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 1.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Wegovy 1.5 mg tablets

Each tablet contains 1.5 mg of semaglutide*.

*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

Tablet

Wegovy 1.5 mg tablets

White to light yellow and round (6.5 mm in diameter) debossed with ‘1.5’ on one side and ‘novo’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Wegovy tablets are 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.

For trial results with respect to the effect on cardiovascular events, obesity-related heart failure, populations studied and background therapies see section 5.1.

4.2 Posology and method of administration

Posology

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

The maximum recommended single daily dose of orally administered semaglutide is 25 mg. Orally administered semaglutide should always be used as only one tablet per day. Taking more than one tablet a day should not be done to achieve the effect of a higher dose.

Switching from semaglutide injection (subcutaneous (s.c)) to semaglutide tablets (oral)

The effect of switching between semaglutide tablets and semaglutide injection cannot easily be predicted because oral semaglutide displays higher pharmacokinetic variability in absorption compared to semaglutide injection.

Patients treated with semaglutide injection 2.4 mg once weekly can be transitioned to semaglutide 25 mg tablets once daily.

Patients can start semaglutide tablets one week after their last dose of semaglutide injection.

Patients with type 2 diabetes

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

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

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/1.73m^2) 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

The safety and efficacy of orally administered semaglutide in children and adolescents below 18 years have not been established. No data is available.

Method of administration

Wegovy is a tablet for once-daily oral use.

- This medicinal product should be taken on an empty stomach after a recommended fasting period of at least 8 hours (see section 5.2).
- It should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 mL). Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of semaglutide.
- Patients should wait at least 30 minutes before eating, drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of semaglutide (see sections 4.5 and 5.2).

Adherence to the dosing regimen is recommended for optimal effect of semaglutide tablets.

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 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.

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.

Acute pancreatitis

Semaglutide has not been studied in patients with a history of pancreatitis and should be used with caution in these patients.

Acute pancreatitis has been reported in patients treated with GLP-1 receptor agonists. This includes post-marketing reports of necrotising pancreatitis and reports with a fatal outcome. Patients should be informed of the symptoms of acute pancreatitis, including persistent, severe abdominal pain. Patients should be advised to seek immediate medical attention if they occur. If pancreatitis is suspected, semaglutide should be discontinued. If the diagnosis of pancreatitis is confirmed, semaglutide should not be restarted.

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 may indicate an increased risk of 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. Patients reporting a sudden loss of vision (including partial loss) should be urgently referred for ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed (see section 4.8).

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).

Treatment response

If the treatment response with semaglutide tablets is lower than expected, the treating physician should be aware that the absorption of orally administered semaglutide may be variable; therefore, adherence to the dosing regimen is recommended for optimal effect.

For patients with diabetes

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

Hypoglycaemia

Semaglutide lowers blood glucose and can cause hypoglycaemia. Patients should be aware of the risk of hypoglycaemia and be educated on the signs and symptoms of 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.

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 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 85 years or more.

Sodium content

The 1.5 mg, 4 mg and 9 mg tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

The 25 mg tablets contain 23 mg sodium per tablet, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

Semaglutide delays gastric emptying which may influence the absorption of other oral medicinal products.

Effects of semaglutide on other medicinal products

Thyroxine

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

Warfarin and other coumarin derivatives

Semaglutide did not change the AUC or C_{max} of R- and S-warfarin following a single dose of warfarin, and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, 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.

Rosuvastatin

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

Digoxin, oral contraceptives, metformin, furosemide

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

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

Effects of other medicinal products on semaglutide

Omeprazole

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

In a trial investigating the pharmacokinetics of semaglutide co-administered with five other tablets, the AUC of semaglutide decreased by 34% and C_{max} by 32%. This suggests that the presence of multiple tablets in the stomach influences the absorption of semaglutide if co-administered at the same time. After administering semaglutide, the patients should wait 30 minutes before taking other oral medicinal products (see section 4.2).

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).

Breast-feeding

No measurable concentrations of semaglutide were found in breast milk of lactating women. Salcaprozate sodium was present in breast milk and some of its metabolites were excreted in breast milk at low concentrations. As a risk to a breast-fed child cannot be excluded, Wegovy 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 (STEP 1-4), 2,650 adult patients were exposed to semaglutide injection. The duration of the trials was 68 weeks. The most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhoea, constipation and vomiting.

In a 64-week phase 3b trial (OASIS 4), 204 adult patients with obesity (BMI $\geq$ 30 kg/m^2) or with overweight (BMI $\geq$ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbidity, were exposed to semaglutide tablets. The safety profile of semaglutide tablets was consistent with the safety profile of semaglutide seen in the phase 3a trials with semaglutide injection.

Tabulated list of adverse reactions

Table 1 lists adverse reactions identified in clinical trials in adults and post-marketing reports. The frequencies are based, unless otherwise specified, on a pool of the semaglutide injection phase 3a trials (STEP 1-4). The adverse reactions in OASIS 4 had similar frequencies to the semaglutide injection phase 3a trials, except for Dyspepsia which had a higher frequency category. Events not relevant for oral administration are omitted in the following overview.

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

Table 1 Frequency of adverse reactions of semaglutide

MedDRA	Very	Common	Uncommon	Rare	Very rare	

system organ class	**common**					**Not known**
Immune system disorders				Anaphylactic reaction		
Metabolism and nutrition disorders		Hypoglycaemia in patients with type 2 diabetes[a]	Hypoglycaemia in patients without type 2 diabetes[a]			
Nervous system disorders	Headache[b]	Dizziness[b] Dysaesthesia[a,c] Dysgeusia[b,c]				
Eye disorders		Diabetic retinopathy in patients with type 2 diabetes[a]			Non-arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders			Increased heart rate[a,c]			
Vascular disorders			Hypotension Orthostatic hypotension			
Gastrointestinal disorders	Vomiting[a,b] Diarrhoea[a,b] Constipation[a,b] Dyspepsia[b,e] Nausea[a,b] Abdominal pain[b, c]	Gastritis[b, c] Gastrooesophageal reflux disease[b] Eructation[b] Flatulence[b] Abdominal distension[b]	Acute pancreatitis[a] Delayed gastric emptying			Intestinal obstruction[c, d]
Hepatobiliary disorders		Cholelithiasis[a]				
Renal and urinary disorders			Urolithiasis[a]			
Skin and subcutaneous tissue disorders		Hair loss[a]		Angioedema		
General disorders and administration site conditions	Fatigue[b,c]					
Investigations			Increased amylase[c] Increased lipase[c] Increased Bilirubin[a]			
Injury				Hip Fracture[a]		

[a)] See description of selected adverse reactions below
[b)] Mainly seen in the dose-escalation period
[c)] Grouped preferred terms
[d)] From post-marketing reports
[e)] The frequency is based on the OASIS 4 phase 3 trial with semaglutide tablets

In a cardiovascular outcomes trial (SELECT), 8,803 patients were exposed to semaglutide injection for a median of 37.3 months and 8,801 patients were exposed to placebo for a median of 38.6 months (See section 5.1). Safety data collection was

limited to serious adverse events (including death), adverse events leading to discontinuation, and adverse events of special interest. Sixteen percent (16%) of semaglutide injection treated patients and 8% of placebo-treated patients, respectively, discontinued study drug due to an adverse event. Additional information from this trial is included in subsequent sections below when relevant.

In the HFpEF trials with semaglutide injection, 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.

Description of selected adverse reactions

The below adverse reactions are applicable for semaglutide tablets. Data on specific adverse reactions, unless otherwise specified, pertains to the OASIS 4 phase 3 trial.

Gastrointestinal adverse reactions

The events were most frequently reported during dose escalation. Over the 64 weeks trial period, nausea occurred in 46.6% of patients when treated with semaglutide tablets (18.6% for placebo), vomiting in 30.9% (5.9% for placebo) and diarrhoea in 17.6% (8.8% for placebo). Most events were mild to moderate in severity and of short duration. Constipation occurred in 20.1% of patients treated with semaglutide tablets (9.8% for placebo) and was mild to moderate in severity and of longer duration.

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

Patients with moderate renal impairment (eGFR $\geq$ 30 to < 60 mL/min/1.73m^2) may experience more gastrointestinal effects when treated with semaglutide.

The gastrointestinal events led to permanent treatment discontinuation in 3.4% of patients treated with semaglutide tablets.

Over 68 weeks trial period for patients treated with semaglutide injection 2.4 mg, 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

Acute pancreatitis was reported in 0% of patients treated with semaglutide tablets and 1.0% of patients treated with placebo. The frequency of adjudication-confirmed acute pancreatitis reported in the STEP semaglutide injection phase 3a clinical trials was 0.2% for semaglutide injection and <0.1% for placebo, respectively.

Acute gallstone disease/Cholelithiasis

Cholelithiasis was reported in 2.5% and led to cholecystitis in 0% of patients treated with semaglutide tablets. Cholelithiasis and cholecystitis were reported in 1% and 0%, respectively, of patients treated with placebo. Cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide injection 2.4 mg.

Hair loss

Hair loss was reported in 6.4% of patients treated with semaglutide tablets and in 2.0% of patients treated with placebo. All events were mild or moderate and half of them recovered by end of the trial.

Hair loss was reported in 2.5% of patients treated with semaglutide injection 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

A mean increase of 2 beats per minute (bpm) from a baseline mean of 72 bpm was observed in patients treated with semaglutide tablets. The proportions of subjects with an increase in pulse from baseline ≥ 20 bpm at any timepoint during the on-treatment period were 26.5% in the semaglutide tablets group vs. 20.8% in the placebo group.

A mean increase of 3 beats per minute (bpm) from a baseline mean of 72 bpm was observed in patients treated with semaglutide injection 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 with semaglutide injection 2.4 mg 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 patients treated with semaglutide injection 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 injection 2.4 mg was used with a sulfonylurea.

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

Hypoglycaemia in patients without type 2 diabetes

In a cardiovascular outcomes trial for semaglutide injection (SELECT) in adult patients without type 2 diabetes, 3 episodes of serious hypoglycaemia were reported in semaglutide injection treated patients versus 1 episode in placebo. Patients with a history of bariatric surgery (a risk factor for hypoglycaemia) had more events of serious hypoglycaemia while taking semaglutide injection (2.3%, 2/87) than placebo (0%, 0/97).

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 injection 2.4 mg vs placebo, respectively) was observed in STEP 2.

Fractures

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

Urolithiasis

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

Bilirubin

In the cardiovascular outcomes trial for semaglutide injection in adults (SELECT), increases in total bilirubin greater than or equal to 3 times the upper limit of normal were observed in 0.3% (30/8585) of semaglutide injection treated patients versus 0.2% (14/8579) of placebo-treated patients.

Dysaesthesia

Events related to a clinical picture of altered skin sensation such as sensitive skin, hyperaesthesia,

paraesthesia, skin burning sensation and allodynia were reported in 4.9% of patients treated with

semaglutide tablets. No events were reported in patients treated with placebo. The events were mild to moderate in severity and most patients recovered while on continued treatment.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes may be 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.

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 Yellow Card Scheme Website: https://yellowcard.mhra.gov.uk/ 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.

The exact mechanism of cardiovascular risk reduction has not been established.

Pharmacodynamic effects

Appetite, energy intake and food choice

In phase 1 trial, energy intake during an *ad libitum* meal was 35% lower with semaglutide injection 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 25 mg orally administered semaglutide tablets once daily for weight management in combination with a reduced calorie intake and increased physical activity have been evaluated in a 64-week double-blinded randomised placebo-controlled phase 3b trial (OASIS 4) including 307 patients (205 randomised to treatment with orally administered semaglutide).

OASIS 4: Weight management – once daily Wegovy 25 mg tablet (semaglutide tablets 25 mg)

In a 64-week phase 3b trial, 307 adult patients with obesity (BMI $\geq$ 30 kg/m^2) or with overweight (BMI $\geq$ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbidity, were randomised to once daily orally administered 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 64), the weight loss was superior and clinically meaningful compared with placebo (see Table 2 and Figure 1).

Furthermore, a higher proportion of patients achieved ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% weight loss with orally administered semaglutide compared with placebo (see Table 2). Among patients with prediabetes at baseline, a higher proportion of patients had a normo-glycaemic status at end of treatment with orally administered semaglutide compared to placebo (71.1% vs. 33.3%). The

reduction in body weight occurred irrespective of the presence of gastrointestinal symptoms such as

nausea, vomiting or diarrhoea.

Efficacy was demonstrated regardless of age, sex, race, ethnicity, baseline body weight, BMI and level of renal function. Variations in efficacy existed within all subgroups. Relatively greater weight loss

was observed in women and in patients with a lower versus higher baseline body weight.

Table 2 OASIS 4: Results at week 64

	Semaglutide 25 mg tablet	**Placebo**
Full analysis set (N)	205	102
Body weight		
Baseline (kg)	106.4	104.8
Change (%) from baseline[1,2]	-13.6	-2.2
Difference (%) from placebo[1] [95% CI]	-11.4 [-13.9; -9]*	
Change (kg) from baseline[1]	-14.2	-2.2
Difference (kg) from placebo[1] [95% CI]	-12.0 [-14.6; -9.5]*	
Patients (%) achieving weight loss ≥ 5%[3]	76.3*	30.5
Patients (%) achieving weight loss ≥ 10%[3]	59.8*	14.1
Patients (%) achieving weight loss ≥ 15%[3]	47.0*	5.4
Patients (%) achieving weight loss ≥ 20%[3]	27.5*	3
Waist circumference (cm)		
Baseline	114	113.6
Change from baseline[1]	-12.2	-2.8
Difference from placebo[1] [95% CI][1]	-9.5 [-12.4; -6.6]*	
BMI (kg/m^2)		
Baseline	37.5	37.8
Patients (%) achieving BMI <30kg/m^2 [3]	26.0*	2.9
Systolic blood pressure (mmHg)		
Baseline	131	131
Change from baseline[1]	-6.8	-5.4

Difference from placebo[1] [95% CI]	-1.4 [-4.6; 1.8]	
Glycaemic status		
Patients (%) with pre-diabetes at baseline	97 (47.3)	47 (46.1)
Patients (%) achieving normo-glycaemic status at end of treatment	64 (71.1)	13 (33.3)

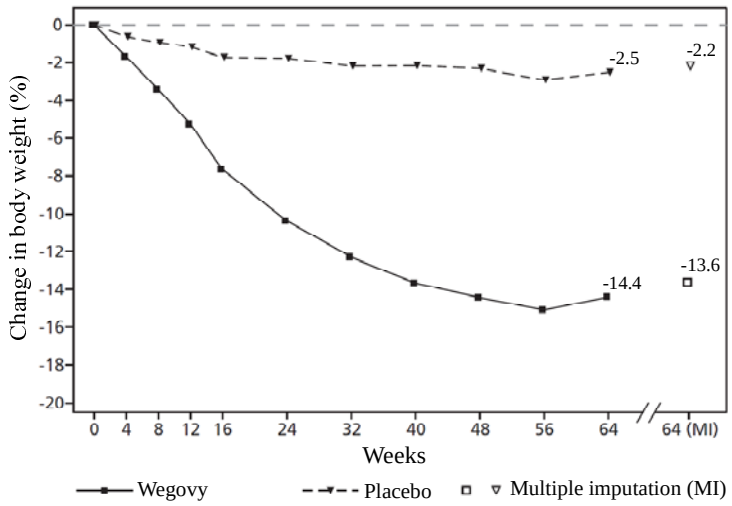
* p<0.0001 (unadjusted 2-sided) for superiority.

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

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

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

Body weight (%) change from baseline by week - mean plot - treatment policy strategy - full analysis set



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

Figure 1 OASIS 4: Mean change in body weight (%) from baseline to week 64

The following studies (STEP, SELECT, SUSTAIN) concern subcutaneously administered semaglutide injection. The efficacy and safety of semaglutide injection 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 subcutaneously administered semaglutide injection) were included in these trials. Furthermore, the two-year efficacy and safety of subcutaneously administered semaglutide injection 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 s.c.).

Treatment with semaglutide injection demonstrated superior, clinically meaningful, and sustained weight loss compared with placebo in patients with obesity (BMI $\geq$ 30 kg/m^2), or overweight (BMI $\geq$ 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 $\geq$ 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 injection 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 (BMI $\geq$30 kg/m^2), or with overweight (BMI $\geq$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 3 and Figure 2). Furthermore, a higher proportion of patients achieved $\geq$5%, $\geq$10%, $\geq$15% and $\geq$20% weight loss with semaglutide 2.4 mg compared with placebo (see Table 3). In STEP 1, after approximately 6 months (28 weeks) of treatment, 89.8% of patients treated with semaglutide 2.4 mg achieved a $\geq$5% weight loss. Out of those who did not, 40.5% nonetheless achieved a weight loss $\geq$5% after 68 weeks of treatment.

Table 3 STEP 1: Results at week 68

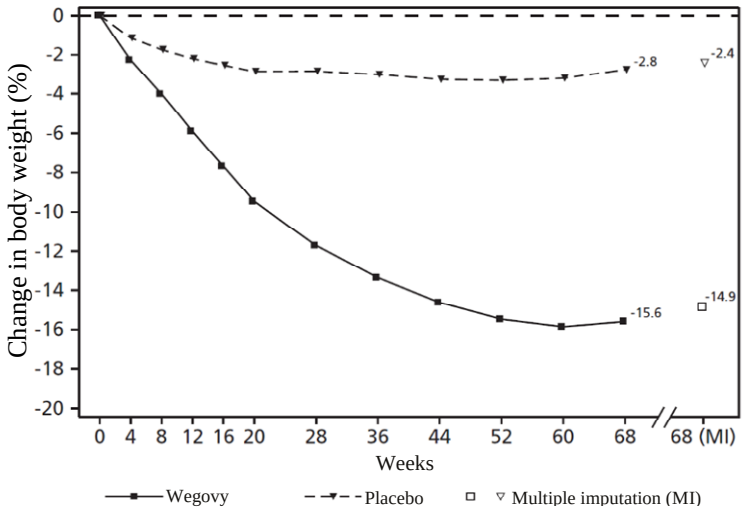
	Semaglutide 2.4 mg	**Placebo**
Full analysis set (N)	1,306	655
Body weight		
Baseline (kg)	105.4	105.2
Change (%) from baseline[1,2]	-14.9	-2.4
Difference (%) from placebo[1] [95% CI]	-12.4 [-13.4; -11.5]*	-
Change (kg) from baseline	-15.3	-2.6
Difference (kg) from placebo[1] [95% CI]	-12.7 [-13.7; -11.7]	-
Patients (%) achieving weight loss ≥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 2 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 4 and Figure 3). 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 4 STEP 2: Results at week 68

	Semaglutide 2.4 mg	**Placebo**

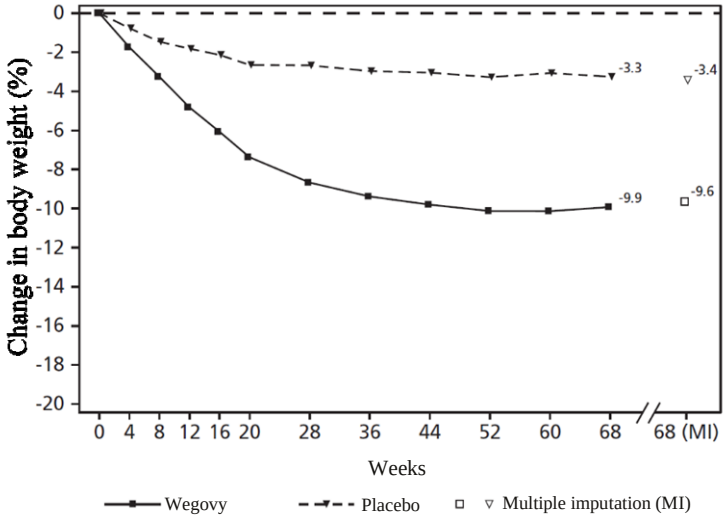
Full analysis set (N)	404	403
Body weight		
Baseline (kg)	99.9	100.5
Change (%) from baseline[1,2]	-9.6	-3.4
Difference (%) from placebo[1] [95% CI]	-6.2 [-7.3; -5.2]*	-
Change (kg) from baseline	-9.7	-3.5
Difference (kg) from placebo[1] [95% CI]	-6.1 [-7.2; -5.0]	-
Patients (%) achieving weight loss ≥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

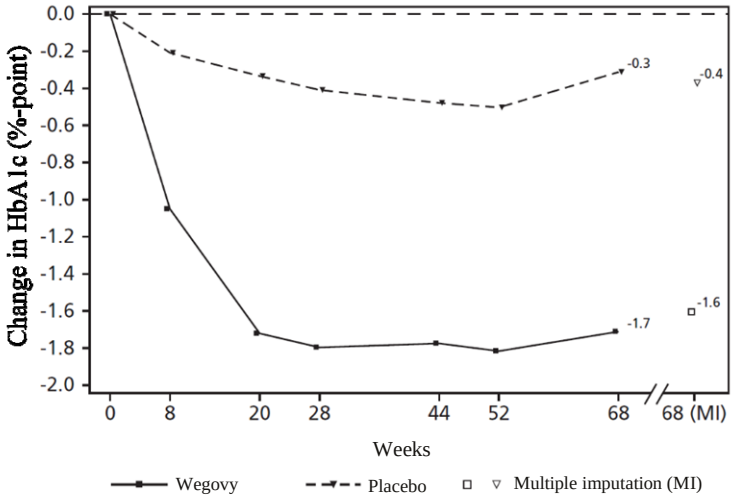
[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.

[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 3 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 behavioural 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 5).

Table 5 STEP 3: Results at week 68

	Semaglutide 2.4mg	**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 6 and Figure 4). 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 4). 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 6 STEP 4: Results from week 20 to week 68

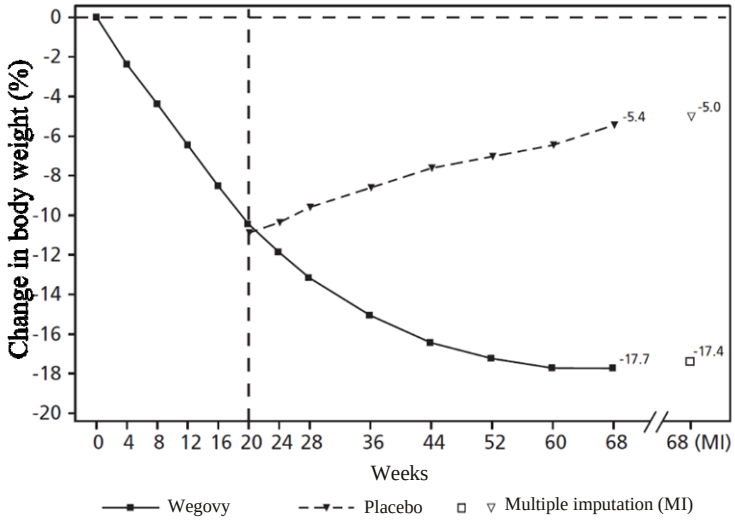
	Semaglutide 2.4mg	**Placebo**
Full analysis set (N)	535	268
Body weight		
Baseline[1] (kg)	96.5	95.4
Change (%) from baseline[2,3]	-7.9	6.9
Difference (%) from placebo[2] [95% CI]	-14.8 [-16.0; -13.5]*	-
Change (kg) from baseline	-7.1	6.1
Difference (kg) from placebo[2] [95% CI]	-13.2 [-14.3; -12.0]	-
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 -8.8% 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 4 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 7 and Figure 5)

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 7 STEP 5: Results at week 104

	Semaglutide 2.4mg	**Placebo**
Full analysis set (N)	152	152
Body weight		
Baseline (kg)	105.6	106.5
Change (%) from baseline[1, 2]	-15.2	-2.6

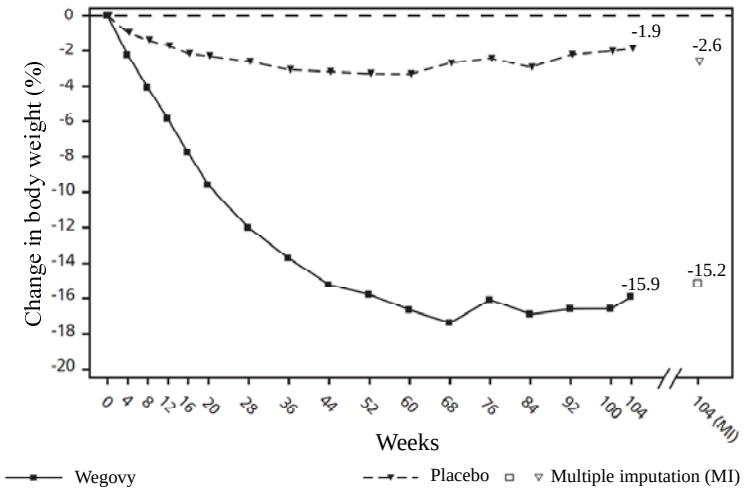
Difference (%) from placebo[1] [95% CI]	-12.6 [-15.3; -9.8]*	-
Change (kg) from baseline	-16.1	-3.2
Difference (kg) from placebo[1] [95% CI]	-12.9 [-16.1; -9.8]	-
Patients (%) achieving weight loss ≥5%[3]	74.7*	37.3
Patients (%) achieving weight loss ≥10%[3]	59.2*	16.8
Patients (%) achieving weight loss ≥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 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 -16.7% 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 5 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 8). 37.4% of the patients treated with semaglutide lost ≥20%, compared to 7.0% treated with liraglutide. Table 8 shows the results of the confirmatory endpoints ≥10%, ≥15% and ≥20% weight loss.

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

	Semaglutide 2.4mg	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 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 and liraglutide 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/m^2 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 9).

Treatment with semaglutide demonstrated a clinically meaningful improvement in knee OA-related pain compared to the placebo (see Table 9). The improvements in knee OA-related pain with semaglutide were achieved without an increase in the use of pain medication.

Table 9 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 ≥5%[3]	85.2*	33.6
WOMAC pain score[4]		
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.

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	
	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	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 improvement2,4	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

SELECT: Cardiovascular Outcomes Trial in Adult Patients with Cardiovascular Disease and BMI ≥ 27 kg/m^2.

SELECT (NCT03574597) was a multi-national, multi-center, placebo-controlled, double-blind trial to determine the effect of Wegovy relative to placebo on major adverse cardiovascular events (MACE) when added to current standard of care, which included management of CV risk factors and individualized healthy lifestyle counseling (including diet and physical activity). The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

All patients were 45 years or older, with an initial BMI of 27 kg/m^2 or greater and established cardiovascular disease (prior myocardial infarction, prior stroke, or peripheral arterial disease). Patients with a history of type 1 or type 2 diabetes were excluded. Concomitant CV therapies could be adjusted, at the discretion of the investigator, to ensure participants were treated according to the current standard of

care for patients with established cardiovascular disease. Adjunct healthy lifestyle counselling were consistent with existing local standards of care (related to diet, physical activity, smoking and alcohol consumption) for adults with established cardiovascular disease and either obesity or overweight (BMI ≥27 kg/m2).

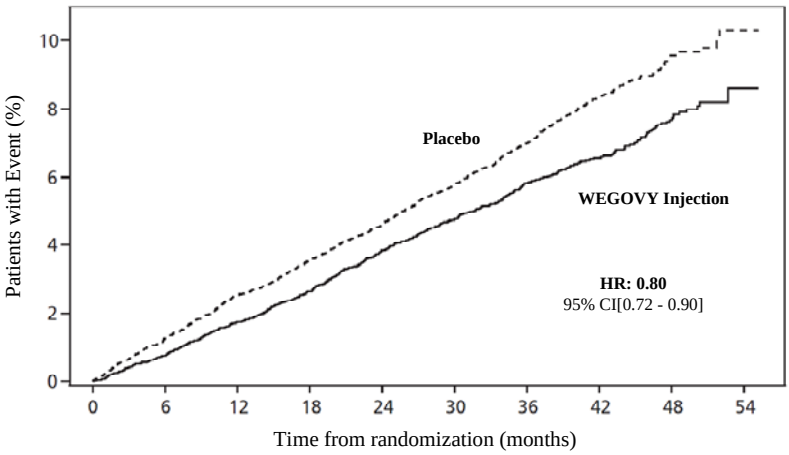
In this trial, 17,604 patients were randomized to Wegovy or placebo. At baseline, the mean age was 62 years (range 45-93), 72% were male, 84% were White, 4% were Black or African American, and 8% were Asian, and 10% were Hispanic or Latino. Mean baseline body weight was 97 kg and mean BMI was 33 kg/m^2. At baseline, prior myocardial infarction was reported in 76% of randomized individuals, prior stroke in 23%, and peripheral arterial disease in 9%. Heart failure was reported in 24% of patients. At baseline, cardiovascular disease and risk factors were managed with lipid-lowering therapy (90%), platelet aggregation inhibitors (86%), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (74%), and beta blockers (70%). A total of 10% had moderate renal impairment (eGFR 30 to <60 mL/min/1.73m^2) and 0.4% had severe renal impairment eGFR <30 mL/min/1.73m^2.

Results

In total, 96.9% of patients completed the trial, and vital status was available for 99.4% of patients. The median follow-up duration was 41.8 months. A total of 31% of Wegovy-treated patients and 27% of placebo-treated patients permanently discontinued study drug.

For the primary analysis, a Cox proportional hazards model was used to test for superiority. Type 1 error was controlled across multiple tests.

Wegovy significantly reduced the risk for first occurrence of MACE. The estimated hazard ratio (95% CI) was 0.80 (0.72, 0.90) (see Figure 6 and Table 11).



Patients at risk										
WEGOVY Injection	8803	8695	8561	8427	8254	7229	5777	4126	1734	71
Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672	59

Figure 6 Cumulative Incidence Function: Time to First Occurrence of MACE in SELECT

Data from the in-trial period. Cumulative incidence estimates are based on time from randomization to first EAC-confirmed cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke with non-CV death modeled as competing risk using the Aalen-Johansen estimator. Patients without events of interest were censored at the end of their in-trial observation period. Time from randomization to first cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor. The hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering.

HR: Hazard ratio; CI: confidence interval; CV: cardiovascular

The treatment effect for the primary composite endpoint, its components, and other relevant endpoints in SELECT are shown in Table 11.

Table 11 Treatment Effect for MACE and Other Events in SELECT

	Patients with events n (%)		
	Placebo N=8,801	**Semaglutide 2.4 mg N=8,803**	**Hazard Ratio (95% CI)**
Primary composite endpoint			
Composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke[1]	701 (8.0%)	569 (6.5%)	0.80 (0.72; 0.90)*[2]
Key secondary endpoints			
Cardiovascular death[3]	262 (3.0%)	223 (2.5%)	0.85 (0.71; 1.01)
All-cause death[4]	458 (5.2%)	375 (4.3%)	0.81 (0.71; 0.93)
Other secondary endpoints			
Fatal or non-fatal myocardial infarction[5]	334 (3.8%)	243 (2.8%)	0.72 (0.61; 0.85)
Fatal or non-fatal stroke[5]	178 (2.0%)	160 (1.8%)	0.89 (0.72; 1.11)

* p-value < 0.001, one-sided p-value

[1] Primary endpoint

[2] Adjusted for group sequential design using the likelihood ratio ordering.

[3] Cardiovascular death was the first confirmatory secondary endpoint in the testing hierarchy and superiority was not confirmed.

[4] Confirmatory secondary endpoint. Not statistically significant based on the prespecified testing hierarchy.

[5] Not included in the prespecified testing hierarchy for controlling type-I error.

NOTE: Time to first event was analyzed in a Cox proportional hazards model with treatment as factor. For patients with multiple events, only the first event contributed to the composite endpoint.

Table 12 Mean Changes in Anthropometry and Cardiometabolic Parameters at Week 104 in SELECT[1,2]

	PLACEBO		**Semaglutide 2.4 mg**		
	Baseline	**Change from Baseline (LSMean)**	**Baseline**	**Change from Baseline (LSMean)**	**Difference from Placebo (LSMean)**
Body Weight (kg)	96.8	-0.9[3]	96.5	-9.4[3]	-8.5[3]
Waist Circumference (cm)	111.4	-1.0	111.3	-7.6	-6.5
Systolic Blood Pressure (mmHg)	131	-0.5	131	-3.8	-3.3
Diastolic Blood Pressure (mmHg)	79	-0.5	79	-1.0	-0.5
Heart Rate	69	0.7	69	3.8	3.1
HbA1c (%)	5.8	0.0	5.8	-0.3	-0.3
	Baseline	**% Change from Baseline (LSMean)**	**Baseline**	**% Change from Baseline (LSMean)**	**Relative difference from placebo (%) (LSMean)**
Total Cholesterol (mg/dL)[4]	156.0	-1.9	155.5	-4.6	-2.8
LDL Cholesterol (mg/dL)[4]	78.5	-3.1	78.5	-5.3	-2.2
HDL Cholesterol (mg/dL)[4]	44.2	0.6	44.1	4.9	4.2
Triglycerides (mg/dL)[4]	139.5	-3.2	138.6	-18.3	-15.6

[1] Parameters listed in the table were not included in the pre-specified hierarchical testing.

[2] Responses were analysed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104.

[3] For body weight the 'change from baseline' and 'difference to placebo' the unit is percentage change from baseline.

[4] Baseline value is the geometric mean.

The reduction of MACE with Wegovy was not impacted by age, sex, race, ethnicity, BMI at baseline, or level of renal function impairment.

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/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.

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/m^2 and 37.9 kg/m^2. 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 13). Benefits were seen both in heart failure symptoms and physical function.

Table 13 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	**Placebo**	**Semaglutide**	**Placebo**

	2.4 mg		**2.4 mg**	
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 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.

5.2 Pharmacokinetic properties

Absorption

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

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

The pharmacokinetic profile of orally administered semaglutide has been characterised in healthy people and patients with overweight or obesity. Following oral administration, maximum plasma concentration of semaglutide occurred 1 hour post dose. The half-life of semaglutide is approximately 1 week indicating that steady-state exposure will be reached after 4-5 weeks of once-daily administration. In patients with overweight or obesity, the average semaglutide 25 mg steady state concentration following oral administration was approximately 77 nmol/L which is comparable to semaglutide 2.4 mg injection (i.e. 75 nmol/L), with higher variability in oral semaglutide concentrations compared to subcutaneous administration (90% of patients had average concentrations between 27 and 186 nmol/L with semaglutide 25 mg tablet versus 51 and 110 nmol/L with semaglutide 2.4 mg injection).

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

Based on in vitro data, salcaprozate sodium facilitates absorption of semaglutide. The absorption of semaglutide predominantly occurs in the stomach.

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

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

Distribution

The mean volume of distribution of semaglutide following oral administration in patients with obesity or overweight is approximately 8.9 L. Semaglutide is extensively bound to plasma albumin (greater than 99%) which results in decreased renal clearance and protection from degradation.

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/m^2 to <30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) is approximately 0.04 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 5 to 7 weeks after the last dose of semaglutide tablets25 mg.

Special populations

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 based on semaglutide s.c. data. The 2.4 mg weekly dose of semaglutide injection and semaglutide tablets 25 mg once daily orally administered dose of semaglutide provided adequate systemic exposures over the body weight range of 52.8−245.6 kg evaluated for exposure response in the clinical trials.

Renal impairment

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown following 10 consecutive days of once-daily oral doses of 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 3 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 studies following 10 consecutive days of once-daily oral doses of semaglutide.

Upper gastrointestinal tract diseases

Upper GI tract disease (chronic gastritis and/or gastroesophageal reflux disease) did not impact the pharmacokinetics of orally administrated semaglutide in a clinically relevant manner. The pharmacokinetics were evaluated in patients with type 2 diabetes with or without upper GI tract disease dosed for 10 consecutive days with once-daily doses of orally administrated semaglutide. This was also shown for subjects with type 2 diabetes and upper GI tract disease based on data from phase 3 studies.

Prediabetes and diabetes

Prediabetes and diabetes did not have any clinically relevant effect on the exposure of semaglutide based on data from semaglutide s.c. 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.

Paediatrics

Safety and efficacy of orally administered semaglutide in children and adolescents below 18 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

Salcaprozate sodium

Magnesium stearate

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in original blister package to protect from moisture and light. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Alu/Alu blisters.

Pack sizes of: 10, 30 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product 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)

PL 04668/0466

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/06/2026

10 DATE OF REVISION OF THE TEXT

11/06/2026