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 2.4 mg, solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Wegovy 2.4 mg solution for injection

Each pre-filled pen contains 2.4 mg of semaglutide* in 0.75 mL

*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

Clear and colourless isotonic solution; pH=7.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

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

- ≥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.

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 ≥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/m2) 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 doses higher than 2.4 mg are not recommended.

If patients have been unable to lose at least 5% of their initial body weight after 6 months on treatment, a decision is required on whether to continue treatment, taking into account the benefit/risk profile in the individual patient (see section 5.1).

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

Adolescents
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.

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
Patients with type 2 diabetes
Semaglutide should not be used in combination with other GLP-1 receptor agonist products.

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

Elderly patients (≥65 years old)
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited.

Patients with renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with end-stage renal disease (see section 5.2).

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

Paediatric population
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.

Method of administration
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.

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

For further information on administration see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Gastrointestinal effects
Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions that can cause dehydration, which in rare cases can lead to a deterioration of renal function. Patients should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

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

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

Hypoglycaemia in patients with 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. The addition of semaglutide 2.4 mg in patients treated with insulin has not been evaluated.

Diabetic retinopathy in patients with type 2 diabetes
In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. 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 semaglutide 2.4 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy.

Populations not studied
There is no experience in patients with congestive heart failure New York Heart Association (NYHA) class IV. There is limited experience in patients aged 75 years or more.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

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.

4.5 Interaction with other medicinal products and other forms of interaction

As with other GLP-1 receptor agonists, semaglutide may delay 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. 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 was observed based on the evaluated medications. Therefore, no dose adjustment is required when co-administered with semaglutide.

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
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 were not affected in a clinically relevant manner.

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.

Pregnancy

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

Breast-feeding

In lactating rats, semaglutide was excreted in milk. 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 4 phase 3a trials, 2,650 adult patients were exposed to semaglutide 2.4 mg. The duration of the trials was 68 weeks. Similar to other GLP-1 receptor agonists, 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 phase 3a clinical trials in adults. The frequencies are based on a pool of the phase 3a trials.

Adverse reactions associated with semaglutide 2.4 mg 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 3 Adverse reactions from controlled phase 3 trials 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 disorder	Headache[b]	Dizziness[b]		
Eye disorders		Diabetic retinopathy in patients with type 2 diabetes[a]		
Cardiac disorders			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] Gastrooesophageal reflux disease[b] Dyspepsia[b] Eructation[b] Flatulence[b] Abdominal distension[b]	Acute pancreatitis[a]	
Hepatobiliary disorders		Cholelithiasis[a]		
Skin and subcutaneous tissue disorders		Hair loss[a]		Angioedema
General disorders and administration	Fatigue[b,c]	Injection site reactions[c]		

site conditions				
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

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 semaglutide 2.4 mg (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 2.4 mg (11.1% for placebo) and was mild to moderate in severity and of longer duration.

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

Acute pancreatitis

The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.2% for semaglutide 2.4 mg and <0.1% for placebo, respectively.

Acute gallstone disease/Cholelithiasis

Cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide 2.4 mg.

Hair loss

Hair loss was reported in 2.5% of patients treated with semaglutide 2.4 mg 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 (≥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 2.4 mg. The proportions of patients with a maximum increase from baseline ≥20 bpm/min at any timepoint during the on-treatment period were 26.0% in the semaglutide 2.4 mg 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 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.

Hypoglycaemia in patients with type 2 diabetes

In STEP 2, clinically significant hypoglycaemia was observed in 6.2% (0.1 events/patient year) of patients treated with semaglutide 2.4 mg compared with 2.5% (0.03 events/patient year) of patients 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 semaglutide 2.4 mg was used with a sulfonylurea.

Diabetic retinopathy in patients with type 2 diabetes
New onset or worsening of diabetic retinopathy (4.0% vs 2.7% of patients treated with semaglutide 2.4 mg vs placebo, respectively) was observed in STEP 2.

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 compared to 0% of patients treated with placebo.

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

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

Great Britain
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem, and direct and indirect effects on areas involved in hedonic regulation of food intake, including the septum, thalamus and amygdala.

In addition, in clinical studies semaglutide has 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.

Pharmacodynamic effects

Appetite, energy intake and food choice

In phase 1 trial, energy intake during an *ad libitum* meal was 35% lower with semaglutide 2.4 mg compared to placebo after 20 weeks of dosing. This was supported by improved control of eating, increased feeling of fullness, greater satiety, reduced hunger, less food cravings (for dairy and savoury foods), less desire for sweet food 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.

Clinical efficacy and safety

The efficacy and safety of semaglutide 2.4 mg 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 2.4 mg) 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).

As an inclusion criterion in STEP 1, 3 and 4, all patients with a BMI $\geq$27 kg/m^2 to <30kg/m^2 were required to have at least one of these weight-related comorbidities: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. In STEP 2, all patients had a BMI $\geq$27 kg/m^2 and type 2 diabetes.

The majority of patients had at least one weight-related comorbidity. These included, however were not limited to hypertension, dyslipidaemia, cardiovascular disease, pre-diabetes, knee or hip osteoarthritis, obstructive sleep apnoea, asthma/chronic obstructive pulmonary disease (COPD), liver disease (non-alcoholic fatty liver

disease (NAFLD) or non-alcoholic steatohepatitis (NASH) and polycystic ovary syndrome (PCOS).

In STEP 1, 2 and 4, all patients received instructions for a reduced calorie diet (500 kcal/day deficit) and increased physical activity (150 min/week).

Treatment with semaglutide 2.4 mg 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. Furthermore, across the trials, a higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with semaglutide 2.4 mg compared with placebo. The reduction in body weight occurred irrespective of the presence of gastrointestinal symptoms such as nausea, vomiting or diarrhoea. Specific data on weight loss and its time course for STEP 1-4 are presented in Tables 4-7 and Figures 1-3.

Efficacy was demonstrated regardless of age, sex, race, ethnicity, baseline body weight, BMI, presence of type 2 diabetes and level of renal function.

STEP 1: Weight Management

In a 68-week double-blind trial, 1,961 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 semaglutide 2.4 mg or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

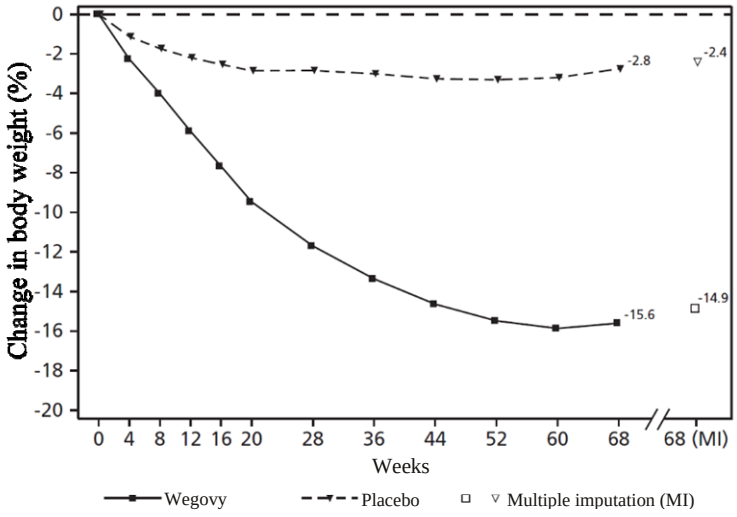
Weight loss occurred early and continued throughout the trial. At end of treatment (week 68), the weight loss was superior and clinically meaningful compared with placebo (see Table 4 and Figure 1). Furthermore, a higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with semaglutide 2.4 mg compared with placebo (see Table 4). In STEP 1, after approximately 6 months (28 weeks) of treatment, 89.8% of patients treated with semaglutide 2.4 mg achieved a ≥5% weight loss. Out of those who did not, 40.5% nonetheless achieved a weight loss ≥5% after 68 weeks of treatment.

Table 4 STEP 1: Results at week 68

	Wegovy	**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 ≥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]*	-
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. 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.

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/m^2) 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 anti-diabetic drugs. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

Treatment with semaglutide 2.4 mg for 68 weeks resulted in superior and a clinically meaningful reduction in body weight and in HbA_{1c} compared to placebo (see Table 5 and Figure 2). In STEP 2, after approximately 6 months (28 weeks) of treatment, 74.7% of patients treated with semaglutide 2.4 mg achieved a ≥5% weight loss. Out of those who did not, 31.9% nonetheless achieved a weight loss ≥5% at week 68 of treatment.

Table 5 STEP 2: Results at week 68

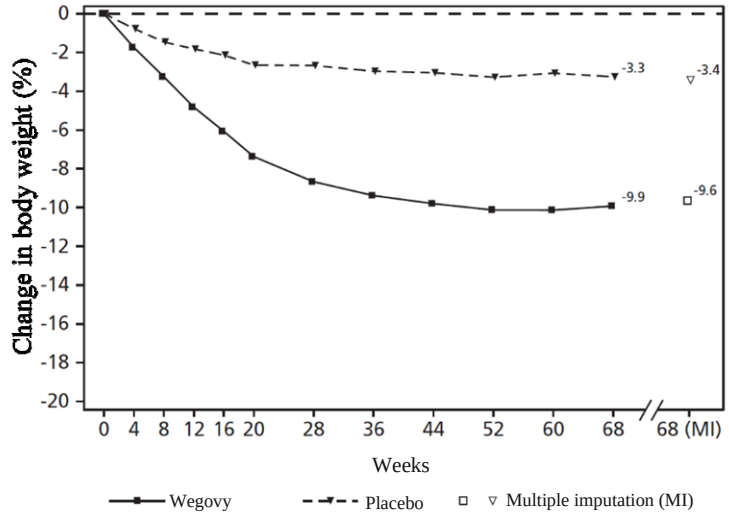
	Wegovy	**Placebo**
Full analysis set (N)	404	403
Body weight		
Baseline (kg)	99.9	100.5
Change (%) from baseline[1,2]	-9.6	-3.4
Difference (%) from placebo[1] [95% CI]	-6.2 [-7.3; -5.2]*	-
Change (kg) from baseline	-9.7	-3.5
Difference (kg) from placebo[1] [95% CI]	-6.1 [-7.2; -5.0]	-
Patients (%) achieving 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]*	-
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[1,2]	-17.5 (-1.6)	-4.1 (-0.4)
Difference from placebo[1] [95% CI]	-13.5 [-15.5; -11.4] (-1.2 [-1.4; -1.0])*	- -
Patients (%) achieving HbA_{1c} <7%[3]	77.4	26.0
Patients (%) achieving HbA_{1c} ≤6.5%[3]	65.9	15.1

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

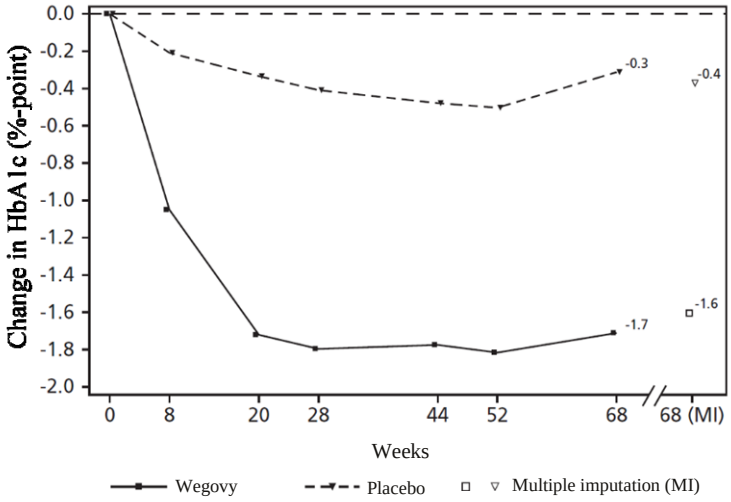
[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[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.



HbA1c: Haemoglobin A1c
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 (kg) and HbA_{1c} (%) 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/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 semaglutide 2.4 mg or placebo. During the trial, all patients received intensive behavioral therapy (IBT) consisting of an initial 8-week low-calorie diet (1000 to 1200 kcal/day) followed by 60 weeks reduced caloric diet (1200-1800 kcal/day), increased physical activity (100 mins/week with gradual increase to 200 mins/week) and behavioural counselling.

Treatment with semaglutide 2.4 mg 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

	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 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/m^2), or with overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) 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/m^2.

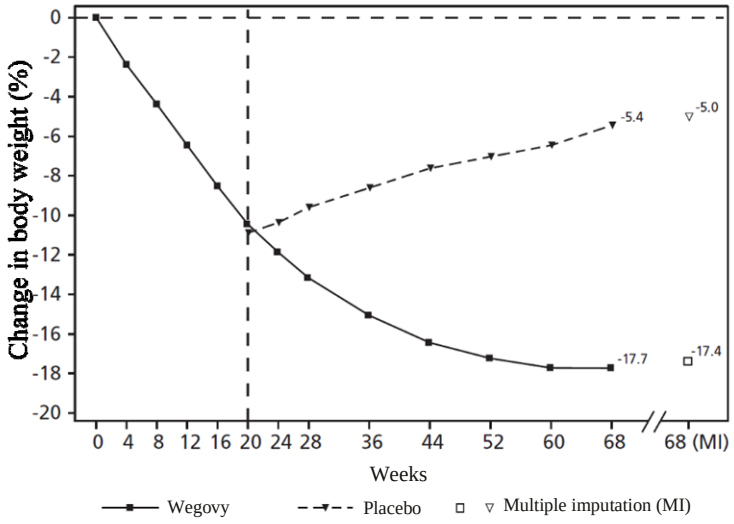
Patients who had reached the maintenance dose of 2.4 mg at week 20 (baseline) and continued treatment with semaglutide 2.4 mg for 48 weeks (week 20–68) continued losing weight and had a superior and clinically meaningful reduction in body weight compared to those switched to placebo (see Table 7 and Figure 3). On the other hand, in patients switching to placebo at week 20 (baseline), body weight increased steadily from week 20 to week 68. 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 the medicinal product 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 7 STEP 4: Results from week 20 to week 68

	Wegovy	**Placebo**
Full analysis set (N)	535	268
Body weight		
Baseline[1] (kg)	96.5	95.4
Change (%) from baseline[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[1]	105.5	104.7
Change from baseline[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 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 -8.1% 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: Long term efficacy

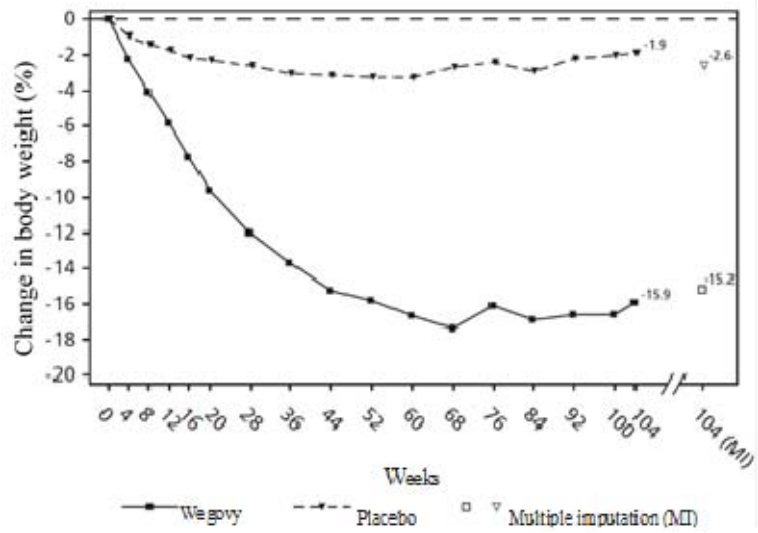
In a 104-week double-blind trial, 304 patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity, were randomised to semaglutide or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial. 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 8 and Figure 4) Patients treated with semaglutide achieved a mean change in body weight of -15.2%, with
weight loss ≥5% achieved by 74.7%, ≥10% achieved by 59.2% and ≥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

	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 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/m^2), or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity, were randomised to semaglutide 2.4 mg 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/m^2, 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 ≥20%, compared to 7.0% treated with liraglutide. Table 9 shows the results of the confirmatory endpoints ≥10%, ≥15% and ≥20% weight loss.

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

	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<0.005 (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 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 semaglutide and liraglutide respectively.
[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

Secondary endpoints
Cardiovascular risk factors
Semaglutide 2.4 mg lowered waist circumference, blood pressure and C-reactive protein (CRP), and improved lipid profile compared with placebo.

Glycaemic control
In STEP 1 and 3, among those patients with pre-diabetes at baseline, more semaglutide 2.4 mg treated patients had achieved normo-glycaemic status compared to placebo-treated patients (STEP 1: 84.1% vs 47.8%; STEP 3: 89.5% vs 55.0%).

Improvement in physical functioning
Semaglutide 2.4 mg showed statistically significant improvement (Table 10) in physical functioning scores and more patients achieved a clinically meaningful improvement compared to placebo (Table 10). Physical functioning was assessed using both the generic health-related quality of life questionnaire Short Form-36v2 Health Survey, Acute Version (SF-36v2) and the obesity-specific questionnaire Impact of Weight on Quality of Life Lite Clinical Trials Version (IWQOL-Lite-CT).

Table 10: Results on physical functioning in STEP 1-2

	STEP 1		STEP 2	
	Wegovy	Placebo	Wegovy	Placebo
SF-36v2 Physical Functioning[1]				
Baseline	51.0	50.8	49.2	49.6
Change from baseline	2.2	0.4	2.5	1.0
Difference from placebo [95% CI]	1.8 [1.2; 2.4]*	-	1.5 [0.4; 2.6]*	-

Patients (%) achieving clinically meaningful improvement[2,4]	39.8	24.1	41.0	27.3
IWQOL-Lite-CT Physical Function				
Baseline	65.4	64.0	67.1	69.2
Change from baseline	14.7	5.3	10.1	5.3
Difference from placebo [95% CI]	9.4 [7.5; 11.4]*	-	4.8 [1.8; 7.9]*	-
Patients (%) achieving clinically meaningful improvement[3,4]	51.8	28.3	39.6	29.5

* $p<0.0001$ (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.

Other patient reported outcomes
Beneficial effects of semaglutide 2.4 mg vs. placebo were demonstrated in STEP 1 and 2 in all additional scores on the obesity-specific questionnaire IWQOL-Lite-CT (Physical, Psychosocial, and Total).

Cardiovascular evaluation
Completed cardiovascular outcome data are not available for semaglutide 2.4 mg. 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/m^2.

Treatment with semaglutide reduced the rate of a major adverse cardiovascular event (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.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with semaglutide 2.4 mg 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 5). Furthermore, a higher proportion of patients achieved ≥5%, 10% and ≥15% weight loss with semaglutide compared with placebo (see Table 11).

Table 11 STEP TEENS: Results at week 68

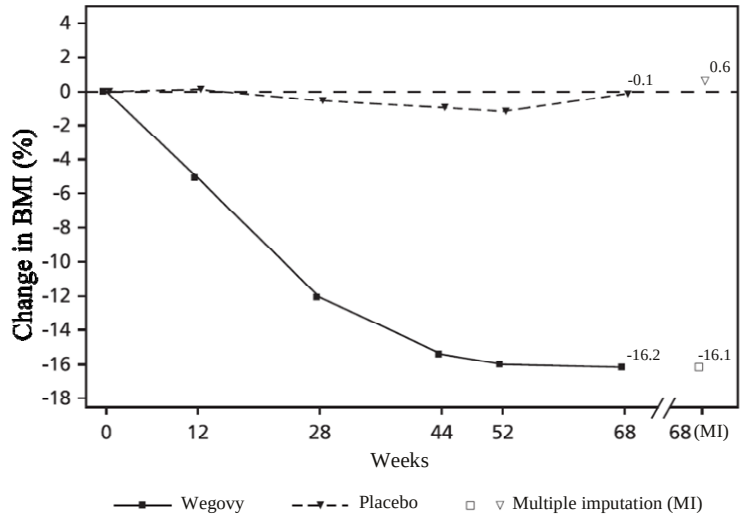
	Wegovy	**Placebo**
Full analysis set (N)	134	67
BMI		
Baseline (BMI)	37.7	35.7
Change (%) from baseline[1,2]	-16.1	0.6
Difference (%) from placebo[1] [95% CI]	-16.7 [-20.3; -13.2][*]	-
Baseline (BMI SDS)	3.4	3.1
Change from baseline in BMI SDS[1]	-1.1	-0.1
Difference from placebo[1] [95% CI]	-1.0 [-1.3; -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 ≥5%[3]	72.5[*]	17.7
Patients (%) achieving weight loss ≥10%[3]	61.8	8.1
Patients (%) achieving weight loss ≥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 5 STEP TEENS: Mean change in BMI (%) from baseline to week 68

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 semaglutide 2.4 mg was approximately 75 nmol/L in patients with overweight (BMI $\geq$27 kg/m^2 to <30 kg/m^2) or obesity (BMI $\geq$ 30 kg/m^2). The steady state exposure of semaglutide increased proportionally with 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%.

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) is expected to be involved in the metabolism of semaglutide.

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/m^2 to <30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) 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

Elderly

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a 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.

Body weight

Body weight had an effect on the exposure of semaglutide. Higher body weight was associated with lower 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/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 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.

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 2.4 mg in children below 12 years of age has 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

Disodium phosphate, dihydrate

Sodium chloride

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

24 months.

6.4 Special precautions for storage

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

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

Store the pen in the original carton in order to protect from light.

Wegovy may be stored at up to 25°C for a single period of up to 21 days. The product must not be returned to the refrigerator.

6.5 Nature and contents of container

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). The syringe is assembled into a disposable pre-filled pen made of stainless steel, polyoxymethylene and acrylonitrile butadiene styrene. For safety, the needle is only exposed when the needle cover is retracted during injection and, following the injection, the needle cover returns to the initial position and locks.

Pack sizes:

Wegovy 2.4 mg solution for injection: Each pre-filled pen contains 0.75 mL solution, delivering 1 dose of 2.4 mg.

4 pre-filled pens

6.6 Special precautions for disposal

The pen is for single-use only.

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, used pen or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd

Denmark

8 MARKETING AUTHORISATION NUMBER(S)

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