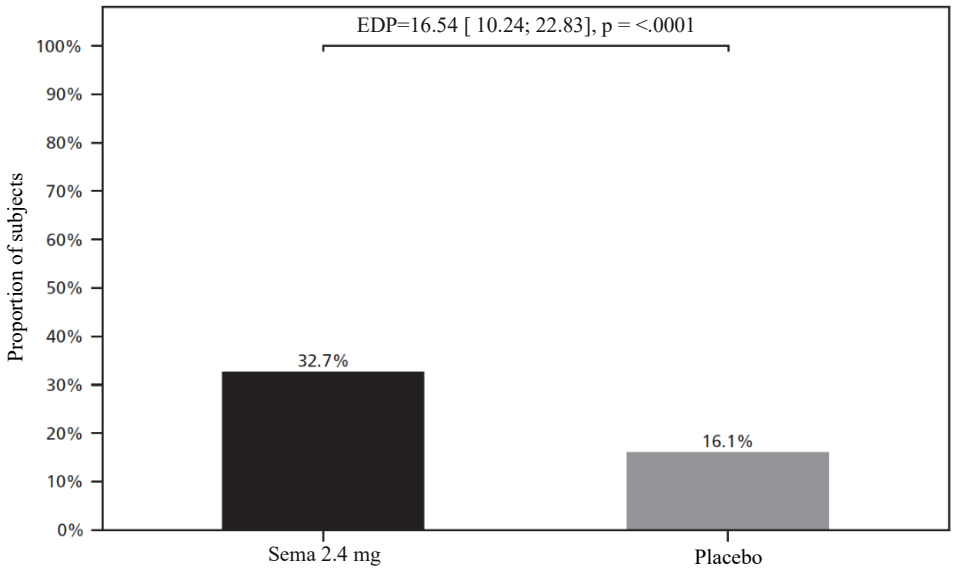


CMH: Cochran-Mantel-Haenszel, EDP: Estimated difference in responder proportions, FAS: Full analysis set for interim, MI: Multiple imputation, NAFLD: Non-alcoholic fatty liver disease, NAS: NAFLD activity score, NASH CRN: Non-Alcoholic Steatohepatitis Clinical Research Network. CMH test stratified by baseline diabetes status and baseline fibrosis stage. Missing data in any treatment group will be handled by MI that is informed by data from placebo subjects. Subjects who experience a liver-related clinical event, including death, before the week 72 visit will be handled as non-responders. Improvement in fibrosis is defined as >= 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation or steatosis.

[15] Module 5.3.5.1: NN9931-4553 CTR (interim) redacted, Section 5.1.2.1, Figure 5-1.

[16] Module 5.3.5.1: NN9931-4553 CTR (interim) redacted, Section 5.1.2.2, Figure 5-2.

Figure 11 ESSENCE – Resolution of steatohepatitis and improvement in liver fibrosis[17]



CMH: Cochran-Mantel-Haenszel, EDP: Estimated difference in responder proportions, FAS: Full analysis set for interim, MI: Multiple imputation, NAS: NAFLD activity score, NASH CRN: Non-Alcoholic Steatohepatitis Clinical Research Network. CMH test stratified by baseline diabetes status and baseline fibrosis stage. Missing data in any treatment group will be handled by MI that is informed by data from placebo subjects. Subjects who experience a liver-related clinical event, including death, before the week 72 visit will be handled as non-responders. IMP: Subjects with an imputed week 72 assessment. Resolution of steatohepatitis is defined as a NAS of 0-1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN.

Trial NN9931-4296

In a phase 2, 72-week, multinational, multicentre, randomised, double-blind, six-armed, parallel-group, placebo-controlled, multiple-dose trial, 320 patients with MASH and F1, F2 or F3 were randomised in a 3:3:3:1:1:1 ratio to semaglutide s.c. 0.1 mg (n=80 patients), 0.2 mg (n=78 patients), 0.4 mg (n=82 patients) once daily or to the corresponding injection volumes of placebo (n=80 patients). At baseline, 28.1 % hadF1, 22.5% had F2 and 49.4% had F3, while the mean age was 55 years, the mean BMI was 35.8 kg/m2, and 62.2% had type 2 diabetes.
At week 72, semaglutide s.c. 0.4 mg once daily (comparable to s.c. 2.4 mg once weekly) was superior to placebo at inducing resolution of steatohepatitis with no worsening of liver fibrosis compared with placebo in patients with MASH and F2 or F3. [18]

STEP UP and STEP UP T2D: Weight management with higher dose of semaglutide.

In two 72-week double-blinded clinical trials, 1407 patients with obesity (STEP UP) and 514 patients with obesity and type 2 diabetes (STEP UP T2D) were randomised 5:1:1 (STEP UP) or 3:1:1 (STEP UP T2D) to semaglutide 7.2 mg, semaglutide 2.4 mg or placebo once weekly. All patients were on a reduced-calorie diet and increased physical activity throughout the trials.

At baseline in STEP UP, patients had a mean age of 47 years, mean BMI of 39.9 kg/m^2, and a mean body weight of 113 kg. There were 26.3% males, 73.7 females, 85.5% Caucasian/white, 8.6% black/African American, 4.5% Asian and 1.2% other. A total of 4.5% were Hispanic or Latino.

[17] Module 5.3.5.1: NN9931-4553 CTR (interim) redacted, Section 5.1.3.2, Figure 5-5.

[18] Module 5.3.5.1: NN9931-4296 CTR, Sections 10.1, 10.2, 11.2, 11.3 and 11.5.

At baseline in STEP UP T2D, patients had a mean age of 56 years, mean BMI of 38.6 kg/m^2, and a mean body weight of 110.1 kg. There were 48.2% males, 51.8% females, 83.6% Caucasian/white, 8.6% black/African American, 6.3% Asian, and 1.6% other. A total of 5.7% were Hispanic or Latino.

In the two trials STEP UP and STEP UP T2D, at end of treatment (week 72), the weight loss with semaglutide 7.2 mg injection was superior and clinically meaningful compared to placebo (See Table 15 and

Figure ***12*** and Figure 13). Furthermore, a higher proportion achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with semaglutide 7.2 mg compared to placebo.

In STEP UP, the weight loss with semaglutide 7.2 mg injection was superior compared with semaglutide 2.4 mg injection based on a higher proportion of participants who achieved ≥20% and ≥25% weight loss compared with semaglutide 2.4 mg injection (See Table 15). Additionally, among patients with pre-diabetes at baseline, 83.4% and 36.6% achieved a normo-glycaemic status at end of treatment with semaglutide 7.2 mg injection and placebo, respectively.

Table 15 Results of a 72-week trial comparing Wegovy 7.2 mg injection with Wegovy 2.4 mg or placebo in adults with obesity (STEP UP) or obesity and T2D (STEP UP T2D)

	STEP UP			**STEP UP T2D**	
	Wegovy 7.2 mg injection	**Wegovy 2.4 mg injection**	**Placebo**	**Wegovy 7.2 mg injection**	**Placebo**
Full analysis set (N)	1005	201	201	307	102
Body weight / composition					
Baseline (kg)	112.4	116.5	112.4	110.5	112.1
Change (%) from baseline[a]	-18.7	-15.6	-3.9	-13.2	-3.9
Change (%) from baseline - Trial product estimand[b]	-20.7	-17.5	-2.4	-14.1	-3.6
Difference (%) from placebo[a] [95% CI]	-14.8 [-16.2; -13.4]*	-	-	-9.3 [-11.0; -7.7]*	-
Difference (%) from 2.4 mg[a] [95% CI]	-3.1 [-4.7; -1.6]*	-	-	-	-
Change (kg) from baseline	-20.9	-17.3	-4.6	-14.5	-4.3
Difference (kg) from placebo[a] [95% CI]	-16.3 [-17.9; -14.8]*	-	-	-10.2 [-12.1; -8.4]*	-
Patients (%) achieving weight loss ≥5%[c]	90.7	89.9	36.8	86.3	34.7
Patients (%) achieving weight loss ≥10%[c]	82.4	75.1	20.5	62.9	11.6
Patients (%) achieving weight loss ≥15%[c]	66.5	54.5	7.6	41.2	7.4
Patients (%) achieving weight loss ≥20%[c,d]	47.7	33.3	2.9	21.3	2.1
Patients (%) achieving weight loss ≥25%[c,e]	31.2	15.3	0	-	-
Waist circumference (cm)					
Baseline	118.4	120.3	118.6	121.8	123.9
Change from baseline[a]	-17.5	-14.6	-5.9	-12.3	-5.8
Difference from placebo[a] [95% CI]	-11.7 [-13.0; -10.4]*	-	-	-6.5 [-9.0; -4.1]*	-

Cardiometabolic factors					
Systolic blood pressure (mmHg)					
Baseline	131	129	130	134	132
Change from baseline[a]	-9.9	-8.7	-4.5	-7.4	-3.4
Difference from placebo[a] [95% CI]	-5.4 [-7.3; -3.6]*	-	-	-4.0 [-6.7; -1.2]*	-
Diastolic blood pressure (mmHg)					
Baseline	84	83	83	82	82
Change from baseline[a]	-4.5	-3.0	-2.1	-2.9	-2.6
Difference from placebo[a] [95% CI]	-2.4 [-3.8; -1.1]*	-	-	-0.3 [-2.0; 1.5]*	-
Lipids					
Total cholesterol (mmol/L)					
Baseline	5.0	4.9	5.0	4.5	4.6
Change (%) from baseline[a]	-5.0	-4.6	-0.0	-2.8	-0.6
Relative Difference (%) from placebo[a] [95% CI]	-5.0 [-9.8; 0.1]*	-	-	-2.2 [-7.4; 3.4]*	-
LDL cholesterol (mmol/L)					
Baseline	3.0	3.0	3.0	2.4	2.4
Change (%) from baseline[a]	-6.8	-6.8	-1.4	0.1	-0.6
Relative Difference (%) from placebo[a] [95% CI]	-5.5 [-10.6; -0.1]*	-	-	0.7 [-7.4; 9.6]*	-
HDL cholesterol (mmol/L)					
Baseline	1.3	1.2	1.3	1.1	1.1
Change (%) from baseline[a]	8.3	5.6	1.9	9.3	6.1
Relative Difference (%) from placebo[a] [95% CI]	6.3 [-3.7; 17.3]*	-	-	3.0 [-0.9; 7.1]*	-
Triglycerides (mmol/L)					
Baseline	1.4	1.4	1.4	2.0	2.0
Change (%) from baseline[a]	-22.9	-15.8	-0.9	-26.9	-9.0
Relative Difference (%) from placebo[a] [95% CI]	-22.2 [-28.3; -15.6]*	-	-	-19.6 [-27.3; -11.2]*	-
High-sensitivity c-reactive protein (hsCRP) (mg/L)					
Baseline	4.4	4.6	4.5	4.2	4.1
Change (%) from baseline[a]	-60.1	-57.7	-9.6	-51.7	-19.4
Relative Difference (%) from placebo[a] [95% CI]	-55.9 [-63.2; -47.2]	-	-	-40.1 [-51.7; -25.7]	-
Glycaemic factors					
HbA_{1c} (%)					
Baseline	5.7	5.6	5.7	8.0	8.2

Change from baseline[a]	-0.3	-0.3	-0.02	-1.7	-0.2
Difference from placebo[a] [95% CI]	-0.3 [-0.4; -0.2]*	-		-1.5 [-1.8; -1.2]*	-
FPG (mmol/L)					
Baseline	5.4	5.5	5.4	9.6	9.8
Change from baseline[a]	-0.6	-0.6	-0.1	-3.3	-1.0
Difference from placebo[a] [95% CI]	-0.5 [-0.6; -0.4]*	-		-2.3 [-3.0; -1.6]*	-
Glycaemic status					
Patients (%) with pre-diabetes at baseline	37.6	-	40.8	-	-
Patients (%) achieving normo-glycaemic status at end of treatment	83.4	-	36.6	-	-

[*] p<0.0001 (unadjusted 2-sided) for superiority.

[a] Estimated using an ANCOVA model using multiple imputations based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

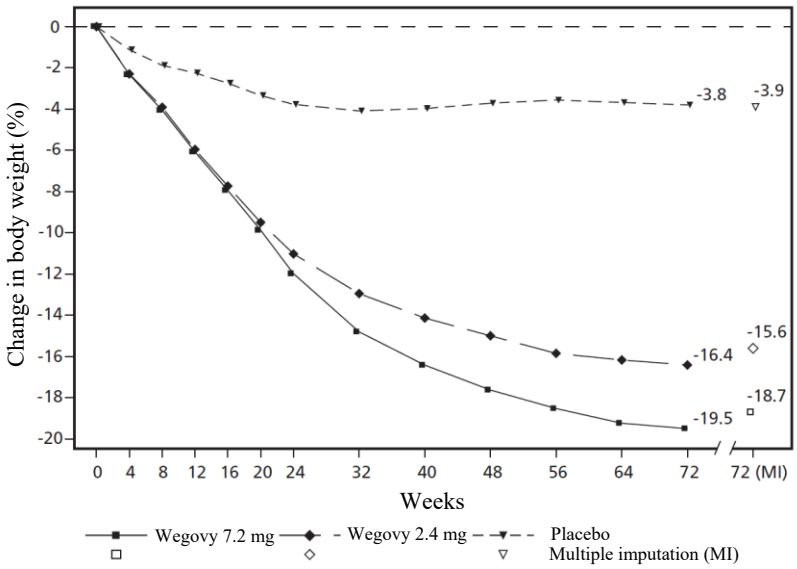
[b] Estimated changes are from randomisation to week 72 using Mixed Model for Repeated Measures that includes all observations until first treatment discontinuation, assuming all randomised patients stayed on treatment and did not initiate other anti-obesity medication or bariatric surgery.

[c] Observed proportions of patients based on in-trial period (uninterrupted period from the date of randomisation until the last trial visit), regardless of discontinuation, dose reduction, or initiation of other anti-obesity medication or bariatric surgery.

[d] Observed proportion of patients based on on-treatment (excluding any off-treatment data triggered by at least two consecutive missed doses), achieved greater than or equal to 20% reduction in body weight among 50.9%, 35.1% and 2.9% of patients randomised Wegovy 7.2 mg injection, Wegovy 2.4 mg injection, and placebo, respectively in STEP UP study.

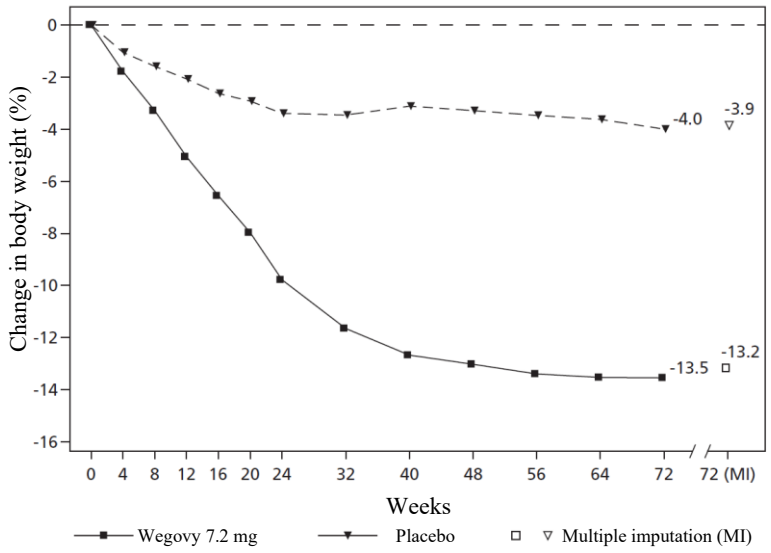
[e] Observed proportion of patients based on on-treatment (excluding any off-treatment data triggered by at least two consecutive missed doses), achieved greater than or equal to 25% reduction in body weight among 33.2%, 16.7% and 0% of patients randomised Wegovy 7.2 mg injection, Wegovy 2.4 mg injection, and placebo, respectively in STEP UP study

Figure 12 STEP UP: Mean change in body weight (%) from week 0 to week 72



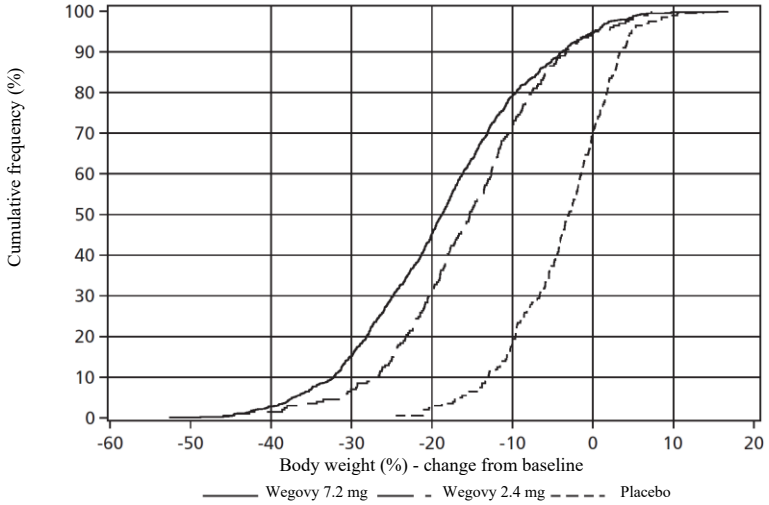
Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Figure 13 STEP UP T2D: Mean change in body weight (%) from week 0 to week 72



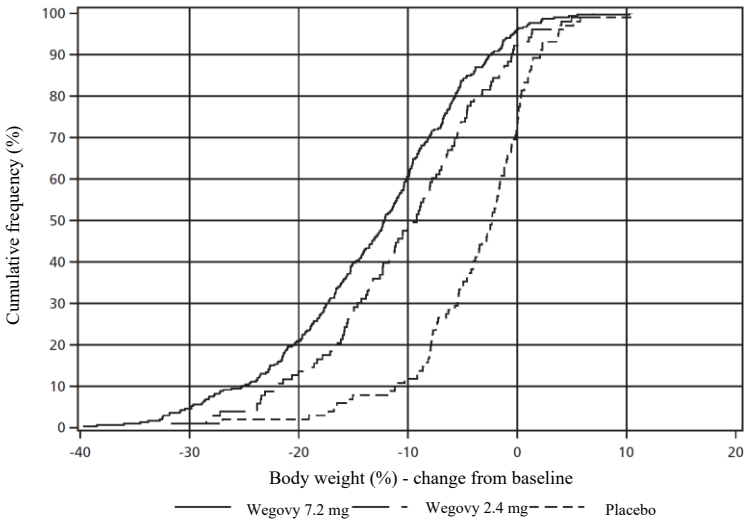
Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Figure 14 STEP UP – Cumulative distribution of change (%) in body weight after 72 weeks of treatment



Observed data from in-trial period including imputed data for missing observations. RD-MI: Missing observations were multiply (x1000) imputed from retrieved participants of the same randomised treatment arm and missing value replaced by the average across imputation

Figure 15 STEP UP T2D - Cumulative distribution of change (%) in body weight after 72 weeks of treatment



Observed data from in-trial period including imputed data for missing observations. RD-MI: Missing observations were multiply (x1000) imputed from retrieved participants of the same randomised treatment arm and missing value replaced by the average across imputation

OASIS 4: Weight management – once daily Wegovy tablet

In a 64-week, double-blind, phase 3b trial, 307 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbidity, were randomised to once daily Wegovy tablets or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

At baseline, patients had a mean BMI of 37.6 kg/m2 and a mean body weight of 105.9 kg. The mean age of patients was 48 years. There were 91.5% White, 7.2% Black/African American, and 0.7% Asian. The majority of patients had at least one weight-related comorbidity. These included, but were not limited to, pre- diabetes (46.9%), dyslipidaemia (30.3%), hypertension (43.3%), knee or hip osteoarthritis (7.8%), obstructive sleep apnoea (8.8%), asthma (9.1%) and liver disease (metabolic dysfunction-associated fatty liver disease [MAFLD] or metabolic dysfunction-associated steatohepatitis [MASH]) (4.2%). Weight loss occurred early and continued throughout the trial. At end of treatment (week 64), the weight loss was superior and clinically meaningful compared with placebo (see Table 16 and Figure 16).

Furthermore, a higher proportion of patients achieved ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% weight loss with orally administered semaglutide compared with placebo (see Table 3). Among patients with prediabetes at baseline, a higher proportion of patients had a normo-glycaemic status at end of treatment with orally administered semaglutide compared to placebo (71.1% vs. 33.3%).

Table 16 OASIS 4: Results at week 64

	Semaglutide 25 mg tablet	**Placebo**
Full analysis set (N)	205	102
Body weight		
Baseline (kg)	106.4	104.8
Change (%) from baseline[1,2]	-13.6	-2.2
Difference (%) from placebo[1] [95% CI]	-11.4 [-13.9; -9.0]*	
Change (kg) from baseline[1]	-14.2	-2.2
Difference (kg) from placebo[1] [95% CI]	-12.0 [-14.6; -9.5]*	
Patients (%) achieving weight loss ≥ 5%[3]	76.3*	30.5
Patients (%) achieving weight loss ≥ 10%[3]	59.8*	14.1
Patients (%) achieving weight loss ≥ 15%[3]	47.0*	5.4
Patients (%) achieving weight loss ≥ 20%[3]	27.5*	3
Waist circumference (cm)		
Baseline	114	113.6
Change from baseline[1]	-12.2	-2.8
Difference from placebo[1] [95% CI][1]	-9.5 [-12.4; -6.6]*	
BMI (kg/m^2)		
Baseline	37.5	37.8
Patients (%) achieving BMI <30kg/m^2 [3]	26.0*	2.9
Systolic blood pressure (mmHg)		
Baseline	131	131
Change from baseline[1]	-6.8	-5.4
Difference from placebo[1] [95% CI]	-1.4 [-4.6; 1.8]	
Diastolic blood pressure (mmHg)		
Baseline	83	83
Change from baseline[a]	-2.7	-2.1
Difference from placebo [95% CI]	-0.7 [-2.8; 1.5]	
Lipids		
Total cholesterol		

Baseline (mmol/L)	5.0	4.9
Change (%) from baseline	-4.1	-1.4
Relative Difference (%) from placebo [95% CI]	-2.7 [-6.8;1.5]	
LDL cholesterol		
Baseline (mmol/L)	3.0	2.9
Change (%) from baseline	-4.4	0.2
Relative Difference (%) from placebo [95% CI]	-4.6 [-10.6;1.7]	
HDL cholesterol		
Baseline (mmol/L)	1.3	1.3
Change (%) from baseline	3.1	-0.4
Relative Difference (%) from placebo [95% CI]	3.5 [-0.7;7.9]	
Triglycerides		
Baseline (mmol/L)	1.3	1.3
Change (%) from baseline	-18.4	-7.5
Relative Difference (%) from placebo [95% CI]	-11.8 [-20.2;-2.5]	
CRP		
Baseline (mg/L)	3.6	3.8
Change (%) from baseline	-46.4	-4.2
Relative Difference (%) from placebo [95% CI]	-44.0 [-57.8;-25.7]	
Glycaemic factors		
HbA1c (mmol/mol)		
Baseline	38.3	38.4
Change from baseline	-3.2	-0.7
Difference from placebo [95% CI]	-2.5 [-3.4; -1.6]	-
FPG (mg/dL)		
Baseline	95.4	95.7
Change from baseline	-6.6	-0.4
Difference from placebo [95% CI]	-7.0 [-11.2; -2.8]	-
Glycaemic status		
Patients (%) with pre-diabetes at baseline	97 (47.3)	47 (46.1)
Patients (%) achieving normo-glycaemic status at end of treatment	64 (71.1)	13 (33.3)

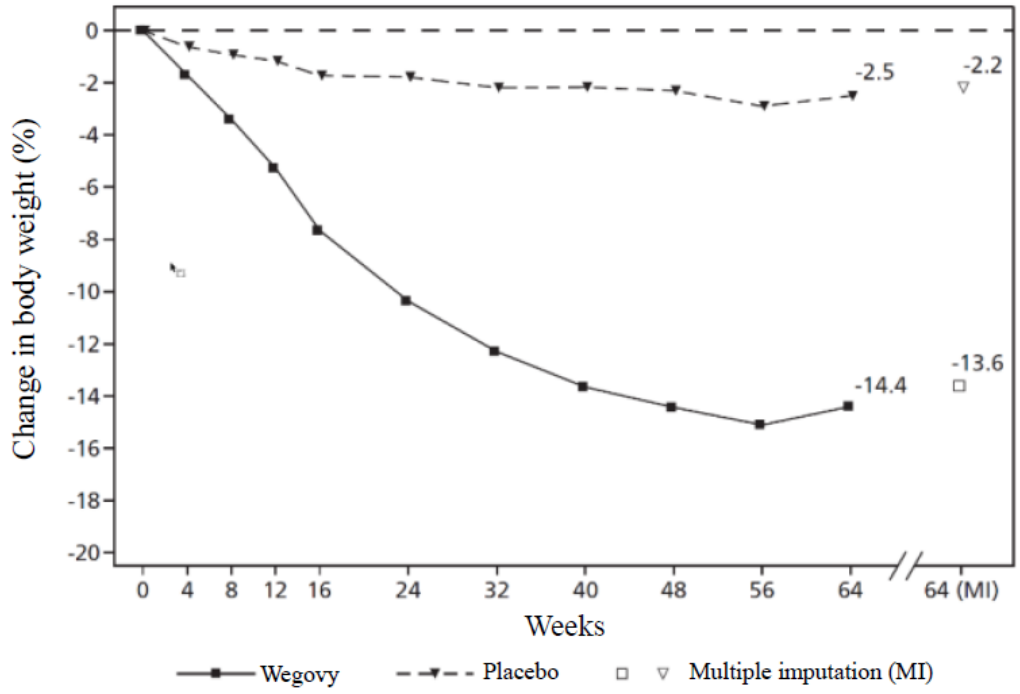
* p<0.0001 (unadjusted 2-sided) for superiority.

[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of premature discontinuation of randomised treatement or initiation of other anti-obesity medication or bariatric surgery.

[2] During the trial, randomised treatment was permanently discontinued by 18% and 25.5% of patients randomised to oral semaglutide 25 mg and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 64 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -16.6% and -2.8% for oral semaglutide 25 mg and placebo respectively.

[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

Figure 16 OASIS 4: Mean change in body weight (%) from baseline to week 64. Body weight (%) change from baseline by week - mean plot - treatment policy strategy - full analysis set



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts.

Body weight

Across all weight management trials, treatment with Wegovy demonstrated clinically meaningful and sustained weight loss for up to 104 weeks compared to placebo in patients with obesity or overweight. In the weight management phase 3a trials, the reduction in body weight was shown to occur irrespective of the presence of gastrointestinal symptoms such as nausea, vomiting or diarrhoea. In ESSENCE, treatment with Wegovy resulted in superior, clinically meaningful and sustained weight loss compared with placebo in patients with MASH and F2 or F3. [19]

Cardiovascular risk factors

Wegovy reduced waist circumference, systolic blood pressure and CRP, and improved lipid profile compared with placebo in the weight management phase 3a trials. Similar results were observed for waist circumference, systolic blood pressure and CRP in the ESSENCE trial after 72 weeks of treatment with semaglutide in patients with MASH and F2 or F3.

Lipids

- STEP results only

Wegovy improved total cholesterol by -0.9% to -5.9%, HDL-cholesterol by 0.3% to 3.8% LDL-cholesterol by 0.4% to -7.1%, and triglycerides by -17.8% to -15.8%, after 68 weeks of treatment in the weight management phase 3a trials.

Blood Pressure

- STEP results only

[19] NN9931 Summary 2.7.3 interim (redacted), Section 3.4.1, p. 81-83

Wegovy reduced systolic and diastolic blood pressure by 3.4 mmHg to 5.1 mmHg and 0.7 mmHg to 2.4 mmHg respectively after 68 weeks of treatment in the weight management phase 3a trials.

- OASIS 4 results only

Wegovy reduced systolic and diastolic blood pressure by 1.39 mmHg and by 0.65 mmHg respectively after 64 weeks of treatment.

Waist circumference

- STEP results only

Wegovy reduced waist circumference by 4.9 cm to 9.4 cm after 68 weeks of treatment in the weight management phase 3a trials.

- OASIS 4 results only

Wegovy reduced waist circumference by 9.5 cm after 64 weeks of treatment.

C-Reactive Protein (CRP)

- STEP results only

Wegovy reduced CRP (marker of systemic inflammation) by 38.7% to 47.6% after 68 weeks of treatment in the weight management phase 3a trials.

- OASIS 4 results only

Wegovy reduced CRP by 44% after 64 weeks of treatment.

Cardiovascular outcomes

- SELECT: Cardiovascular outcome trial in patients with overweight or obesity

SELECT was a randomised, double-blind, placebo-controlled, event driven trial which included 17,604 patients with established cardiovascular disease (67.6 % with prior myocardial infarction only, 17.8 % with prior stroke only and 4.4 % with peripheral arterial disease only; 8.2 % with 2 or more prior CV events) and BMI≥27 kg/m^2. Patients with history of type 1 and type 2 diabetes were excluded. The median time in trial was 41.8 months. The study population consisted of 27.7 % female and 72.3 % male, with a mean age of 61.6 years, including 38.2 % patients ≥ 65 years (n = 6,728) and 7.8 % patients ≥ 75 years (n = 1,366). The mean BMI was 33.3 kg/m^2 and mean body weight was 96.7 kg.

Patients were randomised to either semaglutide 2.4 mg (n=8,803) or placebo (n=8,801) in addition to standard-of-care. At baseline, 92.0 % of patients were receiving cardiovascular medication (70.2 % beta blockers, 45.0 % Angiotensin-Converting Enzyme (ACE) inhibitors, 29.5 % angiotensin receptor blockers and 26.9 % calcium-channel blockers), 90.1 % lipid lowering agents (primarily statins 87.6 %) and 86.2 % anti-platelet agents.

At baseline most patients had cardiovascular related comorbidities including 66.5 % with HbA_{1c} ≥ 5.7% indicative of prediabetes, 24.3 % with chronic heart failure, 81.8 % with hypertension, 46.8 % with inflammation (hsCRP ≥ 2 mg/L) as well as patients with mild (48.7 %), moderate (10.4 %) or severe (0.4 %) renal impairment.

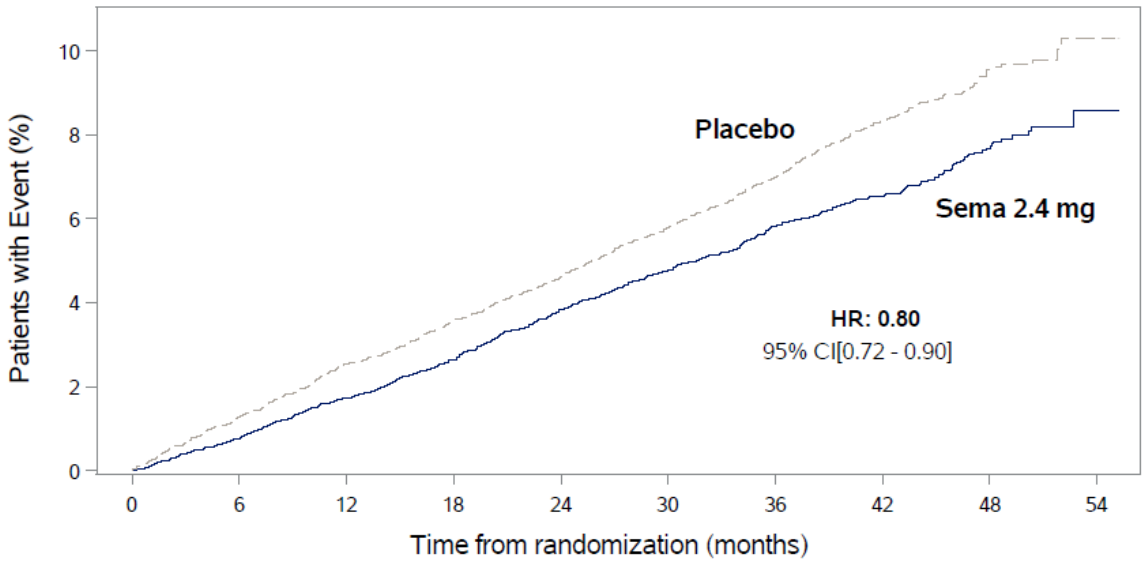
For the primary MACE endpoint, the superiority of semaglutide 2.4 mg to placebo was confirmed demonstrated with a hazard ratio 0.80 [0.72; 0.90] [95% CI], corresponding to a relative risk reduction in MACE of 20 % (see Figure 17). The primary MACE endpoint results showed statistical

significance for one out of the three components, namely non-fatal MI, but not for CV death or non-fatal stroke (Figure 18).

Each component contributed to the reduction of MACE (Figure 18). The cardiovascular risk reduction appeared largely independent of weight loss.

The treatment effect was consistent across all subgroups defined by age, sex, race, ethnicity, region, prior CV disease (MI, stroke, PAD, or any combination thereof), BMI, chronic heart failure status, HbA1c (<5.7% or ≥5.7%), and renal function (eGFR <60 mL/min/1.73m^2 or ≥60mL/min/1.73m^2).

Figure 17 Cumulative incidence function plot – Time from randomisation to first MACE

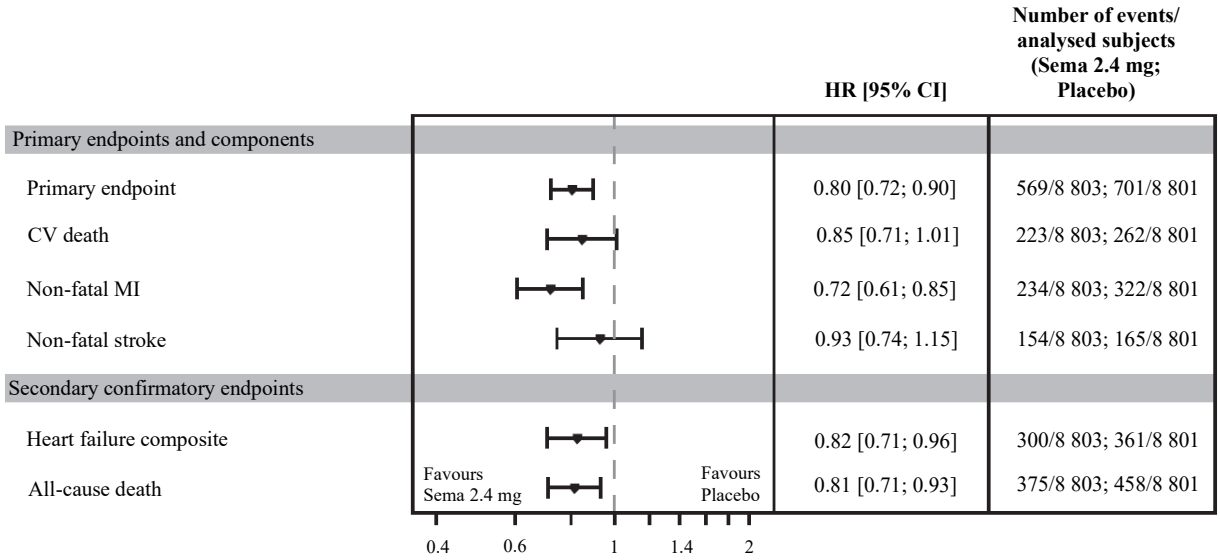


Patients at risk

Sema 2.4 mg	**8803**	**8695**	**8561**	**8427**	**8254**	**7229**	**5777**	**4126**	**1734**	**71**
Placebo	**8801**	**8652**	**8487**	**8326**	**8164**	**7101**	**5660**	**4015**	**1672**	**59**

Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed MACE with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period. Time from randomisation to first MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. The hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering.
HR: hazard ratio CI: Confidence interval.
CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

Figure 18 Forest plot of time from randomisation to first MACE, MACE components and secondary confirmatory endpoints



Data from the in-trial period. Time from randomisation to each endpoint was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. Subjects without events of interest were censored at the end of their in-trial period. For the primary endpoint the HR and CI were adjusted for the group sequential design using likelihood ratio ordering. Secondary endpoints are not under multiplicity control. CV death includes both cardiovascular death and undetermined cause of death.
HR: hazard ratio CI: Confidence interval.
CV: cardiovascular, MI: myocardial infarction.

During the duration of the SELECT trial, 3.5% (n=306) of patients in the semaglutide arm had an HbA1c >6.5% compared to 12% (n=1059) on the placebo arm. The mean changes in selected anthropometric and cardiometabolic parameters at Week 104 in SELECT are shown in **Error! Reference source not found.**.

Table 17 SELECT – Cardiovascular risk factors assessed at week 104

	Wegovy	**Placebo**
Full analysis set (N)	8803	8801
Cardiometabolic factors		
Systolic blood pressure (mmHg)		
Baseline Mean (SD)	131.0 (15.6)	130.9 (15.3)
Change from baseline[1]	-3.82	-0.51
Difference from placebo [95% CI][1]	-3.31 [-3.75; -2.88]	-
Diastolic blood pressure (mmHg)		
Baseline Mean (SD)	79.4 (10.0)	79.2 (9.9)
Change from baseline[1]	-1.02	-0.47
Difference from placebo [95% CI][1]	-0.55 [-0.83; -0.27]	-
Lipids		
Total cholesterol		
Baseline (mmol/L) Geom. Mean (CV)	4.03 (25.82)	4.04 (25.41)
Change (%) from baseline[1]	-4.63	-1.92
Relative difference (%) from placebo[1]	-2.77 [-3.37; -2.16]	-
LDL cholesterol		
Baseline (mmol/L)	2.03 (43.70)	2.03 (43.56)

Geom. Mean (CV)		
Change (%) from baseline[1]	-5.25	-3.14
Relative difference (%) from placebo [95% CI][1]	-2.18 [-3.22; -1.12]	-
HDL cholesterol		
Baseline (mmol/L) Geom. Mean (CV)	1.14 (25.52)	1.15 (25.02)
Change (%) from baseline[1]	4.86	0.59
Relative difference (%) from placebo [95% CI][1]	4.24 [3.70; 4.79]	-
Triglycerides		
Baseline (mmol/L) Geom. Mean (CV)	1.56 (51.75)	1.57 (50.84)
Change (%) from baseline[1]	-18.34	-3.20
Relative difference (%) from placebo [95% CI][1]	-15.64 [-16.7; -14.6]	-
hsCRP		
Baseline (mmol/L) Geom. Mean (CV)	1.96 (162.90)	1.91 (158.22)
Change (%) from baseline[1]	-39.12	-2.08
Relative difference (%) from placebo [95% CI][1]	-37.82 [-39.7; -35.9]	-
Weight-related CV risk factors		
Body weight (%)		
Baseline (kg) Mean (SD)	96.53 (17.52)	96.82 (17.80)
Change from baseline[1]	-9.39	-0.88
Difference from placebo [95% CI][1]	-8.51 [-8.75; -8.27]	-
Waist circumference (cm)		
Baseline Mean (SD)	111.3 (13.1)	111.4 (13.1)
Change from baseline[1]	-7.56	-1.03
Difference from placebo [95% CI][1]	-6.53 [-6.79; -6.27]	-
Glycaemic factors		
HbA_{1c} (%)		
Baseline Mean (SD)	5.78 (0.34)	5.78 (0.33)
Change from baseline[1]	-0.31	0.01
Difference from placebo [95% CI][1]	-0.32 [-0.33; -0.31]	-

[1]The responses were analysed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. Mean estimates were adjusted according to observed baseline distribution.

In the SELECT cardiovascular outcomes trial, 6442 patients at risk of MASH-related fibrosis were identified based on pre-specified criteria (baseline FIB-4 score ≥ 1.3 and exclusion of other disease drivers). A similar risk reduction for MACE was observed for this subpopulation compared with the overall SELECT population.

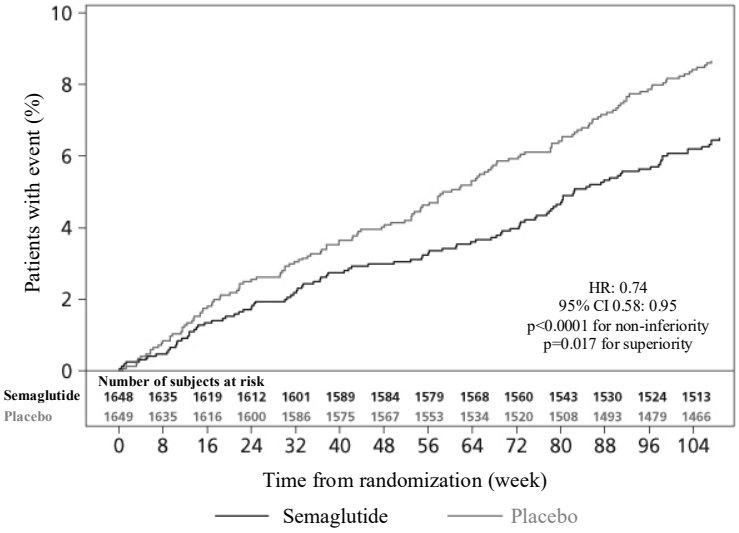
SUSTAIN 6: Cardiovascular outcome trial in patients with type 2 diabetes unrelated to weight loss

In the SUSTAIN 6 trial for OZEMPIC (semaglutide) for a type 2 diabetes indication unrelated to weight loss, 3,297 patients with type 2 diabetes and at high risk of cardiovascular events were randomised to semaglutide s.c. 0.5 mg or 1 mg once-weekly or placebo in addition to standard-of-care. The treatment duration was 104 weeks. The mean age was 65 years and the mean BMI was 33 kg/m^2.

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 the primary component MACE endpoint was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo.

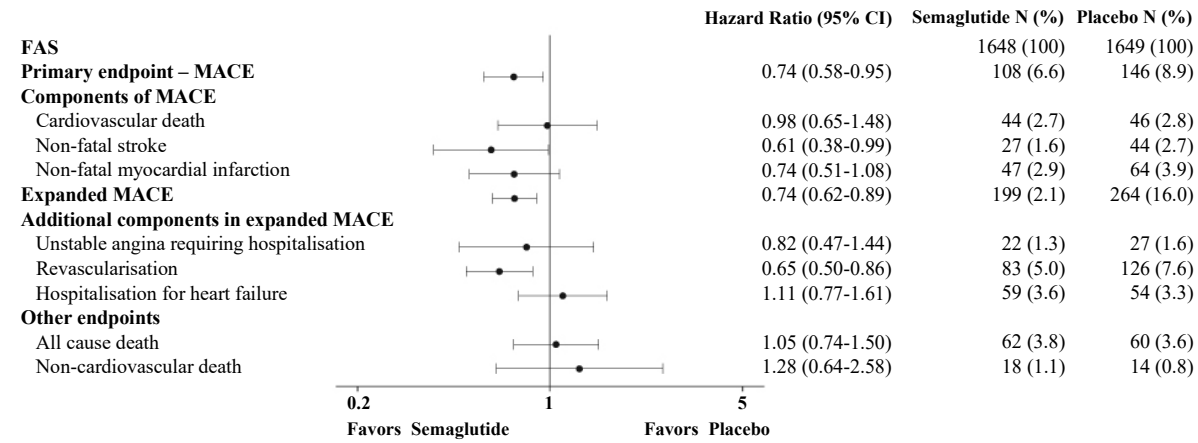
Treatment with semaglutide reduced the rate of MACE vs placebo with a risk reduction of 26%, HR 0.74, [0.58, 0.95] [95% CI]. This was mainly driven by a significant (39%) decrease in the rate of non-fatal stroke and a non-significant (26%) decrease in non-fatal myocardial infarction with no difference in cardiovascular death (see Figure 19).

Figure 19 Kaplan-Maier plot of time to first occurrence of the composite outcome: Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)



Semaglutide also significantly reduced the risk of a composite of coronary or peripheral revascularisation. See Figure 20 for results on primary and secondary cardiovascular endpoints.

Figure 20 Forest plot: Analyses of each individual cardiovascular event types (SUSTAIN 6)



Glycaemic control
Treatment with Wegovy significantly improved glycaemic parameters in patients with type 2 diabetes (Table 18).

Wegovy improved glycaemic control through sustained reduction of HbA_{1c} and fasting plasma glucose (FPG) levels. Reduction in HbA_{1c} was 1.2% and reduction in FPG was 2.0 mmol/L in STEP 2.

In STEP 2, 78.5% of patients with type 2 diabetes treated with Wegovy achieved an HbA_{1c} <7% compared to 26.5% with placebo. A total of 67.5% of the patients treated with Wegovy achieved an HbA_{1c} ≤6.5% compared to 15.5% with placebo.

In STEP 1, STEP 3 and STEP 5, among those patients with pre-diabetes at baseline, more Wegovy-treated patients had achieved normo-glycaemic status by the end of the trials (week 68 or week 104) compared to placebo-treated patients (STEP 1: 84.1% vs 47.8%; STEP 3: 89.5% vs 55.0%; STEP 5: 80% vs 37%).

Table 18 Results on glycaemic factors in STEP 1, 2 and 3

	STEP 1		**STEP 2**		**STEP** 3	
	Wegovy	**Placebo**	**Wegovy**	**Placebo**	**Wegovy**	**Placebo**
Full analysis set (N)	1306	655	404	403	407	204
Glycaemic factors						
HbA_{1c} (mmol/mol)						
Baseline	38.9	39.0	65.3	65.3	39.3	39.5
Change from baseline[1]	−4.9[2]	−1.7[2]	-17.5[3]	-4.1[3]	-5.6	-3.0
Difference from placebo[1] [95% CI]	−3.2 [−3.5; −2.9]	-	-13.5 [-15.5; -11.4]*	-	-2.6 [-3.1; -2.1]	-
FPG (mg/dL)						
Baseline	95.4	94.7	152.7	157.9	93.9	94.0
Change from baseline[1]	−8.4	−0.5	-38.0	-1.4	-6.7	-0.7
Difference from placebo[1] [95% CI]	−7.9 [−9.0; −6.7]	-	-36.6 [-43.2; -30.0]	-	-6.1 [-8.1; -4.0]	-

* p<0.0001 (unadjusted 2-sided) for superiority, [1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

In OASIS 4 (Wegovy tablet), among those patients with pre-diabetes at baseline, more Wegovy-treated patients had achieved normo-glycaemic status by the end of the trial (week 64) compared to placebo-treated patients (71.1% vs. 33.3%).

Paediatric Population

In a 68-week double-blind trial 201 pubertal adolescents, ages 12 to <18 years, with obesity or overweight and at least one weight-related comorbidity were randomised 2:1 to Wegovy or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

At baseline, patients had a mean BMI of 37.0 kg/m^2 and a mean body weight of 107.5 kg. The mean age of patients was 15.4 years. There were 37.8% males, 79.1% Caucasian/White, 8.0% Black/African American and 2.0% Asian. A total of 10.9% were Hispanic or Latino.

At end of treatment (week 68), the improvement in BMI with Wegovy was superior and clinically meaningful compared with placebo (see Table 19 and Figure 21). Furthermore, a higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with Wegovy compared with placebo (see Table 17). Also, improvement in weight category was seen for a larger proportion of patients with Wegovy (71.8%) compared to placebo (21.0%). Improvement was defined as changing from a higher to a lower obesity class, or to overweight or normal weight. At end of treatment, a higher proportion of patients with Wegovy (53.7%) changed at least 2 categories compared to placebo (3.8%).

Greater reductions in absolute BMI, BMI standard deviation score (SDS), BMI percentage of the 95th percentile (sex- and age-specific growth charts) and body weight were observed with Wegovy compared to placebo at week 68.

Table 19 Results of a 68-week trial comparing Wegovy with placebo in adolescents ages 12 years and above with obesity, or overweight and at least one weight-related comorbidity (STEP TEENS)

	Wegovy	**Placebo**
Full analysis set (N)	134	67
BMI		
Baseline (BMI)	37.7	35.7
Change (%) from baseline in BMI[1, 3]	-16.1	0.6
Difference (%) from placebo[1] [95% CI]	-16.7 [-20.3; -13.2]*	-
Baseline (BMI SDS)	3.4	3.1
Change from baseline in BMI SDS[1]	-1.1	-0.1
Difference from placebo[1] [95% CI]	-1.0 [-1.3; -0.8]	-
Baseline (BMI % of the 95th percentile)	133.8	127.8
Change from baseline in BMI percentage of the 95th percentile[1]	-24.6	-4.2
Difference from placebo[1] [95% CI]	-20.4 [-25.0; -15.8]	-
Body Weight		
Baseline (kg)	109.9	102.6
Change (%) from baseline[1]	-14.7	2.8
Difference (%) from placebo[1] [95% CI]	-17.4 [-21.1; -13.8]	-
Change (kg) from baseline[1]	-15.3	2.4
Difference (kg) from placebo[1] [95% CI]	-17.7 [-21.8; -13.7]	-
Patients (%) achieving weight loss ≥5%[4]	72.5*	17.7
Patients (%) achieving weight loss ≥10%[4]	61.8	8.1
Patients (%) achieving weight loss ≥15%[4]	53.4	4.8
Patients (%) achieving weight loss ≥20%[4]	37.4	3.2

	Wegovy	Placebo
Full analysis set (N)	134	67
Waist circumference (cm)		
Baseline	111.9	107.3
Change from baseline[1]	-12.7	-0.6
Difference from placebo[1] [95% CI]	-12.1 [-15.6; -8.7]	-
Cardiometabolic factors		
Systolic blood pressure (mmHg)		
Baseline	120	120
Change from baseline[1]	-2.7	-0.8
Difference from placebo[1] [95% CI]	-1.9 [-5.0; 1.2]	-
Diastolic blood pressure (mmHg)		
Baseline	73	73
Change from baseline[1]	-1.4	-0.8
Difference from placebo[1] [95% CI]	-0.6 [-3.0; 1.8]	-
Lipids		
Total cholesterol		
Baseline (mmol/L)	4.1	4.2
Change (%) from baseline[1]	-8.3	-1.4
Relative Difference (%) from placebo[1] [95% CI]	-7.1 [-10.5; -3.5]	-
LDL cholesterol		
Baseline (mmol/L)	2.3	2.4
Change (%) from baseline[1]	-9.9	-3.6
Relative Difference (%) from placebo[1] [95% CI]	-6.6 [-11.3; -1.6]	-
HDL cholesterol		
Baseline (mmol/L)	1.1	1.1
Change (%) from baseline[1]	8.0	3.2
Relative Difference (%) from placebo[1] [95% CI]	4.7 [-1.0; 10.7]	-
Triglycerides		
Baseline (mmol/L)	1.3	1.2
Change (%) from baseline[1]	-28.4	2.6
Relative Difference (%) from placebo[1] [95% CI]	-30.2 [-38.0; -21.5]	-
Glycaemic factors		
HbA_{1c} (%)[2]		
Baseline	5.5	5.4
Change from baseline[1]	-0.4	-0.1
Difference from placebo[1] [95% CI]	-0.2 [-0.3; -0.1]	-
FPG (mmol/L)[2]		
Baseline	5.0	5.0
Change from baseline[1]	-0.2	-0.02
Difference from placebo[1] [95% CI]	-0.2 [-0.3; -0.03]	-
ALT		
Baseline (U/L)	23	20

	Wegovy	Placebo
Full analysis set (N)	134	67
Change (%) from baseline[1]	-18.3	-4.9
Relative Difference (%) from placebo[1] [95% CI]	-14.1 [-25.2; -1.4]	-

* p<0.0001 (unadjusted 2-sided) for superiority.

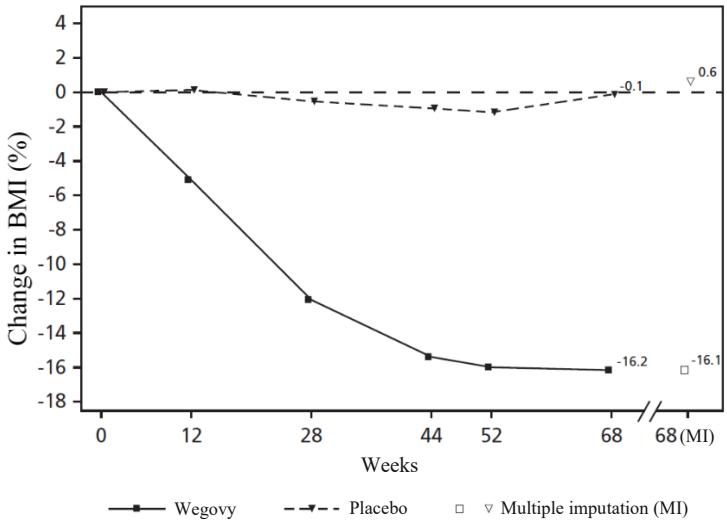
[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[2] The numbers are for patients without type 2 diabetes.

[3] During the trial, randomised treatment was permanently discontinued by 10.4% and 10.4% of patients randomised to Wegovy and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for BMI based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -17.9% and 0.6% for Wegovy and placebo, respectively

[4] Estimated from logistic regression model based on same imputation procedure as in primary analysis.

Figure 21 STEP TEENS – Mean change in BMI (%) from baseline to week 68



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Patient-reported outcomes

Physical functioning response

Wegovy showed statistically significant improvement in physical functioning scores and more patients with Wegovy achieved a clinically meaningful improvement compared to placebo in STEP 1 and STEP 2. Improvement in physical functioning score with Wegovy compared to placebo was also observed in STEP 3; however, not statistically significant (Table 20). Physical functioning was assessed using both the Short Form-36v2 Health Survey, Acute Version (SF-36v2) and the Impact of Weight on Quality of Life Lite Clinical Trials Version (IWQOL-Lite-CT).

Table 20 Results on physical functioning in STEP 1, 2 and 3

	STEP 1		STEP 2		STEP 3	
	Wegovy	Placebo	Wegovy	Placebo	Wegovy	Placebo
SF-36v2 Physical Functioning[1]						

Baseline	51.0	50.8	49.2	49.6	51.9	52.1
Change from baseline	2.2	0.4	2.5	1.0	2.4	1.6
Difference from placebo [95% CI]	1.8 [1.2; 2.4]*	-	1.5 [0.4; 2.6]*	-	0.8 [-0.2; 1.9]	
Patients (%) achieving clinically meaningful improvement[2,4]	39.8	24.1	41.0	27.3	36.3	25.5
IWQOL-Lite-CT Physical Function						
Baseline	65.4	64.0	67.1	69.2	-[5]	-[5]
Change from baseline	14.7	5.3	10.1	5.3	-[5]	-[5]
Difference from placebo [95% CI]	9.4 [7.5; 11.4]*	-	4.8 [1.8 ; 7.9]	-	-[5]	
Patients (%) achieving clinically meaningful improvement[3,4]	51.8	28.3	39.6	29.5	-[5]	-[5]

* p<0.0001 (unadjusted 2-sided) for superiority.

[1] Norm-based score.

[2] Change in norm-based score ≥3.7.

[3]Change in score ≥14.6.

[4]Estimated from binary regression model based on same imputation procedure as in primary analysis.

[5]IWQOL-Lite-CT was not applied in STEP 3.

Wegovy tablet showed statistically significant improvement in physical functioning scores and more patients with Wegovy achieved a clinically meaningful improvement compared to placebo (Table 1). Physical functioning was assessed using the obesity-specific questionnaire Impact of Weight on Quality of Life Lite Clinical Trials Version (IWQOL-Lite-CT).

Table 21 Results on physical functioning in OASIS 4

	OASIS 4	
	Wegovy tablet	**Placebo**
IWQOL-Lite-CT Physical Function		
Baseline	56.8	56.9
Change from baseline[a]	16.2(20.3)[b]	8.5(9.9)[b]
Difference from placebo [95% CI][a]	7.7*(10.4*) [3.3;12.2] ([5.3; 15.5])[b]	

Patients (%) achieving clinically meaningful improvement [c,d]	54.6 (67.9)[b]	33.7 (28.7)[b]

* p< 0.0001 (unadjusted 2-sided) for superiority; **p< 0.01 (unadjusted 2-sided) for superiority

[a] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery. During the trial, randomised treatment was permanently discontinued by 18.0% and 25.5% of patients randomised to Wegovy® tablet and placebo, respectively.
[b]Based on a Mixed Model for Repeated Measures assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, including all observations until first discontinuation.
[c] Change in score ≥ 14.6
[d] Estimated from logistic regression model based on same imputation procedures as for the primary and additional analysis.

In STEP TEENS, the clinical outcome assessments with the IWQOL-Kids questionnaire, improved (higher score) in favour of Wegovy at end of treatment (week 68) compared to baseline for all 4 domain scores and the total score. The estimated treatment differences for the physical comfort score and the total score were statistically significant in favour of Wegovy compared to placebo (Table 22).

Table 22 Results on physical comfort score in STEP TEENS

	Wegovy	**Placebo**
Physical comfort score		
Change from baseline	6.4	-0.3
Difference from placebo [95% CI]	6.6 [2.0; 11.2]	-
Total score		
Change from baseline	5.2	1.0
Difference from placebo [95% CI]	4.3 [0.2; 8.3]	-

Other patient reported outcomes
Beneficial effects of Wegovy vs placebo were demonstrated in STEP 1 and 2 in all additional scores on SF-36v2 (Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health, Physical Component Summary and Mental Component Summary), except for Role-Emotional in STEP 2. Beneficial effects of Wegovy vs. placebo were also demonstrated in STEP 1 and 2 in all additional scores on IWQOL-Lite-CT (Physical, Psychosocial, and Total). In STEP 3, beneficial effects of Wegovy vs. placebo were demonstrated for the following scores in SF-36: General Health, Vitality, Social Functioning, Role-Emotional and Mental Component Summary.

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 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.

Absorption
Solution for injection

The average semaglutide steady state concentration following s.c. administration of the 2.4 mg and 7.2 mg semaglutide maintenance dose was approximately 75 nmol/L and 236 nmol/L, respectively, in patients with either overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) or obesity (BMI ≥ 30 kg/m2) based on data from phase 3 trials, where 90% of patients had average concentrations between 51 nmol/L and 110 nmol/L and between 164 nmol/L and 332 nmol/L, respectively. The steady state exposure of semaglutide increased proportionally with doses up to 7.2 mg once weekly. Steady state exposure was stable with time as assessed up to week 72.The average semaglutide steady state concentration following subcutaneous administration of Wegovy® was approximately 75 nmol/L in patients with either overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) and approximately 80 nmol/L in patients with MASH and F2 or F3 based on data from ESSENCE. The steady state exposure of semaglutide increased proportionally with subcutaneous doses up to 2.4 mg once weekly.

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

Tablet

Orally administered semaglutide has a low absolute bioavailability and a variable absorption. Daily administration according to the recommended posology in combination with a long half-life reduces day-to- day fluctuation of the exposure.

Orally administered semaglutide is co-formulated with salcaprozate sodium which facilitates the absorption of semaglutide after oral administration. The absorption of orally administered semaglutide predominantly occurs in the stomach.

The pharmacokinetic profile of orally administered semaglutide has been characterised in healthy people and patients with overweight or obesity. Following oral administration, maximum plasma concentration of semaglutide occurred 1 hour post dose. The half-life of semaglutide is approximately 1 week indicating that steady-state exposure will be reached after 4-5 weeks of once daily administration. In patients with overweight or obesity, the average semaglutide 25 mg steady state concentration following oral administration was approximately 77 nmol/L.

The steady-state concentrations increased approximately proportionally with doses up to 25 mg once daily.

The estimated absolute bioavailability of semaglutide is approximately 1-2% following oral administration.

Absorption of orally administered semaglutide 25 mg is decreased if taken with food or large volumes of water. Different dosing schedules of semaglutide have been investigated. Studies show that longer pre- and post-dose fasting periods results in higher absorption.

Distribution

The mean volume of distribution of semaglutide following s.c. administration in patients with overweight or obesity is approximately 12.4 L and approximately 13.7 L in patients with MASH and F2 or F3. Semaglutide is extensively bound to plasma albumin (> 99%).

The volume of distribution of semaglutide in patients with overweight or obesity is approximately 8.9 L. Due to differences in bioavailability following oral and subcutaneous administration, the apparent volume of distribution is not comparable across route of administration. Semaglutide is extensively bound to plasma albumin (> 99%).

The mean volume of distribution of semaglutide following s.c. administration in patients with MASH and F2 or F3 is approximately 13.7 L.

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

Excretion
The primary excretion routes of semaglutide-related material are via the urine and faeces. Approximately 3% of the dose was excreted in the urine as intact semaglutide.

Clearance of semaglutide in patient with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) or obesity (BMI≥ 30 kg/m^2) is approximately 0.04 L/h. Due to differences in bioavailability following oral and subcutaneous administration, the apparent clearance is not comparable across route of administration. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 5 to 7 weeks after the last dose of Wegovy tablet 25 mg.

Clearance of semaglutide in patient with MASH and F2 or F3[20] was approximately 0.05 L/h.

Special populations
Based on a population pharmacokinetic analysis across the weight management trials, age, sex, race, and ethnicity, and renal impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. The exposure of semaglutide decreases with an increase in body weight. However, semaglutide 2.4 mg subcutaneously administered provides adequate systemic exposure over the body weight range of 52.8-245.6 kg evaluated in the clinical trials.

Similar results have been shown in patients administered with 7.2 mg once weekly.

Similar results have been shown for orally administered semaglutide. The average semaglutide steady state concentration following 25 mg oral administration was approximately 44 nmol/L in patients with type 2 diabetes and obesity or overweight (BMI greater than or equal to 25 kg/m2) with higher variability in semaglutide concentrations compared to subcutaneous administration (90% of patients had average concentrations between 11 nmol/L and 134 nmol/L with WEGOVY 25 mg tablet versus 47 nmol/L and 99 nmol/L with WEGOVY 2.4 mg once-weekly injection).

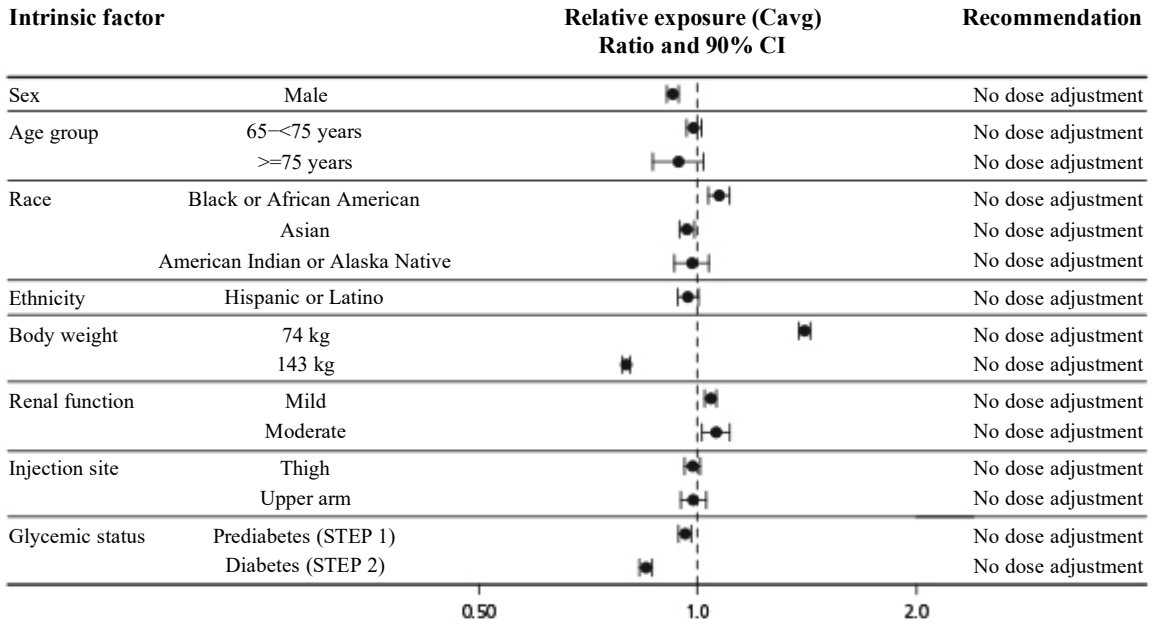
In patients with overweight or obesity, the effects of intrinsic factors on the pharmacokinetics of semaglutide are shown in

[20] Module 5.3.3.5: NN9931 modelling report interim (redacted), table 10-5, p.66

Figure 22. Similar results have been shown in patients with MASH (body weight range 42.7-206.0 kg). Fibrosis stage (F1 to F4c) did not impact semaglutide exposure in patients with MASH.[21]

[21]Module 5.3.3.5: NN9931 modelling report interim (redacted), figure 6-6, p.41

Figure 22 Impact of intrinsic factors on semaglutide exposure



Data are steady-state dose-normalised average semaglutide exposures relative to a reference subject profile (non-Hispanic or Latino, normoglycaemic (STEP 1) white female aged 18-<65 years, with a body weight of 110 kg and normal renal function, who injected in the abdomen). Body weight test categories (74 and 143 kg) represent the 5% and 95% percentiles in the data set.

Age

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3 trials including patients 18−86 years of age.

Subcutaneously administered 7.2 mg semaglutide has not been studied in paediatric patients.

Orally administered semaglutide for weight management has not been studied in paediatric patients.

Sex

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 was associated with lower exposure. The 2.4 mg and 7.2 mg weekly dose of subcutaneously administered semaglutide and the 25 mg once daily orally administered dose of semaglutide provided adequate systemic

exposures over the body weight range of 52.8-245.6 kg evaluated for exposure response in the clinical trials for weight management and 42.7-206.0 kg for MASH.[22]

Renal impairment
Solution for injection

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 subcutaneously administered semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or subjects in dialysis) compared with subjects with normal renal function. This was also shown for subjects with overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) and mild to moderate renal impairment based on data from phase 3a and 3b trials and for patients with MASH and mild to moderate renal impairment based on population PK analysis.

Tablet

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated in patients with mild, moderate or severe renal impairment and in patients with end-stage renal disease on dialysis and compared with people with normal renal function in a study with 10 consecutive days of once daily doses of orally administered semaglutide. This was also shown for patients with overweight (BMI ≥ 27 kg/m2 to < 30 kg/m2) or obesity (BMI ≥ 30 kg/m2) and mild to moderate renal impairment based on data from phase 3 trials.

Liver fibrosis
The stage of liver fibrosis (F1 to F4c) did not have any effect on the exposure of semaglutide based on population PK analysis.

Hepatic impairment
Solution for injection

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.

Tablet

Hepatic impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated in patients with mild, moderate or severe hepatic impairment compared with people with normal hepatic function in a study with 10 consecutive days of once daily doses of orally administered semaglutide.

Upper gastrointestinal tract diseases

Tablet

Upper gastrointestinal tract disease (chronic gastritis and/or gastroesophageal reflux disease) did not impact the pharmacokinetics of orally administered semaglutide in a clinically relevant manner. The pharmacokinetics were evaluated in patients with type 2 diabetes with or without upper

[22] Module 5.3.3.5: NN9931 modelling report interim (redacted), section 6.4, p. 40

gastrointestinal tract disease dosed for 10 consecutive days with once daily doses of orally administered semaglutide.

Paediatrics
Semaglutide has not been studied in children below 12 years of age with obesity or overweight. Subcutaneously administered semaglutide has not been studied in paediatric patients with MASH. Pharmacokinetic properties for semaglutide 2.4 mg were assessed in a clinical trial for adolescent patients with obesity or overweight and at least one weight-related comorbidity ages 12 to less than 18 years (124 patients, body weight 61.6-211.9 kg). The semaglutide exposure in adolescents was similar to that in adults with obesity or overweight.

Subcutaneously administered 7.2 mg 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 clinical relevant exposures (at ≥1.2-fold the clinical AUC in mice and subclinical exposures in rats based on the plasma AUC at a human dose of 2.4 mg/week, and at subclinical exposures in both species based on the plasma AUC at the maximum recommended human dose of 7.2 mg/week; 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 nongenotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be 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

Single-dose pen and Pre-filled syringe
Dibasic sodium phosphate dihydrate
Sodium chloride
Hydrochloric acid
Sodium hydroxide
Water for injections

FlexTouch pen
Dibasic sodium phosphate dihydrate
Propylene glycol
Phenol
Hydrochloric acid
Sodium hydroxide
Water for injections

Tablet
Salcaprozate sodium
Magnesium stearate

6.2 INCOMPATIBILITIES

Substances added to Wegovy may cause degradation of semaglutide. Wegovy 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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Singe-dose pen
Store in a refrigerator (2°C to 8°C). Keep away from the cooling element.

May be stored unrefrigerated for up to 28 days at a temperature not above 30°C.

Always store the pen in the original carton in order to protect from light.

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

Wegovy should be protected from excessive heat.

Wegovy should not be used if it does not appear clear and colourless.

The Wegovy pen is for single use in one patient only.

After use: Discard Wegovy single-dose pen after use.

FlexTouch pen
Do not freeze Wegovy FlexTouch and do not use Wegovy FlexTouch if it has been frozen.

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

Wegovy FlexTouch should be protected from excessive heat.

Wegovy FlexTouch should not be used if it does not appear clear and colourless.

The Wegovy FlexTouch pen is for use by one person only.

Before first use: Store in a refrigerator (2°C to 8°C). Keep away from the cooling element.

After first use: May be stored unrefrigerated for up to 42 days at a temperature below 30°C.

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

Pre-filled syringe
Store in a refrigerator (2°C - 8 C). Keep away from the cooling element.

May be stored unrefrigerated for up to 28 days at a temperature not above 30 C.

Discard the syringe if it has been out of the refrigerator for more than 28 days.

Always store the syringe in the original carton in order to protect from light.

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

Wegovy should be protected from excessive heat.

After use: Discard Wegovy pre-filled syringe after use.

Tablet

Store below 30°C.

Store in original blister package to protect from moisture and light.

6.5 NATURE AND CONTENTS OF CONTAINER

Single-dose pen

The primary packaging contains a 1 mL glass syringe (Type I glass) with attached stainless-steel needle, rigid needle shield (Type II/polyisoprene) and a rubber plunger (Type I/chlorobutyl).

There are five variants of the pre-filled pen for Wegovy:

Wegovy 0.25 mg/dose is provided in a pre-filled, fixed dose, single use disposable pen, which contains the drug solution semaglutide 0.5 mg/mL, 0.5 mL in a 1 mL pre-filled syringe. The pen contains one dose. This pen is intended to be used for dose escalation.

Wegovy 0.5 mg/dose is provided in a pre-filled, fixed dose, single use disposable pen, which contains the drug solution semaglutide 1.0 mg/mL, 0.5 mL in a 1 mL pre-filled syringe. The pen contains one dose. This pen is intended to be used for dose escalation.

Wegovy 1 mg/dose is provided in a pre-filled, fixed dose, single use disposable pen, which contains the drug solution semaglutide 2.0 mg/mL, 0.5 mL in a 1 mL pre-filled syringe. The pen contains one dose. This pen is intended to be used for dose escalation.

Wegovy 1.7 mg/dose is provided in a pre-filled, fixed dose, single use disposable pen, which contains the drug solution semaglutide 2.27 mg/mL, 0.75 mL in a 1 mL pre-filled syringe. The pen contains one dose. This pen is intended to be used for dose escalation.

Wegovy 2.4 mg/dose is provided in a pre-filled, fixed dose, single use disposable pen, which contains the drug solution semaglutide 3.2 mg/mL, 0.75 mL in a 1 mL pre-filled syringe. The pen contains one dose. This pen is intended to be used for maintenance treatment.

Pack sizes of:*
Wegovy 0.25 mg/dose:
2 or 4 pre-filled pens

Wegovy 0.5 mg/dose:
2 or 4 pre-filled pens

Wegovy 1 mg/dose:
2 or 4 pre-filled pens

Wegovy 1.7 mg/dose:
2 or 4 pre-filled pens

Wegovy 2.4 mg/dose:

2 or 4 pre-filled pens

*not all pack sizes may be available

FlexTouch pen

The primary packaging contains a 1.5 mL or 3 mL glass cartridge (Type I glass) closed at the 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/isoprene) inserted.

The cartridge is assembled into a pre-filled, multi-dose disposable pen made of polypropylene polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

There are five strengths of the Wegovy FlexTouch pen:

Wegovy 0.25 mg/dose solution for injection in pre-filled pen delivers 4 doses of 0.25 mg. This pen is intended to be used for dose escalation. The pen contains 1.5 mL solution.

Wegovy 0.5 mg/dose solution for injection in pre-filled pen delivers 4 doses of 0.5 mg. This pen is intended to be used for dose escalation. The pen contains 1.5 mL solution.

Wegovy 1 mg/dose for injection in pre-filled pen delivers 4 doses of 1 mg. This pen is to be used for dose escalation. The pen contains 3 mL solution.

Wegovy 1.7 mg/dose for injection in pre-filled pen delivers 4 doses of 1.7 mg. This pen is to be used for dose escalation. The pen contains 3.0 mL solution

Wegovy 2.4 mg/dose solution for injection in pre-filled pen delivers 4 doses of 2.4 mg. This pen is intended to be used for maintenance treatment. The pen contains 3.0 mL solution.

NovoFine® Plus needles are included in the Wegovy FlexTouch package.

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

Pack sizes of:

Wegovy FlexTouch 0.25 mg/dose: 1 pre-filled pen and 4 disposable NovoFine Plus needles

Wegovy FlexTouch 0.5 mg/dose: 1 pre-filled pen and 4 disposable NovoFine Plus needles

Wegovy FlexTouch 1 mg/dose: 1 pre-filled pen and 4 disposable NovoFine Plus needles

Wegovy FlexTouch 1.7 mg/dose: 1 pre-filled pen and 4 disposable NovoFine Plus needles

Wegovy FlexTouch 2.4 mg/dose: 1 pre-filled pen and 4 disposable NovoFine Plus needles

Pre-filled syringe

The primary packaging contains a 1 mL glass syringe (type I glass) with attached stainless-steel needle, rigid needle shield (type II/polyisoprene - inner shield and polypropylene - outer shield) and a rubber plunger (type I/chlorobutyl). The pre-filled syringe is assembled with a polypropylene plunger rod and a polypropylene finger grip.

There are five variants of the pre-filled syringe for Wegovy:

Wegovy 0.25 mg/dose solution for injection in pre-filled syringe delivers 1 dose of 0.25 mg. This syringe is intended to be used for dose escalation. The syringe contains 0.5 mL solution.

Wegovy 0.5 mg/dose solution for injection in pre-filled syringe delivers 1 dose of 0.5 mg. This syringe is intended to be used for dose escalation. The syringe contains 0.5 mL solution.

Wegovy 1 mg/dose solution for injection in pre-filled syringe delivers 1 dose of 1 mg. This syringe is intended to be used for dose escalation. The syringe contains 0.5 mL solution.

Wegovy 1.7 mg/dose solution for injection in pre-filled syringe delivers 1 dose of 1.7 mg. This syringe is intended to be used for dose escalation. The syringe contains 0.75 mL solution.

Wegovy 2.4 mg/dose solution for injection in pre-filled syringe delivers 1 dose of 2.4 mg. This syringe is intended to be used for maintenance treatment. The syringe contains 0.75 mL solution.

Pack sizes of:

Wegovy 0.25 mg/dose: 4 pre-filled syringes

Wegovy 0.5 mg/dose: 4 pre-filled syringes

Wegovy 1 mg/dose: 4 pre-filled syringes

Wegovy 1.7 mg/dose: 4 pre-filled syringes

Wegovy 2.4 mg/dose: 4 pre-filled syringes

Tablet

Wegovy tablets are provided in blister cards which contain 1.5 mg, 4 mg, 9 mg and 25 mg semaglutide tablets.

Primary packaging: Alu/alu blister cards
Pack sizes of 1.5 mg tablets: 30 and 90 tablets.
Pack sizes of 4 mg tablets: 30 and 90 tablets.
Pack sizes of 9 mg tablets: 30 and 90 tablets.
Pack sizes of 25 mg tablets: 30 and 90 tablets.

Not all pack sizes may be marketed.

Secondary packaging: Carton

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Single-dose pen

The patient should be advised to discard the pre-filled pen after each injection in accordance with local requirements.

FlexTouch pen

The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the Wegovy FlexTouch pen without an injection needle attached.

After the final dose of Wegovy FlexTouch the pen should be discarded in accordance with local requirements.

After having injected the 4 doses, there might still be solution left in the pen despite having administered correctly. Any solution left is insufficient for a dose and the pen should be disposed of.

Pre-filled syringe

The patient should be advised to discard the pre-filled syringe after injection in accordance with local requirements.

Tablet

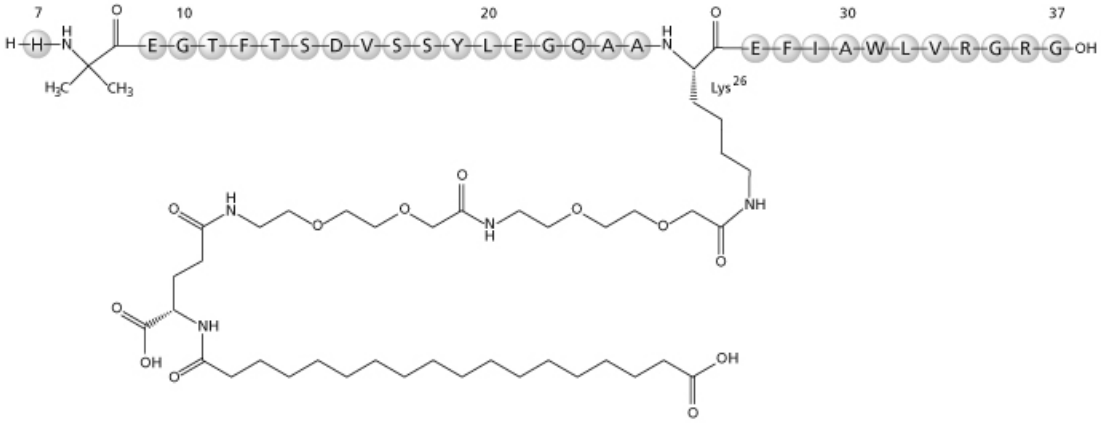
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Molecular formula: $C_{187}H_{291}N_{45}O_{59}$.
Molecular weight: 4113.6 daltons.

Semaglutide is an Aib8, Arg34-GLP-1(7-37) analogue substituted on the ε-amino group of the lysine residue in position 26 with an (S)-22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl side chain. The side chain consists of two 8-amino-3,6-dioxaoctanoic acid (ADO) spacers, one γ-glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.



CAS number

RN910463-68-2.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 10, 118 Mount Street,
North Sydney,
NSW 2060,
Australia.

www.novonordisk.com.au

9 DATE OF FIRST APPROVAL

01 September 2022

10 DATE OF REVISION

03 November 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Addition of Wegovy oral tablet