

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Wegovy 0.25 mg FlexTouch solution for injection in pre-filled pen
Wegovy 0.5 mg FlexTouch solution for injection in pre-filled pen
Wegovy 1 mg FlexTouch solution for injection in pre-filled pen
Wegovy 1.7 mg FlexTouch solution for injection in pre-filled pen
Wegovy 2.4 mg FlexTouch solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled pen, FlexTouch

Wegovy 0.25 mg FlexTouch solution for injection pre-filled pen

Each pre-filled pen contains 1 mg semaglutide* in 1.5 mL solution. One mL of solution contains 0.68 mg semaglutide*. One pre-filled pen contains 4 doses of 0.25 mg.

Wegovy 0.5 mg FlexTouch solution for injection pre-filled pen

1.5 mL: Each pre-filled pen contains 2 mg semaglutide* in 1.5 mL solution. One mL of solution contains 1.34 mg semaglutide*. One pre-filled pen contains 4 doses of 0.5 mg.

3 mL: Each pre-filled pen contains 2 mg semaglutide* in 3 mL solution. One mL of solution contains 0.68 mg semaglutide*. One pre-filled pen contains 4 doses of 0.5 mg.

Wegovy 1 mg FlexTouch solution for injection pre-filled pen

Each pre-filled pen contains 4 mg semaglutide* in 3 mL solution. One mL of solution contains 1.34 mg semaglutide*. One pre-filled pen contains 4 doses of 1 mg.

Wegovy 1.7 mg FlexTouch solution for injection pre-filled pen

Each pre-filled pen contains 6.8 mg semaglutide* in 3 mL solution. One mL of solution contains 2.27 mg semaglutide*. One pre-filled pen contains 4 doses of 1.7 mg.

Wegovy 2.4 mg FlexTouch solution for injection pre-filled pen

Each pre-filled pen contains 9.6 mg semaglutide* in 3 mL solution. One mL of solution contains 3.2 mg semaglutide*. One pre-filled pen contains 4 doses of 2.4 mg.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)
Clear and colourless isotonic solution; pH=7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult

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

- $\geq 30 \text{ kg/m}^2$ (obesity), or
- $\geq 27 \text{ kg/m}^2$ to $< 30 \text{ kg/m}^2$ (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.
- 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 and either obesity or overweight.
- for the treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults.

For trial results with respect to cardiovascular risk reduction, obesity-related heart failure, and populations studied, see section 5.1.

Adolescents (≥ 12 years)

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity* and
- body weight above 60 kg.

Treatment with Wegovy should be discontinued and re-evaluated if 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 $\geq 95^{\text{th}}$ percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1).

Table 1 BMI cut-off points for obesity ($\geq 95^{\text{th}}$ 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

4.2 Posology and method of administration

Posology

Adults

The maintenance dose of semaglutide 2.4 mg once-weekly is reached by starting with a dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see Table 2). In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved. Weekly dose higher than 2.4 mg are not recommended.

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

Noncirrhotic MASH with Moderate to Advanced Liver Fibrosis

- The recommended maintenance dosage of Wegovy for the treatment of noncirrhotic MASH with moderate to advanced liver fibrosis is 2.4 mg injected subcutaneously once weekly.
- If patients do not tolerate the maintenance dosage of 2.4 mg once weekly, the dosage can be decreased to 1.7 mg once weekly. Consider reescalation to 2.4 mg once weekly

Adolescents for weight management:

For adolescents ages 12 years and above, 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 maximum tolerated dose has been reached. Weekly doses higher than 2.4 mg are not recommended.

Patients with type 2 diabetes

When initiating semaglutide in patients with type 2 diabetes, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia, see section 4.4.

Missed dose

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

Special populations

Elderly (≥65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥85 years of age is limited.

Patients with renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min/1.73m²) including patients with end-stage renal disease (see sections 4.4, 4.8 and 5.2).

Patients with hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Semaglutide is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

Weight management:

No dose adjustment is required for adolescents ages 12 years and above. The safety and efficacy of semaglutide in children below 12 years of age have not been established.

For major adverse cardiovascular events:

The safety and efficacy of semaglutide to reduce the risk of major adverse cardiovascular events have not been established in pediatric patients below 18 years.

Noncirrhotic MASH

The safety and efficacy of semaglutide for treatment of noncirrhotic MASH have not been established in pediatric patients below 18 years.

Method of administration

Subcutaneous use.

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

It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It should not be administered intravenously or intramuscularly.

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

When administering Wegovy, the pen should be pressed firmly against the skin until the yellow bar has stopped moving. The injection takes about 5–10 seconds.

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

For further information before administration see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Aspiration in association with general anaesthesia or deep sedation

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

Gastrointestinal effects and Dehydration

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function, as nausea, vomiting, and diarrhoea may cause dehydration, which in rare cases can lead to a deterioration of renal function (see section 4.8). Patients treated with semaglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists (see section 4.8). Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

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

Patients with type 2 diabetes

Semaglutide should not be used as a substitute for insulin in patients with type 2 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 type 2 diabetes

Insulin and sulfonylurea are known to cause hypoglycaemia. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with a GLP-1 receptor agonist.

Diabetic retinopathy in patients with type 2 diabetes

In patients with diabetic retinopathy treated with semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (see section 4.8). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Patients with diabetic retinopathy using semaglutide should be monitored closely and treated according to 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.

Patients with gastroparesis

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

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 severe renal impairment (see section 4.2),
- with severe hepatic impairment (see section 4.2),

with congestive heart failure New York Heart Association (NYHA) class IV. Use in these patients is not recommended.

There is limited experience with Wegovy in patients:

- aged 85 years or more (see section 4.2),
- with mild or moderate hepatic impairment (see section 4.2),
- with inflammatory bowel disease,
- with MASH and a body mass index (BMI) of less than 25 kg/m².

Use with caution in these patients.

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

Semaglutide delays gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, probably due to a tolerance effect. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

Paracetamol

Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardised meal test. Paracetamol AUC_{0-60min} and C_{max} were decreased by 27% and 23%, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure (AUC_{0-5h}) was not affected. No clinically relevant effect on paracetamol was observed with semaglutide. No dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives

Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives. It 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential are recommended to use contraception when treated with semaglutide (see section 4.5).

Pregnancy

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

There may be risks to the mother and fetus related to underlying MASH with advanced liver fibrosis such as increased risks of gestational diabetes, hypertensive complications, preterm birth, and postpartum hemorrhage. Whether semaglutide treatment during pregnancy reduces these risks is unknown. WEGOVY for the treatment of MASH should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

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.

Fertility

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

4.7 Effects on ability to drive and use machines

Semaglutide 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.

Patients with type 2 diabetes

If semaglutide is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of safety profile

In four phase 3a trials, 2,650 adult patients were exposed to Wegovy. The duration of the trials were 68 weeks. The most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhoea, constipation and vomiting.

Tabulated list of adverse reactions

Table 3 lists adverse reactions identified in clinical trials in adults and post-marketing reports. The frequencies are based on a pool of the phase 3a trials.

Adverse reactions associated with Wegovy are listed by system organ class and frequency. Frequency categories are defined as: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Table 3 Frequency of adverse reactions of semaglutide

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very Rare	Not known
Immune system disorders				Anaphylactic reaction		
Metabolism and nutrition disorders		Hypoglycaemia in patients with type 2 diabetes ^a				
Nervous system disorders	Headache ^b	Dizziness ^b Dysgeusia ^{b,c} Dysaesthesia ^a				
Eye disorders		Diabetic retinopathy in patients with type 2 diabetes ^a			Non-arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders			Hypotension Orthostatic hypotension Increased heart rate ^{a,c}			
Gastrointestinal disorders	Vomiting ^{a,b} Diarrhoea ^{a,b} Constipation ^{a,b} Nausea ^{a,b} Abdominal pain ^{b,c}	Gastritis ^{b,c} Gastroesophageal reflux disease ^b Dyspepsia ^b Eructation ^b Flatulence ^b Abdominal distension ^b	Acute pancreatitis ^a Delayed gastric emptying			Intestinal obstruction ^d

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very Rare	Not known
Hepatobiliary disorders		Cholelithiasis ^a				
Skin and subcutaneous tissue disorders		Hair loss ^a		Angioedema ^a		
General disorders and administration site conditions	Fatigue ^{b,c}	Injection site reactions ^c				
Investigations			Increased amylase ^c Increased lipase ^c			

^{a)} see description of selected adverse reactions below

^{b)} mainly seen in the dose-escalation period

^{c)} Grouped preferred terms

Description of selected adverse reactions

The below information on specific adverse reactions, unless otherwise specified, pertains to the phase 3a trials.

Gastrointestinal adverse reactions

Over the 68 weeks trial period, nausea occurred in 43.9% of patients when treated with semaglutide (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 semaglutide (11.1% for placebo) and was mild to moderate in severity and of longer duration. In patients treated with semaglutide, median duration of nausea was 8 days, vomiting 2 days, diarrhoea 3 days, and constipation 47 days.

Patients with moderate renal impairment (eGFR ≥ 30 to <60 mL/min/1.73m²) 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 semaglutide and $<0.1\%$ for placebo, respectively. In SELECT, the cardiovascular outcomes trial, the frequency of acute pancreatitis confirmed by adjudication was 0.2% for semaglutide and 0.3% for placebo.

Acute gallstone disease/Cholelithiasis

Cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide. Cholelithiasis and cholecystitis was 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 semaglutide and in 1.0% of patients treated with 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 ($\geq 20\%$).

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 semaglutide. The proportions of subjects with an increase in pulse from baseline ≥ 10 bpm at any timepoint during the on-treatment period were 67.0% in the semaglutide group vs. 50.1% 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 low (2.9%) and 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.

Hypoglycaemia in patients with type 2 diabetes

In STEP 2, clinically significant hypoglycaemia was observed in 6.2% (0.1 events/patient year) of subjects treated with semaglutide compared with 2.5% (0.03 events/patient year) of subjects treated with placebo. Hypoglycaemia with semaglutide was seen both with and without concomitant use of sulfonylurea. One episode (0.2% of subjects, 0.002 events/patient year) was reported as severe in a subject not concomitantly treated with a sulfonylurea. The risk of hypoglycaemia was increased when semaglutide was used with a sulfonylurea.

In STEP-HFpEF-DM, clinically significant hypoglycaemia was observed in 4.2% of subjects in both the semaglutide and placebo groups when used in combination with sulfonylurea and/or insulin (0.065 events/patient year with semaglutide and 0.098 events/patient year with placebo).

Diabetic retinopathy in patients with type 2 diabetes

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).

Dysaesthesia

Events related to a clinical picture of altered skin sensation such as paraesthesia, pain of skin, sensitive skin, dysaesthesia and burning skin sensation were reported in 2.1% of patients treated with semaglutide 2.4 mg and 1.2% of patients treated with placebo. The events were mild to moderate in severity and most patients recovered while on continued treatment.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

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

Adverse Reactions in Clinical Trials in Adults with MASH

The safety of WEGOVY was evaluated in a randomized, double-blind, placebo-controlled trial that included 1,195 adult patients with MASH, including 800 patients who were exposed to WEGOVY for a median of 95.3 weeks and 395 patients who were exposed to placebo for a median of 83.1 weeks [see Clinical efficacy & safety].

The most commonly reported adverse reactions were consistent with the other approved WEGOVY indications. There is limited information in patients with MASH and a BMI <25 kg/m². Unless indicated, the incidence of the adverse reactions in MASH patients was similar to other approved indications.

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 and 0% of patients treated with placebo.

No effects on growth or pubertal development were found after 68 weeks of treatment.

The safety and effectiveness of WEGOVY have not been established in pediatric patients:

- To reduce the risk of major adverse CV events.
- To reduce excess body weight and maintain weight reduction long term in those less than 12 years of age.
- For the treatment of noncirrhotic MASH.

Other special populations

In the SELECT and SUSTAIN 6 trials, in adults with established cardiovascular disease, the adverse reaction profile was similar to that seen in the weight management phase 3a trials.

In the HFpEF trials, in adults with obesity related heart failure with preserved ejection fraction (HFpEF), the adverse reaction profile was similar to that seen in the weight management phase 3a trials.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.

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 may affect the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala.

Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fullness and control of eating, reduces feelings of hunger, and frequency and intensity of cravings. In addition, semaglutide reduces the preference for high fat foods.

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 in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys. Semaglutide has a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. Furthermore, animal studies have shown that semaglutide attenuated the development of atherosclerosis and had an anti-inflammatory action in the cardiovascular system.

The mechanism of action of semaglutide for cardiovascular risk reduction is likely multifactorial, in part driven by weight loss effects and effects on known cardiovascular risk factors (reduction in blood pressure, improvements in lipid profile and glucose metabolism, and anti-inflammatory effects as demonstrated by reductions in high-sensitivity C-reactive protein (hsCRP)). The exact mechanism of cardiovascular risk reduction has not been established.

For treatment of MASH in humans, the precise mechanism of action of semaglutide is not fully understood and may involve multiple pathways mediated by weight loss and other factors. In a mouse model of diet-induced MASH, treatment with semaglutide resulted in histological improvements in steatosis, inflammation, and fibrosis in liver compared to baseline, which was associated with body weight loss, intermittent periods of reduced food intake, and improvements in relevant biomarkers. The relationship between the pathophysiology of MASH in animal models and humans has not been fully established.

Pharmacodynamic effects

Appetite, energy intake and food choice

Semaglutide 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 semaglutide compared to placebo after 20 weeks of dosing. This was supported by improved control of eating, less food cravings and a relative lower preference for high fat food. Food cravings were further assessed in STEP 5 by a Control of Eating Questionnaire (CoEQ). At week 104, the estimated treatment difference both for control of cravings and craving of savoury food significantly favoured semaglutide, whereas no clear effect was seen for craving of sweet food.

Fasting and postprandial lipids

Semaglutide 1 mg compared to placebo lowered fasting triglyceride and very low density lipoproteins (VLDL) concentrations by 12% and 21%, respectively. The postprandial triglyceride and VLDL response to a high fat meal was reduced with >40%.

Noninvasive Liver Disease Markers

Semaglutide decreases liver fat content measured by Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF), liver stiffness assessed by transient elastography (TE), Enhanced Liver Fibrosis (ELF) score, and the levels of the pro-peptide of type III collagen biomarker (Pro-C3). The clinical relevance of these changes is yet to be confirmed.

Clinical efficacy and safety

The efficacy and safety of semaglutide for weight management in combination with a reduced calorie intake and increased physical activity were evaluated in four 68 weeks double-blinded randomised placebo-controlled phase 3a trials (STEP 1-4). A total of 4,684 patients (2,652 randomised to treatment with semaglutide) were included in these trials. Furthermore, the two-year efficacy and safety of semaglutide compared to placebo were evaluated in a double-blinded randomised placebo-controlled phase 3b trial (STEP 5) including 304 patients (152 in treatment with semaglutide).

Treatment with semaglutide demonstrated superior, clinically meaningful, and sustained weight loss compared with placebo in patients with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight ($\text{BMI} \geq 27 \text{ kg/m}^2$ to $<30 \text{ kg/m}^2$) and at least one weight-related comorbidity. Furthermore, across the trials, a higher proportion of patients achieved $\geq 5\%$, $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$ weight loss with semaglutide compared with placebo. The reduction in body weight occurred irrespective of the presence of gastrointestinal symptoms such as nausea, vomiting or diarrhoea.

Treatment with semaglutide also showed statistically significant improvements in waist circumference, systolic blood pressure and physical functioning compared to placebo.

Efficacy was demonstrated regardless of age, sex, race, ethnicity, baseline body weight, BMI, presence of type 2 diabetes and level of renal function. Variations in efficacy existed within all subgroups. Relatively greater weight loss was observed in women and in patients without type 2 diabetes as well as in patients with a lower versus higher baseline body weight.

STEP 1: Weight management

In a 68-week double-blind trial, 1,961 patients with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), or with overweight ($\text{BMI} \geq 27 \text{ kg/m}^2$ to $<30 \text{ kg/m}^2$) and at least one weight-related comorbidity were randomised to semaglutide or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

Weight loss occurred early and continued throughout the trial. At end of treatment (week 68), the weight loss was superior and clinically meaningful compared with placebo (see Table 4 and Figure 1). Furthermore, a higher proportion of patients achieved $\geq 5\%$, $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$ weight loss with

semaglutide compared with placebo (see Table 4). Among patients with prediabetes at baseline, a higher proportion of patients had a normo-glycaemic status at end of treatment with semaglutide compared to placebo (84.1% vs. 47.8%).

Table 4 STEP 1: Results at week 68

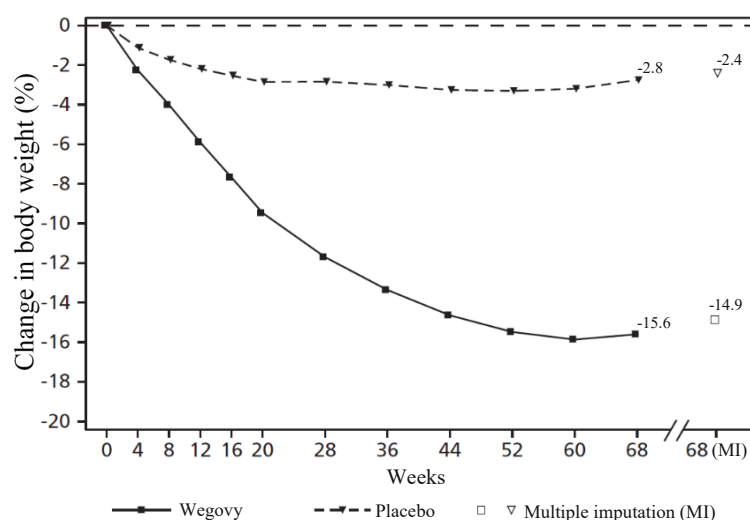
	Semaglutide 2.4 mg	Placebo
Full analysis set (N)	1,306	655
Body weight		
Baseline (kg)	105.4	105.2
Change (%) from baseline ^{1,2}	-14.9	-2.4
Difference (%) from placebo ¹ [95% CI]	-12.4 [-13.4; -11.5]*	-
Change (kg) from baseline	-15.3	-2.6
Difference (kg) from placebo ¹ [95% CI]	-12.7 [-13.7; -11.7]	-
Patients (%) achieving weight loss $\geq 5\%$ ³	83.5*	31.1
Patients (%) achieving weight loss $\geq 10\%$ ³	66.1*	12.0
Patients (%) achieving weight loss $\geq 15\%$ ³	47.9*	4.8
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]*	-
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]*	-

*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 semaglutide 2.4 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 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 semaglutide 2.4 mg and placebo respectively.

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



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

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

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 semaglutide or placebo. 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.

STEP 2: Weight management in patients with type 2 diabetes

In a 68-week, double-blind trial, 1,210 patients with overweight or obesity (BMI ≥ 27 kg/m²) and type 2 diabetes were randomised to either semaglutide 2.4 mg, 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 antidiabetic drugs. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

Treatment with semaglutide for 68 weeks resulted in superior and clinically meaningful reduction in body weight and in HbA_{1c} compared to placebo (see Table 4 and Figure 2).

Table 5 STEP 2: Results at week 68

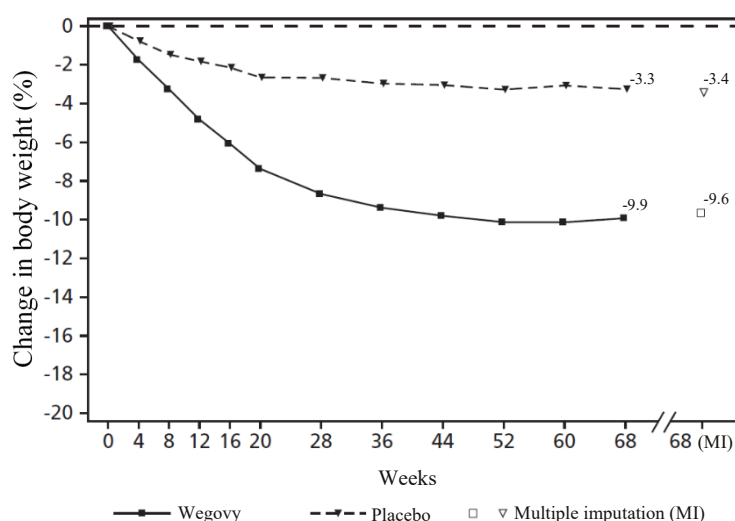
	Semaglutide 2.4 mg	Placebo
Full analysis set (N)	404	403
Body weight		
Baseline (kg)	99.9	100.5
Change (%) from baseline ^{1,2}	-9.6	-3.4
Difference (%) from placebo ¹ [95% CI]	-6.2 [-7.3;-5.2]*	-
Change (kg) from baseline	-9.7	-3.5
Difference (kg) from placebo ¹ [95% CI]	-6.1 [-7.2;-5.0]	-
Patients (%) achieving weight loss $\geq 5\%$ ³	67.4*	30.2
Patients (%) achieving weight loss $\geq 10\%$ ³	44.5*	10.2
Patients (%) achieving weight loss $\geq 15\%$ ³	25.0*	4.3
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]*	-
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]**	-
HbA_{1c} (mmol/mol (%))		
Baseline	65.3 (8.1)	65.3 (8.1)
Change from baseline ¹	-17.5 (-1.6)	-4.1 (-0.4)
Difference from placebo ¹ [95% CI]	-13.5 [-15.5; -11.4] (-1.2 [-1.4; -1.1])*	- -

* 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 semaglutide 2.4 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 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 semaglutide 2.4 mg and placebo respectively

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



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

Figure 2 STEP 2: Mean change in body weight (%) from baseline to week 68

STEP 3: Weight management with intensive behavioural therapy

In a 68-week double-blind trial, 611 patients with obesity (BMI ≥ 30 kg/m²), or with overweight (BMI ≥ 27 kg/m² to <30 kg/m²) and at least one weight-related comorbidity were randomised to semaglutide or placebo. During the trial, all patients received intensive behavioural therapy (IBT) consisting of a very restrictive diet, increased physical activity and behavioural counselling.

Treatment with semaglutide and IBT for 68 weeks resulted in superior and clinically meaningful reduction in body weight compared to placebo (see Table 6).

Table 6 STEP 3: Results at week 68

	Semaglutide 2.4 mg	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 $\geq 5\%$ ³	84.8*	47.8
Patients (%) achieving weight loss $\geq 10\%$ ³	73.0*	27.1
Patients (%) achieving weight loss $\geq 15\%$ ³	53.5*	13.2
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]*	-
Systolic blood pressure (mmHg)		
Baseline	124	124
Change from baseline ¹	-5.6	-1.6
Difference from placebo ¹ [95% CI]	-3.9 [-6.4;-1.5]*	-

* p<0.005 (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 semaglutide 2.4 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 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 semaglutide

2.4 mg and placebo respectively

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

STEP 4: Sustained weight management

In a 68-week double-blind trial, 902 patients with obesity (BMI ≥ 30 kg/m²), or with overweight (BMI ≥ 27 kg/m² to <30 kg/m²) and at least one weight-related comorbidity were included in the trial. All patients were on a reduced-calorie diet and increased physical activity throughout the trial. From week 0 to week 20 (run-in), all patients received semaglutide. At week 20 (baseline), patients who had reached the maintenance dose of 2.4 mg were randomised to continue treatment or switch to placebo. At week 0 (start of run-in period) patients had a mean body weight of 107.2 kg and a mean BMI of 38.4 kg/m².

Patients who had reached the maintenance dose of 2.4 mg at week 20 (baseline) and continued treatment with semaglutide for 48 weeks (week 20–68) continued losing weight and had a superior and clinically meaningful reduction in body weight compared to those switched to placebo (see Table 7 and Figure 3). The body weight increased steadily from week 20 to week 68 in patients switching to placebo at week 20 (baseline). Nevertheless, the observed mean body weight was lower at week 68 than at start of the run-in period (week 0) (see Figure 3). Patients treated with semaglutide from week 0 (run-in) to week 68 (end of treatment) achieved a mean change in body weight of 17.4%, with weight loss $\geq 5\%$ achieved by 87.8%, $\geq 10\%$ achieved by 78.0%, $\geq 15\%$ achieved by 62.2% and $\geq 20\%$ achieved by 38.6% of these patients.

Table 7 STEP 4: Results from week 20 to week 68

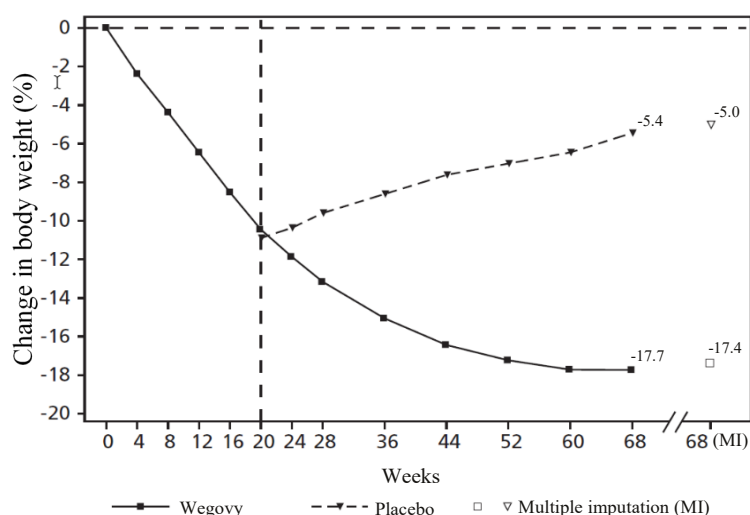
	Semaglutide 2.4 mg	Placebo
Full analysis set (N)	535	268
Body weight		
Baseline ¹ (kg)	96.5	95.4
Change (%) from baseline ^{1,2,3}	-7.9	6.9
Difference (%) from placebo ² [95% CI]	-14.8 [-16.0; -13.5]*	-
Change (kg) from baseline	-7.1	6.1
Difference (kg) from placebo ² [95% CI]	-13.2 [-14.3; -12.0]	-
Waist circumference (cm)		
Baseline	105.5	104.7
Change from baseline ¹	-6.4	3.3
Difference from placebo ² [95% CI]	-9.7 [-10.9; -8.5]*	-
Systolic blood pressure (mmHg)		
Baseline ¹	121	121
Change from baseline ^{1,2}	0.5	4.4
Difference from placebo ² [95% CI]	-3.9 [-5.8; -2.0]*	

* $p < 0.0001$ (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 semaglutide 2.4 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 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -8.8% and 6.5% for semaglutide 2.4 mg and placebo respectively.



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

Figure 3 STEP 4: Mean change in body weight (%) from week 0 to week 68

STEP 5: 2-year data

In a 104-week double-blind trial, 304 patients with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), or with overweight ($\text{BMI} \geq 27$ to $< 30 \text{ kg/m}^2$) and at least one weight-related comorbidity, were randomised to semaglutide 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 38.5 kg/m^2 , a mean body weight of 106.0 kg .

Treatment with semaglutide for 104 weeks resulted in a superior and clinically meaningful reduction in body weight compared to placebo. Mean body weight decreased from baseline through to week 68 with semaglutide after which a plateau was reached. With placebo, mean body weight decreased less, and a plateau was reached after approximately 20 weeks of treatment (see Table 7 and Figure 4). Patients treated with semaglutide achieved a mean change in body weight of -15.2% , with weight loss $\geq 5\%$ achieved by 74.7% , $\geq 10\%$ achieved by 59.2% and $\geq 15\%$ achieved by 49.7% of these patients. Among patients with prediabetes at baseline, 80% and 37% achieved a normo-glycaemic status at end of treatment with semaglutide and placebo, respectively.

Table 8 STEP 5: Results at week 104

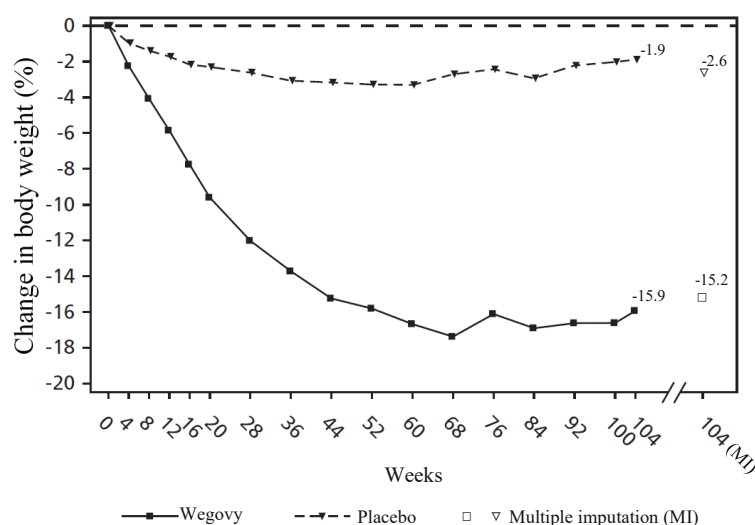
	Semaglutide 2.4 mg	Placebo
Full analysis set (N)	152	152
Body weight		
Baseline (kg)	105.6	106.5
Change (%) from baseline ^{1,2}	-15.2	-2.6
Difference (%) from placebo ¹ [95% CI]	-12.6 [-15.3; -9.8]*	-
Change (kg) from baseline	-16.1	-3.2
Difference (kg) from placebo ¹ [95% CI]	-12.9 [-16.1; -9.8]	-
Patients (%) achieving weight loss $\geq 5\%$ ³	74.7*	37.3
Patients (%) achieving weight loss $\geq 10\%$ ³	59.2*	16.8
Patients (%) achieving weight loss $\geq 15\%$ ³	49.7*	9.2
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 randomised to semaglutide 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 semaglutide and placebo respectively.

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



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

Figure 4 STEP 5: Mean change in body weight (%) from week 0 to week 104

STEP 8: Semaglutide vs liraglutide

In a 68-week, randomised, open-label, pairwise placebo-controlled trial, 338 patients with obesity (BMI ≥ 30 kg/m²), or with overweight (BMI ≥ 27 to <30 kg/m²) and at least one weight-related comorbidity, were randomised to semaglutide once weekly, liraglutide 3 mg once daily or placebo. Semaglutide 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/m², a mean body weight of 104.5 kg.

Treatment with semaglutide 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 semaglutide. With liraglutide, mean body weight decreased less (see Table 9). 37.4% of the patients treated with semaglutide lost $\geq 20\%$, compared to 7.0% treated with liraglutide. Table 9 shows the results of the confirmatory endpoints $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$ weight loss.

Table 9 STEP 8: Results of a 68-week trial comparing semaglutide with liraglutide

	Semaglutide 2.4 mg	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 $\geq 10\%$ ³	69.4*	27.2
Patients (%) achieving weight loss $\geq 15\%$ ³	54.0*	13.4
Patients (%) achieving weight loss $\geq 20\%$ ³	37.4*	7.0

* $p < 0.005$ (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 semaglutide 2.4 mg and liraglutide 3 mg, 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 semaglutide 2.4 mg and liraglutide 3 mg respectively.

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

STEP 9: Weight management in patients with knee osteoarthritis

In a 68-week double-blind trial, 407 patients with obesity and moderate knee osteoarthritis (OA) of one or both knees were randomised to either semaglutide or placebo, as an adjunct to counselling on a reduced-calorie diet and increased physical activity. The treatment effect on knee OA-related pain was assessed by the Western Ontario and McMaster Universities Osteoarthritis 3.1 Index (WOMAC). This index is designed to evaluate changes in symptoms and lower extremity functioning associated with treatment in patients suffering from OA of the hip and/or knee. At baseline, patients had a mean BMI of 40.3 kg/m² and a mean body weight of 108.6 kg. All patients had a clinical diagnosis of knee OA with a mean baseline WOMAC pain score of 70.9 (on a scale of 0-100).

Treatment with semaglutide for 68 weeks resulted in superior and clinically significant reduction in body weight compared to placebo (see Table 10).

Treatment with semaglutide demonstrated a clinically meaningful improvement in knee OA-related pain compared to the placebo (see Table 10). The improvements in knee OA-related pain with semaglutide were achieved without an increase in the use of pain medication.

Table 10 STEP 9: Results at week 68

	Semaglutide 2.4 mg	Placebo
Full analysis set (N)	271	136
Body weight		
Baseline (kg)	108.7	108.5
Change (%) from baseline ^{1,2}	-13.7	-3.2
Difference (%) from placebo ¹ [95% CI]	-10.5 [-12.3; -8.6]*	-
Patients (%) achieving weight loss $\geq 5\%$ ³	85.2*	33.6
WOMAC pain score⁴		
Baseline	72.8	67.2
Change from baseline ^{1,2}	-41.7	-27.5
Difference from placebo ¹ [95% CI]	-14.1 [-20.0, -8.3]*	-
Patients (%) achieving clinically meaningful improvement ^{3, 5}	59.0	35.0

* 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 therapies or other knee OA interventions and regardless of compliance with wash out period for pain medication (the latter only relevant for WOMAC related endpoint). During the trial, randomised treatment was permanently discontinued by 12.5% and 21.3% of patients randomised to semaglutide 2.4 mg and placebo, respectively.

² Based on a Mixed Model for Repeated Measures assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies or additional knee OA interventions and complied with washout period for pain medication (the latter only relevant for knee OA related pain), including all observations until first discontinuation the estimated changes from baseline to week 68 for body weight were -14.5% and -2.3% (semaglutide 2.4 mg and placebo, respectively) and for WOMAC pain score: -43.0 and -28.3 (semaglutide 2.4 mg and placebo, respectively).

³ Estimated from logistic regression model based on same imputation procedure as for the primary analysis.

⁴ WOMAC scores are presented on a scale from 0-100, with lower scores representing less disability.

⁵ The change in WOMAC pain score of ≤ -37.3 was used as a threshold for meaningful improvement. The threshold was derived from trial data using anchor-based methods.

Effect on body composition

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 semaglutide 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. These results suggest that most of the total weight loss was attributable to a reduction in fat tissue, including visceral fat.

Improvement in physical functioning

Semaglutide showed small improvements in physical functioning scores. Physical functioning was assessed using both the generic health-related quality of life questionnaire Short Form-36v2 Health Survey, Acute Version (SF-36) and the obesity-specific questionnaire Impact of Weight on Quality of Life Lite Clinical Trials Version (IWQOL-Lite-CT).

Cardiovascular evaluation

SELECT: Cardiovascular outcomes 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 and BMI ≥ 27 kg/m². Patients were randomised to either semaglutide 2.4 mg (n=8 803) or placebo (n=8 801) in addition to standard-of-care. The median time in trial was 41.8 months. Vital status was available for 99.4% of subjects in the trial.

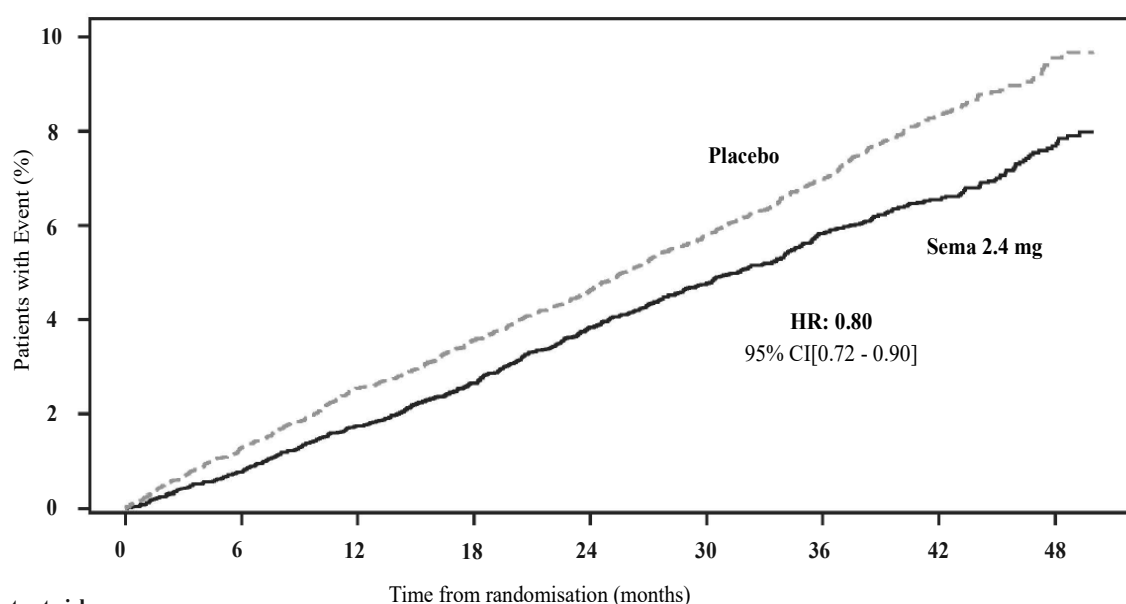
The study population consisted of 27.7% female and 72.3% male patients, with a mean age of 61.6 years, including 38.2% patients ≥ 65 years (n=6 728) and 7.8% patients ≥ 75 years (n=1 366). The mean BMI was 33.3 kg/m² and mean body weight was 96.7 kg. Patients with history of type 1 and type 2 diabetes were excluded.

The primary endpoint was the time from randomisation to first occurrence of major adverse cardiovascular events (MACE), defined as a composite endpoint consisting of cardiovascular death (including undetermined cause of death), non-fatal myocardial infarction, or non-fatal stroke. The primary endpoint, time to first MACE, occurred in 1 270 of the 17 604 patients included in the SELECT trial. Specifically, 569 first MACE (6.5%) were recorded among the 8 803 patients treated with semaglutide, compared to 701 first MACE (8.0%) among the 8 801 patients treated with placebo. A total of 63 (11.1%) of the first MACE with semaglutide and 80 (11.4%) with placebo were undetermined cause of death.

Superiority of semaglutide 2.4 mg versus placebo for MACE was confirmed with a hazard ratio of 0.80 [0.72; 0.90][95% CI], corresponding to a relative risk reduction in MACE of 20 % (see Figure 5). The effect on each component to the reduction of MACE is shown in Figure 6. The reduction of

MACE with semaglutide 2.4 mg was not impacted by age, sex, race, ethnicity, BMI at baseline, or level of renal function impairment.

Analysis of the cardiovascular death (the first confirmatory secondary endpoint) resulted in a hazard ratio of 0.85 [0.71; 1.01][95% CI].



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. The x-axis is truncated at 50 months where approximately 10% of the population was still in the trial.

HR: hazard ratio, CI: Confidence interval, Sema 2.4 mg: semaglutide 2.4 mg.

CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

Figure 5: Time from randomisation to first MACE Cumulative incidence function plot

		HR [95% CI]	Number of events/ analysed subjects (Sema 2.4 mg; Placebo)
Primary endpoints and components			
Primary endpoint		0.80 [0.72; 0.90]	569/8 803; 701/8 801
CV death		0.85 [0.71; 1.01]	223/8 803; 262/8 801
Non-fatal MI		0.72 [0.61; 0.85]	234/8 803; 322/8 801
Non-fatal stroke		0.93 [0.74; 1.15]	154/8 803; 165/8 801
Secondary confirmatory endpoints			
Heart failure composite		0.82 [0.71; 0.96]	300/8 803; 361/8 801
All-cause death		0.81 [0.71; 0.93]	375/8 803; 458/8 801

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, Sema 2.4 mg: semaglutide 2.4 mg.

CV: cardiovascular, MI: myocardial infarction, Heart failure (HF) composite consisting of HF hospitalisation, urgent HF visit or CV death.

Figure 6: Forest plot of time from randomisation to first MACE, MACE components and secondary confirmatory endpoints

SUSTAIN 6: Cardiovascular outcomes trial in patients with type 2 diabetes

In the SUSTAIN 6 trial, 3 297 patients with insufficiently controlled 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/m².

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 total number of the MACE was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo.

The cardiovascular safety of treatment with semaglutide 0.5 or 1 mg was confirmed as the hazard ratio (HR) for semaglutide vs. placebo was 0.74, [0.58, 0.95] [95% CI], driven by a decrease in the rate of non-fatal stroke and non-fatal myocardial infarction with no difference in cardiovascular death (see Figure 7).

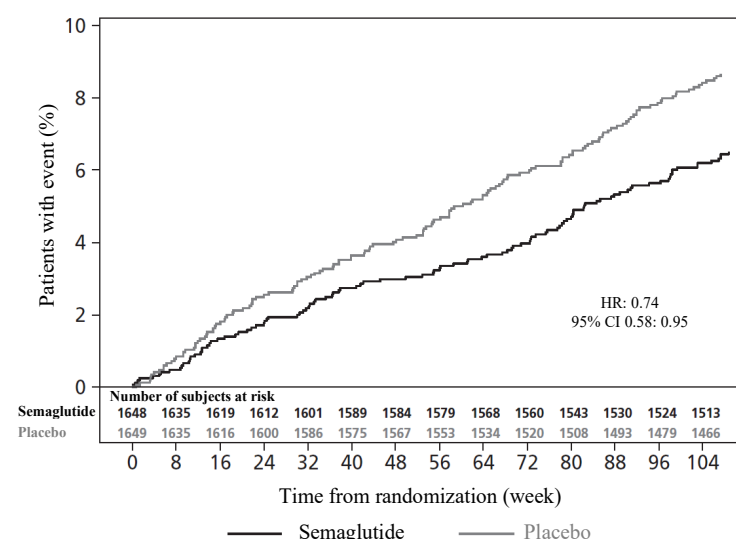


Figure 7: Kaplan-Meier plot of time to first occurrence of the composite outcome: Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

STEP-HFpEF and STEP-HFpEF-DM: Functional outcome trials in patients with heart failure with preserved ejection fraction without and with type 2 diabetes

In two 52-week double-blinded clinical trials, 529 patients with obesity-related heart failure with preserved ejection fraction (STEP-HFpEF), and 616 patients with obesity-related HFpEF and type 2 diabetes (STEP-HFpEF-DM) were randomised to be treated with either semaglutide 2.4 mg or placebo once weekly in addition to standard of care treatment.

At baseline, 66.2% and 70.6% of the patients were classified as New York Heart Association (NYHA) class II, 33.6% and 29.2% were NYHA class III and 0.2% and 0.2% were NYHA class IV, in STEP-

HFpEF and STEP HFpEF-DM respectively. Mean age was 68 years in both trials, median left ventricular ejection fraction (LVEF) was 57.0% and 56.0%, and mean BMI was 38.5 kg/m² and 37.9 kg/m². The STEP-HFpEF trial included 56.1% females, whereas 44.3% were female in STEP-HFpEF-DM. A high proportion of patients were on cardiovascular medications including ~ 81% on diuretics, ~ 81% on beta blockers, ~ 34% on angiotensin converting enzyme (ACE) inhibitors and ~ 45% on angiotensin receptor blockers (ARBs).

In STEP-HFpEF-DM patients were also receiving standard of care glucose lowering medications of which 32.8% were treated with sodium/glucose cotransporter-2 inhibitor (SGLT-2i) and 20.8% were treated with insulin.

The treatment effect of semaglutide 2.4 mg on heart failure symptoms was assessed using the Clinical Summary Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-CSS) which includes the domains of symptom (frequency and burden) and physical limitation. The score ranges from 0 to 100, with higher scores representing better health status. The treatment effect of semaglutide 2.4 mg on 6-Minute Walk Distance (6MWD) was assessed by the 6-Minute Walk Test (6MWT). Baseline values of KCCQ-CSS and 6MWD reflect a highly symptomatic population.

In both trials treatment with semaglutide 2.4 mg resulted in a superior effect on both KCCQ-CSS and 6MWD (Table 11). Benefits were seen both in heart failure symptoms and physical function **Table 10**

Results of 6MWD, KCCQ-CSS and body weight from the two 52-week randomised trials (STEP-HFpEF and STEP-HFpEF-DM)

	STEP-HFpEF		STEP-HFpEF-DM	
	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo
Full analysis set (N)	263	266	310	306
KCCQ-CSS (score)				
Baseline (mean) ¹	57.9	55.5	58.8	56.4
Change from baseline ²	16.6	8.7	13.7	6.4
Difference from placebo ² [95% CI]	7.8 [4.8; 10.9]		7.3 [4.1; 10.4]	
Patients (%) experiencing meaningful change ³	43.2	32.5	42.7	30.5
6MWD (metres)				
Baseline (mean) ¹	319.6	314.6	279.7	276.7
Change from baseline ²	21.5	1.2	12.7	-1.6
Difference from placebo ² [95% CI]	20.3 [8.6; 32.1]		14.3 [3.7; 24.9]	
Patients (%) with meaningful change ⁴	47.9	34.7	43.8	30.6
Body weight				
Baseline (kg) ¹	108.3	108.4	106.4	105.2
Change (%) from baseline ²	-13.3	-2.6	-9.8	-3.4
Difference (%) from placebo ² [95% CI]	-10.7 [-11.9; -9.4]		-6.4 [-7.6; -5.2]	

¹ Observed mean.

² Estimated using an ANCOVA model using multiple imputation and for KCCQ and 6MWD, also a composite imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

³ Meaningful within patient change threshold of 17.2 points for STEP-HFpEF trial and 16.3 points for STEP-HFpEF-DM trial (derived using an anchor-based method based on a 1-category improvement in Patient Global Impression of Status (PGI-S)). Percentages are based on subjects with an observation at the visit.

⁴ Meaningful within patient change threshold of 22.1 metres for STEP-HFpEF trial and 25.6 metres for STEP-HFpEF-DM trial (derived using an anchor-based method using “moderately better” in Patient Global Impression of Change (PGI-C)). Percentages are based on subjects with an observation at the visit.

The treatment benefit of semaglutide over placebo was consistent across all subpopulations defined by age, sex, BMI, race, ethnicity, region, SBP, LVEF and concomitant heart failure therapy.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Wegovy in one or more subsets of the paediatric population in the treatment of weight management (see section 4.2 for information on paediatric use).

STEP TEENS: Weight management in adolescent patients

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 semaglutide or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

At end of treatment (week 68), the improvement in BMI with semaglutide was superior and clinically meaningful compared with placebo (see Table 11 and Figure 8). Furthermore, a higher proportion of patients achieved $\geq 5\%$, 10% and $\geq 15\%$ weight loss with semaglutide compared with placebo (see Table 11).

Table 11 STEP TEENS: Results at week 68

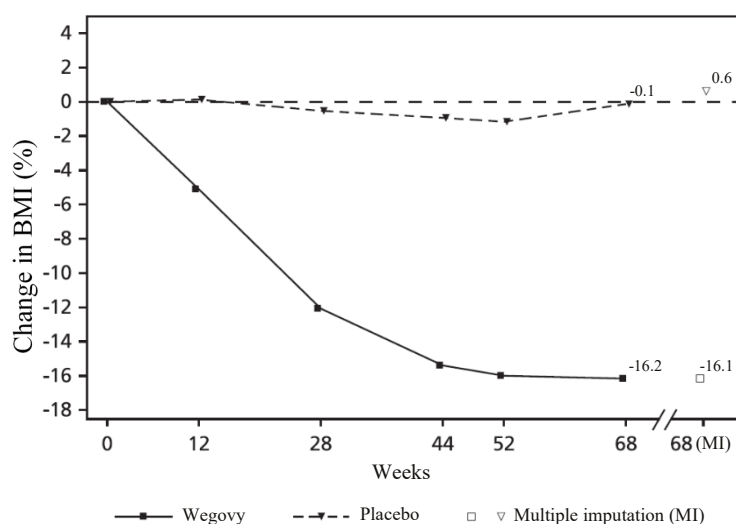
	Semaglutide 2.4 mg	Placebo
Full analysis set (N)	134	67
BMI		
Baseline (BMI)	37.7	35.7
Change (%) from baseline ^{1,2}	-16.1	0.6
Difference (%) from placebo ¹ [95% CI]	-16.7 [-20.3; -13.2]*	-
Baseline (BMI SDS)	3.4	3.1
Change from baseline in BMI SDS ¹	-1.1	-0.1
Difference from placebo ¹ [95% CI]	-1.0 [-1.3; -0.8]	-
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 $\geq 5\%$ ³	72.5*	17.7
Patients (%) achieving weight loss $\geq 10\%$ ³	61.8	8.1
Patients (%) achieving weight loss $\geq 15\%$ ³	53.4	4.8
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]	-
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; 1.1]	-

* $p < 0.0001$ (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 10.4% and 10.4% of patients randomised to semaglutide 2.4 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 68 for BMI based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -17.9% and 0.6% for semaglutide 2.4 mg and placebo respectively

³ Estimated from logistic regression model based on same imputation procedure as in primary analysis.



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

Figure 8 STEP TEENS: Mean change in BMI (%) from baseline to week 68

Noncirrhotic Metabolic Dysfunction-associated Steatohepatitis with Moderate to Advanced Liver Fibrosis in Adults

Overview of Clinical Trial

The efficacy of WEGOVY was evaluated based on an efficacy analysis at Week 72 in Study 8 (NCT#04822181), a 240-week, randomized, double-blind, placebo-controlled trial. Enrolled patients had a baseline or recent liver biopsy showing clinically significant MASLD (metabolic dysfunction-associated steatotic liver disease), defined as MASH with fibrosis stage 2 or 3 and a non-alcoholic fatty liver disease (NAFLD) Activity Score (NAS) ≥ 4 with a score of 1 or more in steatosis, lobular inflammation, and hepatocyte ballooning. Efficacy determination was based on the effect of WEGOVY on resolution of steatohepatitis without worsening of liver fibrosis and on at least one stage improvement in liver fibrosis without worsening of steatohepatitis, on post-baseline liver biopsies collected at 72 weeks.

The Week 72 analysis included 800 F2 and F3 (at eligibility) patients randomized 1:2 to receive placebo (n=266) or WEGOVY once weekly (n=534), in addition to standard of care for cardiometabolic comorbidities and healthy lifestyle counselling. WEGOVY or matching placebo was escalated to 2.4 mg once weekly during the initial 16 weeks of the treatment period. Dose escalation could be prolonged or patients could remain at a lower dose if 2.4 mg once weekly was not tolerable.

Demographic and baseline characteristics were balanced between treatment and placebo groups. Overall, the median (Q1 to Q3) age of patients at baseline was 57 (49 to 65) years, 57% were female, 18% were Hispanic, 68% were White, 27% were Asian, and 0.6% were Black or African American. Median (Q1 to Q3) body mass index (BMI) was 34 (30 to 38) kg/m² and median (Q1 to Q3) body weight was 93 (79 to 110) kg. Baseline characteristics are presented in Table 12.

Table 12. Baseline Characteristics in Adults Patients with Noncirrhotic MASH with Stage 2 to Stage 3 Fibrosis in Study 8

Characteristic	Overall (N = 800)
Fibrosis stage, n (%)	
F2	250 (31)
F3	550 (69)
Body Mass Index (BMI, kg/m ²), n (%) ^a	
<25	53 (7)

25-30	164 (21)
30-35	252 (32)
≥35	330 (41)
Lean MASH, n (%) ^b	22 (3)
Type 2 Diabetes, n (%)	447 (56)
Hypertension, n (%)	503 (63)
Dyslipidemia, n (%)	198 (25)
Statin use, n (%)	300 (38)
Fibrosis Index Based on 4 Factors (FIB-4), Median (Q1, Q3) ^a	1.6 (1.1, 2.3)
Enhanced Liver Fibrosis (ELF), Median (Q1, Q3)	9.9 (9.3, 10.5)

a. Less than 5% missingness in the variable is omitted.

b. Lean MASH defined as BMI <25 kg/m² for non-Asian patients and BMI <23 kg/m² for Asian patients.

Among the 79% of the patients with vibration-controlled transient elastography (VCTE) at baseline, median (Q1 to Q3) VCTE was 10.9 (8.6 to 15.5) kPa, which may not be representative of the entire study population. The 21% of patients with missing VCTE at baseline had higher percentages of being female and having baseline diabetes, hypertension, and dyslipidemia.

Results

Table 13 presents the Week 72 histopathology primary endpoint results comparing WEGOVY with placebo on 1) the estimated percentage of patients with resolution of steatohepatitis and no worsening of liver fibrosis and 2) the estimated percentage of patients with at least one stage improvement in liver fibrosis and no worsening of steatohepatitis. The secondary endpoint results of the estimated percentage of patients with resolution of steatohepatitis and improvement in liver fibrosis at Week 72 are also presented. Two pathologists independently read the liver biopsies for each patient; a third pathologist performed adjudication if consensus could not be reached between the two pathologists. WEGOVY demonstrated improvement on these histopathology endpoints at Week 72 compared to placebo.

Table 13. Efficacy Results at Week 72 in Adult Patients with Noncirrhotic MASH with Stage 2 or Stage 3 Fibrosis in Study 8

	Placebo N=266	WEGOVY N=534
Resolution of steatohepatitis and no worsening of liver fibrosis		
Response Rate (%)	34	63
Difference in response rate vs. placebo (95% CI)		29 (21, 36)*
Improvement in liver fibrosis and no worsening of steatohepatitis		
Response Rate (%)	22	37
Difference in response rate vs. placebo (95% CI)		14 (8, 21)*
Resolution of steatohepatitis and improvement in liver fibrosis		
Response Rate (%)	16	33
Difference in response rate vs. placebo (95% CI)		17 (10, 23)*

* Results were statistically significant.

Endpoints were evaluated according to the MASH Clinical Research Network (CRN). Resolution of steatohepatitis is defined as a score of 0 to 1 for lobular inflammation, 0 for ballooning, and any value for steatosis. No worsening of steatohepatitis is defined as no increase from baseline in score for ballooning, lobular inflammation, or steatosis.

Estimated using pooled Mantel-Haenszel (MH) estimates stratified by baseline type 2 diabetes status (presence or absence) and baseline fibrosis stage (F2 or F3) with missing data handled by reference-based multiple imputation and 95% confidence intervals (CIs) calculated using Rubin's rule to pool Sato's estimate of standard errors across the imputed datasets.

Another secondary endpoint was the percent change in body weight from baseline to Week 72. Patients treated with WEGOVY (mean baseline body weight 95.4 kg) achieved an average of 10.5% weight loss from baseline at Week 72, and patients treated with placebo (mean baseline weight 97.6 kg) achieved an average of 2% weight loss from baseline at Week 72;

treatment with WEGOVY resulted in an average of 8.5% greater weight loss from baseline compared to placebo (95% CI: 7.4% to 9.5%).

Starting at Week 12 and through Week 72, there was a trend of greater reductions from baseline in average ALT and AST in the WEGOVY group as compared to the placebo group.

5.2 Pharmacokinetic properties

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

Absorption

The average semaglutide steady state concentration following s.c. administration of the semaglutide maintenance dose was approximately 75 nmol/L in patients with overweight (BMI ≥ 27 kg/m² to <30 kg/m²) or obesity (BMI ≥ 30 kg/m²) based on data from phase 3a trials, where 90% of patients had average concentrations between 51 nmol/L and 110 nmol/L. Bioequivalence was established between exposure associated with semaglutide administered with the marketed drug product and the exposure obtained with the drug product used in phase 3a trials. The steady state exposure of semaglutide increased proportionally with doses from 0.25 mg up to 2.4 mg once weekly. Steady state exposure was stable with time as assessed up to week 68. Similar exposure was achieved with s.c. administration of semaglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of semaglutide was 89%.

Distribution

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

Metabolism/biotransformation

Prior to excretion, semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) was identified as one of the active metabolic enzymes.

Elimination

The primary excretion routes of semaglutide-related material are via the urine and faeces. Approximately 3% of the absorbed dose was excreted in the urine as intact semaglutide. The clearance of semaglutide in patients with overweight (BMI ≥ 27 kg/m² to <30 kg/m²) or obesity (BMI ≥ 30 kg/m²) was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 7 weeks after the last dose of 2.4 mg.

Special populations

There is no difference observed in the exposure of semaglutide following subcutaneous administration of WEGOVY between patients with MASH and patients with overweight or obesity.

Elderly

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

Gender, race and ethnicity

Gender, race (White, Black or African American, Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) had no effect on the pharmacokinetics of semaglutide based on data from phase 3a trials.

Body weight

Body weight had an effect on the exposure of semaglutide. Higher body weight was associated with lower exposure; a 20% difference in body weight between individuals will result in an approximate 18% difference in exposure. The 2.4 mg weekly dose of semaglutide provided adequate systemic exposures over the body weight range of 54.4–245.6 kg evaluated for exposure response in the clinical trials.

Renal impairment

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with patients with normal renal function. 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 3a trials.

Hepatic impairment

Hepatic impairment did not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) and compared with patients with normal hepatic function in a study with a single dose of 0.5 mg semaglutide.

Liver fibrosis

Fibrosis stage (F2 or F3) did not impact semaglutide exposure in patients with MASH.

Prediabetes and diabetes

Prediabetes and diabetes did not have any clinically relevant effect on the exposure of semaglutide based on data from phase 3 trials.

Immunogenicity

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

In the patients with MASH treated with WEGOVY for 72 weeks in Study 8 [see Clinical efficacy and safety], 3/763 (0.4%) of patients developed anti-semaglutide antibodies which were also cross-reactive to native GLP-1.

Paediatrics

Pharmacokinetic properties for semaglutide were assessed in a clinical trial for adolescent patients with obesity or overweight and at least one weight-related comorbidity ages 12 to <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.

Safety and efficacy of semaglutide in children and adolescents below 12 years of age have not been studied.

5.3 Preclinical safety data

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

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at

clinically relevant exposures. No other treatment-related tumours were observed. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded.

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pre-filled pen, single-use

Disodium phosphate, dihydrate

Sodium chloride

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

Pre-filled pen, FlexTouch

Disodium phosphate, dihydrate

Propylene glycerol

Phenol

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Pre-filled pen, FlexTouch

Before use: 3 years.

After first use: 6 weeks. Store below 30°C or in a refrigerator (2°C to 8°C).

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Pre-filled pen, FlexTouch (0.25, 0.5 mg) 1.5 mL pre-filled pen

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

Pre-filled pen, FlexTouch (0.5, 1, 1.7 and 2.4 mg) 3 mL pre-filled pen

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

Pack sizes

Pre-filled pen, FlexTouch (0.25, 0.5, 1 and 1.7 mg)

Pack size of 1 pre-filled pen and 4 disposable NovoFine Plus needles.

Pre-filled pen, FlexTouch (2.4 mg)

Pack sizes:

1 pre-filled pen and 4 disposable NovoFine Plus needles.

3 pre-filled pens and 12 disposable NovoFine Plus needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Wegovy should not be used if it does not appear clear and colourless.
The pen should not be used if it has been frozen.

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

Pre-filled pen, FlexTouch

This pen is for multi-use. It contains 4 doses. 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.

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

The pen is for use by one person only.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

12/2025