Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Reglutide solution for Injection

2. Qualitative and quantitative composition
Each 1ml contains
Semaglutide……1.34mg
For full list of excipients see section 6.1

3. Pharmaceutical form
Clear & colorless solution free from visible particle.

4. Clinical particulars

4.1 Therapeutic indications

Reglutide is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
• as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
• in addition to other medicinal products for the treatment of diabetes.
For trial results with respect to combinations, effects on glycaemic control and cardiovascular events, peripheral arterial disease, renal outcomes and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. After at least 4 weeks with a dose of 1 mg once weekly, the dose can be increased to 2 mg once weekly to further improve glycaemic control.
Semaglutide 0.25 mg is not a maintenance dose. Weekly doses higher than 2 mg are not recommended.
When Reglutide is added to existing metformin and/or thiazolidinedione therapy or to a sodium-glucose cotransporter 2 (SGLT2) inhibitor, the current dose of metformin and/or thiazolidinedione or SGLT2 inhibitor can be continued unchanged.
When Reglutide is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).
Self-monitoring of blood glucose is not needed in order to adjust the dose of Reglutide. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Reglutide is started and insulin is reduced. A stepwise approach to insulin reduction is 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.

Changing the dosing day

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.

Special populations

Elderly

No dose adjustment is required based on age.

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.

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

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

Method of administration

Subcutaneous use.

Reglutide is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Reglutide should not be administered intravenously or intramuscularly.

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

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

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.

General

Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Semaglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients whom had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started (see section 4.2).

There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep

sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Gastrointestinal effects and dehydration

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

Acute pancreatitis

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 (see section 4.8).

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 semaglutide (see section 4.8).

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).

Diabetic retinopathy

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

There is no experience with semaglutide 2 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy and semaglutide 2 mg is therefore not recommended in these patients.

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).

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

Paracetamol

Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardised meal test. Paracetamol $AUC_{0\text{-}60min}$ and C_{max} were decreased by 27% and 23%, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure ($AUC_{0\text{-}5h}$) was not affected. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, following 20 weeks of administration of semaglutide, probably due to a tolerance effect. No dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives

Semaglutide is not anticipated to decrease the effect of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. C_{max} was not affected for any of the compounds.

Atorvastatin

Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin C_{max} was decreased by 38%. This was assessed not to be clinically relevant.

Digoxin

Semaglutide did not change the overall exposure or C_{max} of digoxin following a single dose of digoxin (0.5 mg).

Metformin

Semaglutide did not change the overall exposure or C_{max} of metformin following dosing of 500 mg twice daily over 3.5 days.

Warfarin and other coumarin derivatives

Semaglutide did not change the overall exposure or C_{max} of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, cases of decreased INR have been reported during concomitant use of acenocoumarol and semaglutide. Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

4.6 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. As 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of safety profile

In 8 phase 3a trials 4 792 patients were exposed to semaglutide up to 1 mg. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration.

Tabulated list of adverse reactions

Table 1 lists adverse reactions identified in all phase 3 trials (including the long-term cardiovascular outcomes trial) and post-marketing reports in patients with type 2 diabetes mellitus (further described in section 5.1). The frequencies of the adverse reactions (except diabetic retinopathy complications, see footnote in Table 1) are based on a pool of the phase

3a trials excluding the cardiovascular outcomes trial (see text below the table for additional details).
The reactions are listed below by system organ class and absolute frequency. Frequencies are defined as: very common: (≥1/10); common: (≥1/100 to <1/10); uncommon: (≥1/1 000 to <1/100); rare: (≥1/10 000 to <1/1 000); very rare: (<1/10 000) and not known: (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequency of adverse reactions of semaglutide

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very Rare	Not known
Immune system disorders			Hypersensitivity[c]	Anaphylactic reaction		
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulfonylurea	Hypoglycaemia[a] when used with other oral antidiabetics (OAD) Decreased appetite				
Nervous system disorders		Dizziness Headache	Dysgeusia			Dysaesthesia[d]
Eye disorders		Diabetic retinopathy complications[b]			Non- arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders			Increased heart rate			
Gastrointesti-nal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Eructation Flatulence	Acute pancreatitis Delayed gastric emptying			Intestinal obstruction[d]

Hepatobiliary disorders		Cholelithiasis				
Skin and subcutaneous tissue disorders						Angioedema[d]
General disorders and administration site conditions		Fatigue	Injection site reactions			
Investigations		Increased lipase Increased amylase Weight decreased				

[a)] Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.

[b)] Diabetic retinopathy complications is a composite of: retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage, diabetes-related blindness (uncommon). Frequency based on cardiovascular outcomes trial.

[c)] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.

[d)] From post-marketing reports.

2-year cardiovascular outcomes and safety trial

In cardiovascular high risk population the adverse reaction profile was similar to that seen in the other phase 3a trials (described in section 5.1).

Kidney outcomes trial

In the FLOW trial in patients with type 2 diabetes mellitus and chronic kidney disease, safety data collection was limited to serious adverse events and selected predefined categories of adverse events regardless of seriousness. There were no new serious or severe adverse reactions identified in this trial.

Description of selected adverse reactions

Hypoglycaemia

No episodes of severe hypoglycaemia were observed when semaglutide was used as monotherapy. Severe hypoglycaemia was primarily observed when semaglutide was used with a sulfonylurea (1.2% of subjects, 0.03 events/patient year) or insulin (1.5% of subjects, 0.02 events/patient year). Few episodes (0.1% of subjects, 0.001 events/patient year) were

observed with semaglutide in combination with oral antidiabetics other than sulfonylureas.

American Diabetes Association (ADA) classified hypoglycaemia occurred in 11.3% (0.3 events/patient year) of patients when semaglutide 1 mg was added to SGLT2 inhibitor in SUSTAIN 9 compared to 2.0% (0.04 events/patient year) of placebo-treated patients. Severe hypoglycaemia was reported in 0.7% (0.01 events/patient year) and 0% of patients, respectively.

In a 40-week phase 3b trial in patients receiving semaglutide 1 mg and 2 mg, the majority of the hypoglycaemic episodes (45 out of 49 episodes) occurred when semaglutide was used in combination with sulfonylurea or insulin. Overall, there was no increased risk of hypoglycaemia with semaglutide 2 mg.

Gastrointestinal adverse reactions

Nausea occurred in 17% and 19.9% of patients when treated with semaglutide 0.5 mg and 1 mg, respectively, diarrhoea in 12.2% and 13.3% and vomiting in 6.4% and 8.4%. Most events were mild to moderate in severity and of short duration. The events led to treatment discontinuation in 3.9% and 5% of patients. The events were most frequently reported during the first months on treatment.

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

In a 40-week phase 3b trial in patients receiving semaglutide 1 mg and 2 mg, nausea occurred in similar proportions of patients when treated with semaglutide 1 mg and 2 mg, respectively. Diarrhoea and vomiting occurred in higher proportions of patients when treated with semaglutide 2 mg compared to semaglutide 1 mg. The gastrointestinal adverse reactions led to treatment discontinuation in similar proportions in the semaglutide 1 mg and 2 mg treatment groups.

In concomitant use with an SGLT2 inhibitor in SUSTAIN 9, constipation and gastro-oesophageal reflux disease occurred in 6.7% and 4% respectively of patients treated with semaglutide 1 mg compared to no events for placebo-treated patients. The prevalence of these events did not decrease over time.

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

Acute pancreatitis

The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.3% for semaglutide and 0.2% for the

comparator, respectively. In the 2-year cardiovascular outcomes trial the frequency of acute pancreatitis confirmed by adjudication was 0.5% for semaglutide and 0.6% for placebo (see section 4.4).

Diabetic retinopathy complications

A 2-year clinical trial investigated 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial. In clinical trials up to 1 year involving 4 807 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

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.

Discontinuation due to an adverse event

The incidence of discontinuation of treatment due to adverse events was 6.1% and 8.7% for patients treated with semaglutide 0.5 mg and 1 mg, respectively, versus 1.5% for placebo. The most frequent adverse events leading to discontinuation were gastrointestinal.

Injection site reactions

Injection site reactions (e.g. injection site rash, erythema) have been reported by 0.6% and 0.5% of patients receiving semaglutide 0.5 mg and 1 mg, respectively. These reactions have usually been mild.

Immunogenicity

Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of patients tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1−3%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

Heart rate increase

Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean increases of 1 to 6 beats per minute (bpm) from a baseline of 72 to 76 bpm were observed in subjects treated with Reglutide. In a long-term trial in subjects with cardiovascular risk factors, 16% of Reglutide-treated subjects had an increase in heart rate of >10 bpm compared to 11% of subjects on placebo after 2 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 to National regulatory Authority

4.9 Overdose

Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications. There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see section 5.2).

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 hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Semaglutide reduces 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.

Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.
GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys.
Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.
The mechanism of kidney-related risk reduction has not been established.

Pharmacodynamic effects

All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg once weekly.

Fasting and postprandial glucose

Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline (mmol/L) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/L; 22% reduction), 2 hour postprandial glucose (4.1 mmol/L; 37% reduction), mean 24 hour glucose concentration (1.7 mmol/L; 22% reduction) and postprandial glucose excursions over 3 meals (0.6-1.1 mmol/L) compared with placebo. Semaglutide lowered fasting glucose after the first dose.

Beta-cell function and insulin secretion

Semaglutide improves beta-cell function. Compared to placebo, semaglutide improved first- and second-phase insulin response with a 3– and 2–fold increase, respectively, and increased maximal beta-cell secretory capacity in patients with type 2 diabetes. In addition, semaglutide treatment increased fasting insulin concentrations compared to placebo.

Glucagon secretion

Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in glucagon compared to placebo: fasting glucagon (8–21%), postprandial glucagon response (14–15%) and mean 24 hour glucagon concentration (12%).

Glucose dependent insulin and glucagon secretion

Semaglutide lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that of healthy subjects.
During induced hypoglycaemia, semaglutide compared to placebo did not alter the counter regulatory responses of increased glucagon and did not impair the decrease of C-peptide in patients with type 2-diabetes.

Gastric emptying

Semaglutide caused a minor delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

Appetite, energy intake and food choice

Semaglutide compared to placebo lowered the energy intake of 3 consecutive *ad libitum* meals by 18-35%. This was supported by a semaglutide-induced suppression of appetite in the fasting state as well as postprandially, improved control of eating, less food cravings and a relative lower preference for high fat food.

Fasting and postprandial lipids

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

Cardiac electrophysiology (QTc)

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

Clinical efficacy and safety

Improvement of glycaemic control, reduction of cardiovascular morbidity and mortality and risk reduction of chronic kidney disease progression are an integral part of the treatment of type 2 diabetes.

The efficacy and safety of semaglutide 0.5 mg and 1 mg once weekly were evaluated in six randomised controlled phase 3a trials that included 7 215 patients with type 2 diabetes mellitus (4 107 treated with semaglutide). Five trials (SUSTAIN 1–5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective.

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

A phase 3b trial (SUSTAIN OPTIMIZE) including 573 patients was conducted to investigate the efficacy and safety of once-weekly semaglutide subcutaneous 2 mg as add-on to dose reduced insulin glargine versus dose-titrated insulin glargine alone.

In addition, a phase 3b trial (SUSTAIN 7) including 1 201 patients was conducted to compare the efficacy and safety of semaglutide 0.5 mg and 1 mg once weekly to dulaglutide 0.75 mg and 1.5 mg once weekly, respectively. A phase 3b trial (SUSTAIN 9), was conducted to investigate the efficacy and safety of semaglutide as add-on to SGLT2 inhibitor treatment.

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

The efficacy of semaglutide was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

Results target the on-treatment period in all randomised subjects (analyses based on mixed models for repeated measurements or multiple imputation).
In addition, a phase 3b trial (SUSTAIN 11), was conducted to investigate the effect of semaglutide versus insulin aspart, both as add-on to metformin and optimised insulin glargine (U100).
A phase 3b functional capacity trial (STRIDE) including 792 patients was conducted to investigate the effects of semaglutide 1 mg once weekly versus placebo in patients with type 2 diabetes and peripheral arterial disease.
A phase 3b kidney outcomes trials (FLOW) including 3 533 patients was conducted to investigate the effects of semaglutide 1 mg once weekly versus placebo on the progression of kidney impairment in patients with type 2 diabetes and chronic kidney disease.
Detailed information is provided below.

SUSTAIN 1 – Monotherapy

In a 30-week double-blind placebo-controlled trial, 388 patients inadequately controlled with diet and exercise, were randomised to semaglutide 0.5 mg or semaglutide 1 mg once weekly or placebo.

Table 2 SUSTAIN 1: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Placebo**
Intent-to-Treat (ITT) Population (N)	128	130	129
HbA_{1c} (%)			
Baseline (mean)	8.1	8.1	8.0
Change from baseline at week 30	-1.5	-1.6	0
Difference from placebo [95% CI]	-1.4 [-1.7, -1.1][a]	-1.5 [-1.8, -1.2][a]	-
Patients (%) achieving HbA_{1c} <7%	74	72	25
FPG (mmol/L)			
Baseline (mean)	9.7	9.9	9.7
Change from baseline at week 30	-2.5	-2.3	-0.6
Body weight (kg)			
Baseline (mean)	89.8	96.9	89.1
Change from baseline at week 30	-3.7	-4.5	-1.0
Difference from placebo [95% CI]	-2.7 [-3.9, -1.6][a]	-3.6 [-4.7, -2.4][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 2 – Semaglutide vs. sitagliptin both in combination with 1–2 oral antidiabetic medicinal products (metformin and/or thiazolidinediones)

In a 56-week active-controlled double-blind trial, 1 231 patients were randomised to semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly or sitagliptin 100 mg once daily, all in combination with metformin (94%) and/or thiazolidinediones (6%).

Table 3 SUSTAIN 2: Results at week 56

	Semaglutide 0.5 mg	Semaglutide 1 mg	Sitagliptin 100 mg
Intent-to-Treat (ITT) Population (N)	409	409	407
HbA_{1c} (%)			
Baseline (mean)	8.0	8.0	8.2
Change from baseline at week 56	-1.3	-1.6	-0.5
Difference from sitagliptin [95% CI]	-0.8 [-0.9, -0.6][a]	-1.1 [-1.2, -0.9][a]	-
Patients (%) achieving HbA_{1c} <7%	69	78	36
FPG (mmol/L)			
Baseline (mean)	9.3	9.3	9.6
Change from baseline at week 56	-2.1	-2.6	-1.1
Body weight (kg)			
Baseline (mean)	89.9	89.2	89.3
Change from baseline at week 56	-4.3	-6.1	-1.9
Difference from sitagliptin [95% CI]	-2.3 [-3.1, -1.6][a]	-4.2 [-4.9, -3.5][a]	-

[a]p <0.0001 (2-sided) for superiority

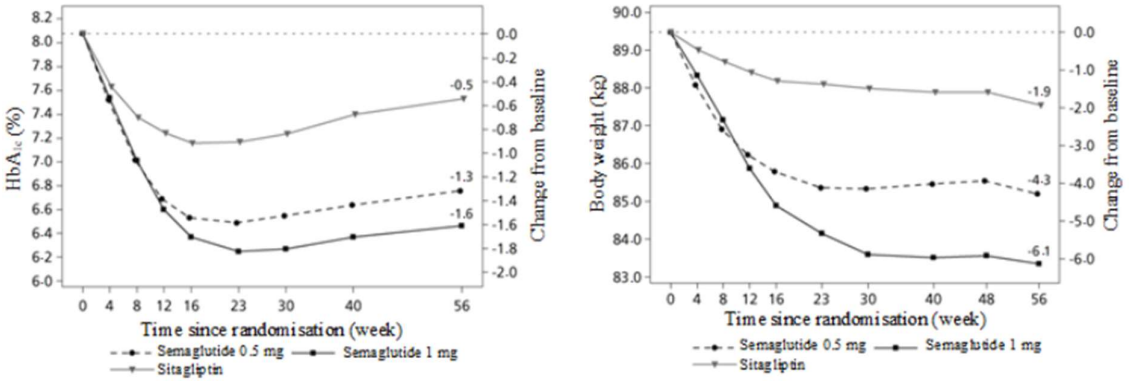


Figure 1 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 56

SUSTAIN 7 – Semaglutide vs. dulaglutide both in combination with metformin

In a 40-week, open-label trial, 1 201 patients on metformin were randomised 1:1:1:1 to once weekly semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1 mg or dulaglutide 1.5 mg, respectively .
The trial compared 0.5 mg of semaglutide to 0.75 mg of dulaglutide and 1 mg of semaglutide to 1.5 mg of dulaglutide.
Gastrointestinal disorders were the most frequent adverse events, and occurred in similar proportion of patients receiving semaglutide 0.5 mg (129 patients [43%]), semaglutide 1 mg (133 [44%]), and dulaglutide 1.5 mg (143 [48%]); fewer patients had gastrointestinal disorders with dulaglutide 0.75 mg (100 [33%]).

At week 40, the increase in pulse rate for semaglutide (0.5 mg and 1 mg) and dulaglutide (0.75 mg and 1.5 mg) was 2.4, 4.0, and 1.6, 2.1, beats/min, respectively.

Table 4 SUSTAIN 7: Results at week 40

	Semaglutide 0.5 mg	Semaglutide 1 mg	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
Intent-to-Treat (ITT) Population(N)	301	300	299	299
HbA_{1c} (%)				
Baseline (mean)	8.3	8.2	8.2	8.2
Change from baseline at week 40	-1.5	-1.8	-1.1	-1.4
Difference from dulaglutide [95% CI]	-0.4[b] [-0.6, -0.2][a]	-0.4[c] [-0.6, -0.3][a]	-	-
Patients (%) achieving HbA_{1c} <7%	68	79	52	67
FPG (mmol/L)				
Baseline (mean)	9.8	9.8	9.7	9.6
Change from baseline at week 40	-2.2	-2.8	-1.9	-2.2
Body weight (kg)				
Baseline (mean)	96.4	95.5	95.6	93.4
Change from baseline at week 40	-4.6	-6.5	-2.3	-3.0
Difference from dulaglutide [95% CI]	-2.3[b] [-3.0, -1.5][a]	-3.6[c] [-4.3, -2.8][a]	-	-

[a] *p <0.0001 (2-sided) for superiority*
[b] *semaglutide 0.5 mg vs dulaglutide 0.75 mg*
[c] *semaglutide 1 mg vs dulaglutide 1.5 mg*

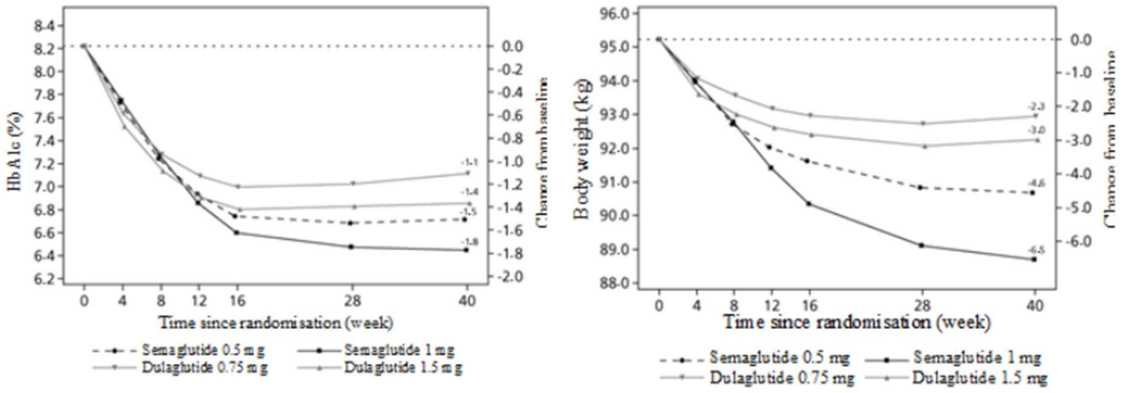


Figure 2 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 40

SUSTAIN 3 – Semaglutide vs. exenatide ER both in combination with metformin or metformin with sulfonylurea

In a 56-week open-label trial, 813 patients on metformin alone (49%), metformin with sulfonylurea (45%) or other (6%) were randomised to semaglutide 1 mg or exenatide ER 2 mg once weekly.

Table 5 SUSTAIN 3: Results at week 56

	Semaglutide 1 mg	**Exenatide ER 2 mg**
Intent-to-Treat (ITT) Population (N)	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change from baseline at week 56	-1.5	-0.9
Difference from exenatide [95% CI]	-0.6 [-0.8, -0.4][a]	-
Patients (%) achieving HbA_{1c} <7%	67	40
FPG (mmol/L)		
Baseline (mean)	10.6	10.4
Change from baseline at week 56	-2.8	-2.0
Body weight (kg)		
Baseline (mean)	96.2	95.4
Change from baseline at week 56	-5.6	-1.9
Difference from exenatide [95% CI]	-3.8 [-4.6, -3.0][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 4 – Semaglutide vs. insulin glargine both in combination with 1–2 oral antidiabetic medicinal products (metformin or metformin and sulfonylurea)

In a 30-week open-label comparator trial 1 089 patients were randomised to semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly, or insulin glargine once-daily on a background of metformin (48%) or metformin and sulfonylurea (51%).

Table 6 SUSTAIN 4: Results at week 30

	Semaglutide 0.5 mg	Semaglutide 1 mg	Insulin Glargine
Intent-to-Treat (ITT) Population (N)	362	360	360
HbA_{1c} (%)			
Baseline (mean)	8.1	8.2	8.1
Change from baseline at week 30	-1.2	-1.6	-0.8
Difference from insulin glargine [95% CI]	-0.4 [-0.5, -0.2][a]	-0.8 [-1.0, -0.7][a]	-
Patients (%) achieving HbA_{1c} <7%	57	73	38
FPG (mmol/L)			
Baseline (mean)	9.6	9.9	9.7
Change from baseline at week 30	-2.0	-2.7	-2.1
Body weight (kg)			
Baseline (mean)	93.7	94.0	92.6
Change from baseline at week 30	-3.5	-5.2	+1.2
Difference from insulin glargine [95% CI]	-4.6 [-5.3, -4.0][a]	-6.34 [-7.0, -5.7][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 5 – Semaglutide vs. placebo both in combination with basal insulin

In a 30-week double-blind placebo-controlled trial, 397 patients inadequately controlled with basal insulin with or without metformin were randomised to semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly or placebo.

Table 7 SUSTAIN 5: Results at week 30

	Semaglutide 0.5 mg	Semaglutide 1 mg	Placebo
Intent-to-Treat (ITT) Population (N)	132	131	133
HbA_{1c} (%)			
Baseline (mean)	8.4	8.3	8.4
Change from baseline at week 30	-1.4	-1.8	-0.1
Difference from placebo [95% CI]	-1.4 [-1.6, -1.1][a]	-1.8 [-2.0, -1.5][a]	-
Patients (%) achieving HbA_{1c} <7%	61	79	11
FPG (mmol/L)			
Baseline (mean)	8.9	8.5	8.6
Change from baseline at week 30	-1.6	-2.4	-0.5
Body weight (kg)			
Baseline (mean)	92.7	92.5	89.9
Change from baseline at week 30	-3.7	-6.4	-1.4
Difference from placebo [95% CI]	-2.3 [-3.3, -1.3][a]	-5.1 [-6.1, -4.0][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN FORTE – Semaglutide 2 mg vs. semaglutide 1 mg

In a 40-week double-blind trial, 961 patients inadequately controlled with metformin with or without sulfonylurea were randomised to semaglutide 2 mg once weekly or semaglutide 1 mg once weekly. Treatment with semaglutide 2 mg resulted in a statistically superior reduction in HbA_{1c} after 40 weeks of treatment compared to semaglutide 1 mg.

Table 8 SUSTAIN FORTE: Results at week 40

	Semaglutide 1 mg	**Semaglutide 2 mg**
Intent-to-Treat (ITT) Population (N)	481	480
HbA_{1c} (%)		
Baseline (mean)	8.8	8.9
Change from baseline at week 40	-1.9	-2.2
Difference from semaglutide 1 mg [95% CI]	-	-0.2 [-0.4, -0.1][a]
Patients (%) achieving HbA_{1c} <7%	58	68
FPG (mmol/L)		
Baseline (mean)	10.9	10.7
Change from baseline at week 40	-3.1	-3.4
Body weight (kg)		
Baseline (mean)	98.6	100.1
Change from baseline at week 40	-6.0	-6.9
Difference from semaglutide 1 mg [95% CI]		-0.9 [-1.7, -0.2][b]

[a]p<0.001 (2-sided) for superiority

[b]p<0.05 (2-sided) for superiority

SUSTAIN OPTIMIZE – Semaglutide 2 mg as add-on to dose-reduced insulin glargine vs. dose-titrated insulin glargine

In a 40-week, open-label comparator trial, 573 participants with type 2 diabetes and overweight or obesity (BMI ≥ 25 kg/m²) and a basal insulin dose ≤ 40 U/day were randomised to receive once-weekly semaglutide subcutaneous 2 mg as add-on to dose-reduced insulin glargine or dose-titrated insulin glargine alone. The insulin glargine dose was reduced by 10 U at initiation of semaglutide and each subsequent escalation step, with titration during the whole duration of the study.

Treatment with semaglutide 2 mg as add-on to dose-reduced insulin glargine, resulted in a statistically superior reduction in HbA_{1c}, body weight and daily basal insulin dose after 40 weeks of treatment compared to dose-titrated insulin glargine alone.

Table 9 SUSTAIN OPTIMIZE: Results at week 40

	Semaglutide 2 mg as add-on to dose-reduced insulin glargine	Insulin Glargine (dose-titrated)
Intent-to-Treat (ITT) Population (N)	288	285
HbA_{1c} (%)		
Baseline (mean)	7.9	7.9
Change from baseline at week 40	-1.4	-0.6
Difference from insulin glargine [95% CI]	-0.74 [-0.90, -0.59][a]	-
Body weight (kg)		
Baseline (mean)	93	95
Change from baseline at week 40	-8	0.5
Difference from insulin glargine [95% CI]	-8.5 [-9.52, -7.39][a]	-
Daily insulin dose (U)		
Baseline (mean)	26	26.5
Relative change from baseline at week 40 (%)	-17.8	104.1
Difference from insulin glargine [95% CI]	-121.9 [-143.1, -100.6][a]	-
Patients (%) achieving insulin dose 0U at week 40	12.91	0.1
Patients (%) achieving insulin dose reduction from baseline by at least 50% at week 40	35.62	0.71

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 9 – Semaglutide vs. placebo as add-on to SGLT2 inhibitor ± metformin or sulfonylurea

In a 30-week double-blind placebo-controlled trial, 302 patients inadequately controlled with SGLT2 inhibitor with or without metformin or sulfonylurea were randomised to semaglutide 1 mg once weekly or placebo.

Table 10 SUSTAIN 9: Results at week 30

	Semaglutide 1 mg	Placebo
Intent-to-Treat (ITT) Population (N)	151	151
HbA_{1c} (%)		
Baseline (mean)	8.0	8.1
Change from baseline at week 30	-1.5	-0.1
Difference from placebo [95% CI]	-1.4 [-1.6, -1.2][a]	-
Patients (%) achieving HbA_{1c} <7%	78.7	18.7
FPG (mmol/L)		
Baseline (mean)	9.1	8.9
Change from baseline at week 30	-2.2	0.0
Body weight (kg)		
Baseline (mean)	89.6	93.8
Change from baseline at week 30	-4.7	-0.9
Difference from placebo [95% CI]	-3.8 [-4.7, -2.9][a]	-

[a]p < 0.0001 (2-sided) for superiority, adjusted regarding multiplicity based on hierarchical testing of the HbA_{1c} value and body weight

SUSTAIN 11 - Semaglutide vs. insulin aspart as add-on to insulin glargine + metformin

In a 52-week open-label trial, 1748 subjects with inadequately controlled T2D after a 12-week run-in period on insulin glargine and metformin were randomised to 1:1 to receive either semaglutide once-weekly (0.5 mg or 1.0 mg) or insulin aspart three times daily. The included population had a mean diabetes duration of 13.4 years and a mean HbA_{1c} of 8.6%, with a target HbA_{1c} of 6.5-7.5%.

Treatment with semaglutide resulted in reduction in HbA_{1c} at week 52 (-1.5% for semaglutide vs. -1.2% for insulin aspart).

The number of severe hypoglycaemic episodes in both treatment arms was low (4 episodes with semaglutide vs. 7 episodes with insulin aspart).

Mean baseline body weight decreased with semaglutide (-4.1 kg) and increased with insulin aspart (+2.8 kg) and the estimated treatment difference was -6.99 kg (95%CI -7.41 to -6.57) at week 52.

Combination with sulfonylurea monotherapy

In SUSTAIN 6 (see subsection “Cardiovascular disease”) 123 patients were on sulfonylurea monotherapy at baseline. HbA_{1c} at baseline was 8.2%, 8.4% and 8.4% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.6%, -1.5% and 0.1% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively.

Combination with premix insulin ± 1–2 OADs

In SUSTAIN 6 (see subsection “Cardiovascular disease”) 867 patients were on premix insulin (with or without OAD(s)) at baseline. HbA_{1c} at

baseline was 8.8%, 8.9% and 8.9% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.3%, -1.8% and -0.4% for semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively.

Cardiovascular disease

In a 104-week double-blind trial (SUSTAIN 6), 3 297 patients with type 2 diabetes mellitus at high cardiovascular risk were randomised to either semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly or corresponding placebo in addition to standard-of-care hereafter followed for 2 years. In total 98% of the patients completed the trial and the vital status was known at the end of the trial for 99.6% of the patients.

The trial population was distributed by age as: 1 598 patients (48.5%) ≥65 years, 321 (9.7%) ≥75 years, and 20 (0.6%) ≥85 years. There were 2 358 patients with normal or mild renal impairment, 832 with moderate and 107 with severe or end stage renal impairment. There were 61% males, the mean age was 65 years and mean BMI was 33 kg/m^2. The mean duration of diabetes was 13.9 years.

The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The total number of primary component MACE endpoints was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo. See figure 4 for results on primary and secondary cardiovascular endpoints. Treatment with semaglutide resulted in a 26% risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. The total numbers of cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes were 90, 111, and 71, respectively, including 44 (2.7%), 47 (2.9%), and 27 (1.6%), respectively, with semaglutide (figure 4). The risk reduction in the primary composite outcome was mainly driven by decreases in the rate of non-fatal stroke (39%) and non-fatal myocardial infarction (26%) (figure 3).

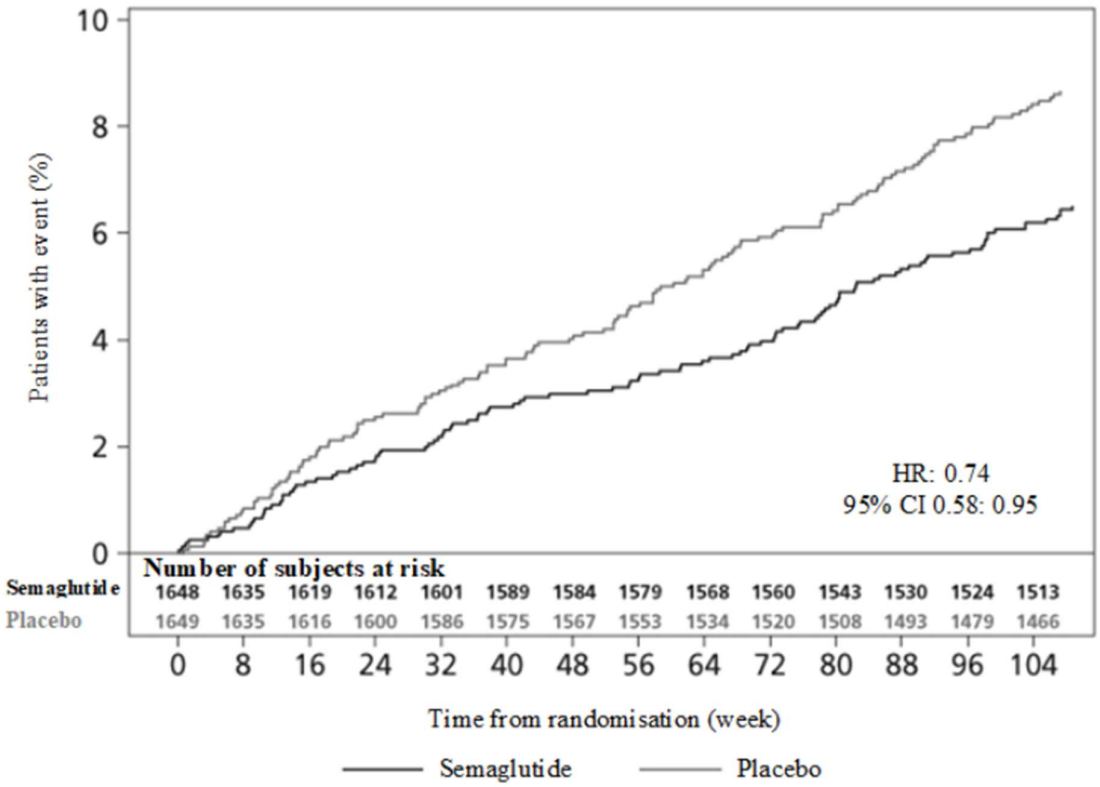


Figure 3 Kaplan-Meier plot of time to first occurrence of the composite outcome: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

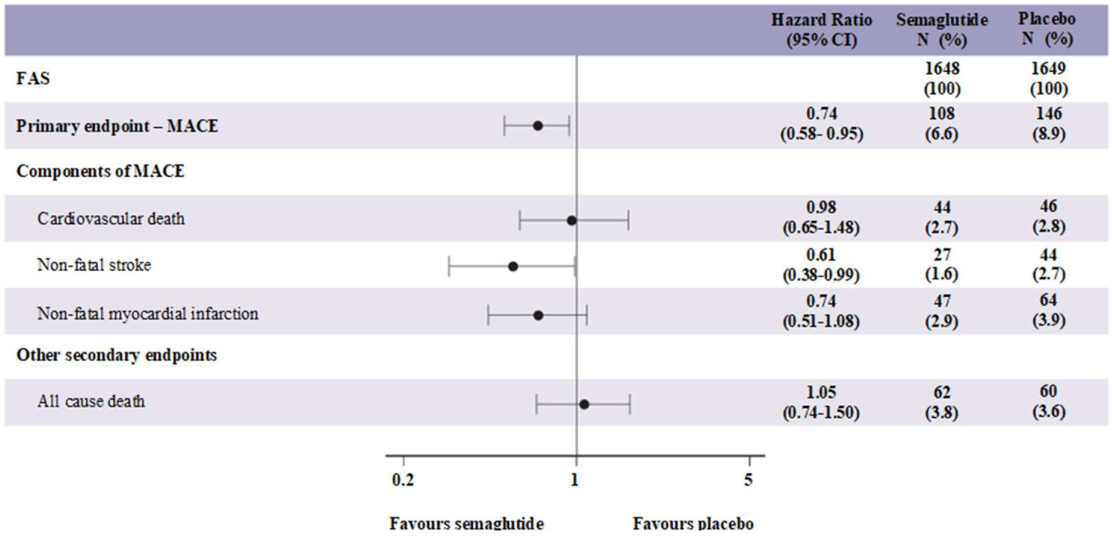


Figure 4 Forest plot: analyses of time to first occurrence of the composite outcome, its components and all cause death (SUSTAIN 6)

There were 158 events of new or worsening nephropathy. The hazard ratio [95% CI] for time to nephropathy (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, need for continuous renal replacement therapy and death due to renal disease)

was 0.64 [0.46; 0.88] driven by new onset of persistent macroalbuminuria.

Body weight

After one year of treatment, a weight loss of ≥5% and ≥10% was achieved for more subjects with semaglutide 0.5 mg (46% and 13%) and 1 mg (52 – 62% and 21 – 24%) compared with the active comparators sitagliptin (18% and 3%) and exenatide ER (17% and 4%).

In the 40-week trial versus dulaglutide a weight loss of ≥5% and ≥10% was achieved for more subjects with semaglutide 0.5 mg (44% and 14%) compared with dulaglutide 0.75 mg (23% and 3%) and semaglutide 1 mg (up to 63% and 27%) compared with dulaglutide 1.5 mg (30% and 8%).

A significant and sustained reduction in body weight from baseline to week 104 was observed with semaglutide 0.5 mg and 1 mg vs placebo 0.5 mg and 1 mg, in addition to standard-of-care (-3.6 kg and -4.9 kg vs -0.7 kg and -0.5 kg , respectively) in SUSTAIN 6.

Blood pressure

Significant reductions in mean systolic blood pressure were observed when semaglutide 0.5 mg (3.5-5.1 mmHg) and 1 mg (5.4–7.3 mmHg) were used in combination with oral antidiabetic medicinal products or basal insulin. For diastolic blood pressure, there were no significant differences between semaglutide and comparators. The observed reductions in systolic blood pressure for semaglutide 2 mg and 1 mg at week 40 were 5.3 mmHg and 4.5 mmHg, respectively.

Functional capacity in patients with type 2 diabetes (T2D) and peripheral arterial disease (PAD)

STRIDE (NCT04560998) was a 52-week, randomised, double-blind, placebo-controlled trial comparing semaglutide 1 mg versus placebo added to standard-of-care and administered once-weekly in patients with T2D and PAD with intermittent claudication (Fontaine staging IIa). The treatment duration is 52 weeks including an eight weeks dose escalation period. The follow-up period is 5 weeks. The primary objective was to demonstrate the effect of semaglutide 1 mg once-weekly on walking ability compared with placebo, added to standard-of-care, in patients with T2D and PAD with intermittent claudication. The primary endpoint was change in maximum walking distance on a constant load treadmill test with fixed inclination of 12% and a fixed speed of 3.2 km/h (2 mph) from baseline to week 52. The confirmatory secondary endpoints were follow-up change in maximum walking distance from baseline to week 57, change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score from baseline to week 52 and change in pain-free walking distance from baseline to week 52.

A total of 792 patients were randomised 1:1 to receive either semaglutide 1 mg or placebo for 52 weeks and followed for an additional 5 weeks off-treatment.

STRIDE included a population of patients with T2D and stable symptomatic PAD with intermittent claudication corresponding to Fontaine stage IIa (Rutherford classification grade I, category 1 and 2)

with ankle-brachial index (ABI) ≤0.90 or toe-brachial index (TBI) ≤0.70 (the leg with lowest index was chosen in case of bilateral disease) and MWD ≤600 meters on a constant load treadmill test. The mean age of the study population was 67 years, and 75.4% of patients were male and 24.6 % of patients were female.

The effect of semaglutide 1 mg once-weekly on patient-perceived symptoms and the impact of intermittent claudication for patients living with T2D and PAD was assessed using the VascuQoL-6 questionnaire. The questionnaire comprises 6 items addressing symptoms, pain, social and emotional impact, and activity limitations. Each item is scored on a 4-point numeric response scale (1 = worst; 4 = best), with higher scores indicating a better health status, resulting in a total score ranging from 6 to 24 points.

In STRIDE, treatment with semaglutide 1 mg once-weekly resulted in a statistically significant improvement in the functional capacity outcomes (maximum walking distance, pain-free walking distance) and patient reported symptoms and impacts of intermittent claudication (VascuQol-6 total score) at week 52 compared to placebo. For the primary endpoint, the estimated treatment effect was 13% (95% CI: 1.06-1.2) relative improvement , which represents a median change in maximum walking distance of 26 meters (95% CI: 12-41) on a constant load treadmill. This treatment effect is estimated regardless of treatment discontination or use of rescue medication and where death or inability to perform the treadmill test were incorporated into the endpoint as unfavourable outcome. Figure 5 displays placebo-corrected change in maximum walking distance at Week 52 (Hodges-Lehmann estimate in %) in relevant subgroups.

Table 11: **Analysis of the Primary and Secondary endpoints from the STRIDE trial**

Intention-to-treat[a]	Ozempic N = 396	Placebo N = 396
Maximum walking distance (meters)		
Baseline[b] median (IQR)	185 (127, 274)	186 (134, 262)
Primary endpoint		
Week 52		
Ratio to baseline median (IQR)	1.21 (0.95, 1.55)	1.08 (0.86, 1.36)
Treatment ratio (HL Estimate) [95% CI][c]	1.13 [1.06, 1.21]*	
Change from baseline median (IQR)	37 (–8, 109)	13 (–27, 70)
Treatment difference (HL Estimate) [95% CI][c]	26 [12, 41]+	
Patients (%) experiencing meaningful within-patient change[d]	49.1	35.1
Secondary endpoints		
Week 57		
Ratio to baseline median (IQR)	1.16 (0.92; 1.48)	1.10 (0.87; 1.40)
Treatment ratio (HL Estimate) [95% CI][c]	1.08 [1.00, 1.16]*	
VascuQol-6 total score, week 52		
Baseline median (IQR)	15 (13, 18)	15 (13, 17)
Change from baseline median (IQR)	2 (0, 4)	1 (–1, 4)
Treatment difference (HL Estimate) [95% CI][c]	1.00 [0.48, 1.52]*	
Pain-free walking distance (meters), week 52		
Baseline[b] median (IQR)	119 (76, 174)	109 (78, 170)
Ratio to baseline median (IQR)	1.21 (0.92, 1.52)	1.10 (0.86, 1.44)
Treatment ratio (HL Estimate) [95% CI][c]	1.11 [1.03, 1.20]*	

IQR = interquartile range, 25th percentile to 75th percentile; HL = Hodges-Lehmann estimate of location shift (median of all paired differences between semaglutide and placebo); CI = confidence interval.

[a] The intention-to-treat population includes all randomized patients. Missing data at week 52/57 due to death or physical inability to perform treadmill assessments were handled using composite strategy by assigning worst ranks. Missing data at post-baseline visits for other reasons were imputed using multiple imputation within groups defined by randomised treatment and completion status at week 52.

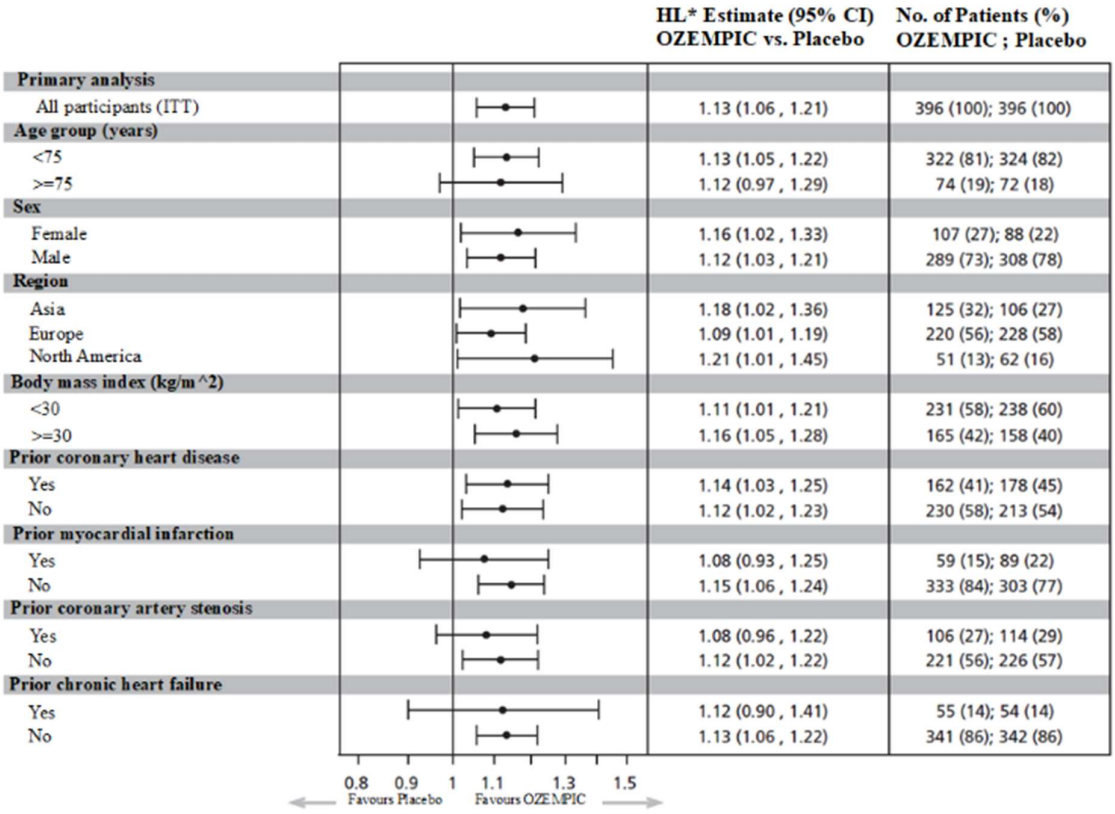
[b] Baseline was defined as the average of the walking distance measurements taken at baseline visit (week 0).

[c] 95% CIs were estimated with the Hodges-Lehmann method.

* $p < 0.05$ (two-sided) for superiority of semaglutide vs. placebo obtained from Wilcoxon-rank sum test, adjusted for multiplicity. The primary and confirmatory secondary endpoints were tested in a pre-

specified hierarchical order to control the overall type I error at 5% level of significance.
[+] p <0.05 (two-sided) obtained from Wilcoxon-rank sum test, unadjusted for multiplicity.
[d] The meaningful within-patient change for maximum walking distance at week 52 is defined as an improvement of at least 1.2 (20%) relative to baseline maximum walking distance. The 20% improvement was obtained from the anchor-based analysis based on 1-category improvement in the PGI-S (Patient Global Impression of Severity) scale. This threshold applies to the individual patient level, classifying patients into "responders" and "non-responders". The binary endpoint (responder versus non-responder) was analysed using a logistic regression model with randomised treatment as a fixed factor.

Figure 5: Forest plot: Ratio to baseline in Maximum walking distance at week 52 in subgroups (STRIDE)



ITT - Intention-to-treat population, HL* - Hodges-Lehmann estimate of location shift (median of all paired differences between semaglutide and placebo), CI -confidence interval.

Kidney Outcomes Trial of Reglutide in Adults with Type 2 Diabetes Mellitus and Chronic Kidney Disease

FLOW (NN9535-4321) was a randomised, double-blind, placebo-controlled, event driven trial in adults with type 2 diabetes mellitus and chronic kidney disease (eGFR 25 to 75 mL/min/1.73 m^2 with urine albumin-to-creatinine ratio [UACR] >100 mg/g and <5000 mg/g). All patients needed to have an HbA_{1c} ≤10% at screening and be receiving standard of care background therapy, including a maximum

tolerated labeled dose of a renin-angiotensin-aldosterone system (RAAS) blocking agent including an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), unless such treatment was contraindicated or not tolerated. The trial excluded patients with congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations.

A total of 3 533 patients were randomized to receive Reglutide 1 mg once weekly or placebo and were followed for a median of 41 months. The mean age of the study population was 67 years, and 70% of patients were male. Approximately 66% of the trial population was White, 24% Asian, and 5% Black or African American. At baseline, the mean eGFR was 47 mL/min/1.73m^2, with 11% of patients having an eGFR <30 mL/min/1.73m^2. Median baseline UACR was 568 mg/g with 69% of patients with a UACR >300 mg/g. At baseline, 95% of patients were treated with an ACE inhibitor or ARB, 16% were on sodium-glucose cotransporter 2 (SGLT2) inhibitors, 76% were on a statin, and 50% were on an antiplatelet agent.

Reglutide was superior to placebo in reducing the incidence of the primary composite endpoint of a sustained decline in eGFR of ≥50%, sustained eGFR <15 mL/min/1.73 m^2, chronic renal replacement therapy, renal death, CV death (HR 0.76 [95% CI 0.66, 0.88], p=0.0003) as shown in **Table 12** and **Figure 6**. The treatment effect reflected a reduction in a sustained decline in eGFR of ≥50%, progression to kidney failure and CV death. There were few renal deaths during the trial.

Reglutide also reduced the annual rate of change in eGFR (**Figure 8**), the incidence of a composite cardiovascular endpoint, consisting of non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular death, and the incidence of all-cause death (**Table 12** and **Figure 7**).

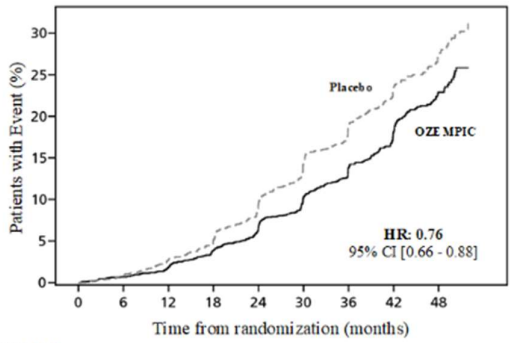
The treatment effect on the primary composite endpoint was generally consistent across the pre-specified subgroups examined, including age, biological sex, eGFR and UACR. The treatment benefit on the primary composite endpoint was not evident in patients taking SGLT2 inhibitors at baseline, but there were few events in these patients.

Table 12: Analyses of the Primary and Secondary Endpoints and their Individual Components in FLOW Trial

	Placebo N=1766 (%)	OZEMPIC 1 mg N=1767 (%)	Hazard ratio vs placebo (95% CI)[1]	p-value[2]
	Number of Patients (%)			
Composite Endpoint (≥ 50% sustained eGFR decline, sustained eGFR < 15 mL/min/1.73 m^2, chronic renal replacement therapy, or renal or cardiovascular death (time to first occurrence)[3]	410 (23.2)	331 (18.7)	0.76 (0.66, 0.88)	0.0003
≥ 50% sustained eGFR decline[3]	213 (12.1)	165 (9.3)	0.73 (0.59, 0.89)	
Sustained eGFR <15mL/min/1.73 m^2 [3]	110 (6.2)	92 (5.2)	0.80 (0.61, 1.06)	
Chronic renal replacement therapy	100 (5.7)	87 (4.9)	0.84 (0.63, 1.12)	
Renal death	5 (0.3)	5 (0.3)	0.97 (0.27, 3.49)	
Cardiovascular death	169 (9.6)	123 (7.0)	0.71 (0.56, 0.89)	
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)	254 (14.4)	212 (12.0)	0.82 (0.68, 0.98)	0.0289
All-cause death	279 (15.8)	227 (12.8)	0.80 (0.67, 0.95)	0.0104

[1] Cox proportional hazards model with treatment as factor and stratified by baseline use of SGLT2-inhibitor at baseline (yes or no).
[2] Two-sided p-value for the test of no difference. The significance level was 0.03224.
[3] Sustained was defined as having 2 consecutive measurements ≥28 days apart fulfilling the criteria.

Figure 6. Cumulative Incidence: Time to First Occurrence of the Primary Composite Endpoint - Sustained Decline in eGFR ≥50%, Sustained eGFR<15 mL/min/1.73m², Chronic Renal Replacement Therapy, Renal Death or CV death

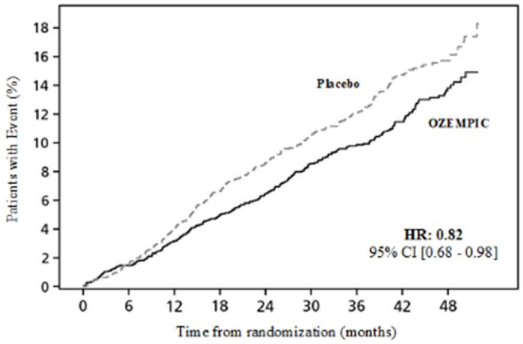


Patients at risk

OZEMPIC	1767	1738	1693	1640	1572	1489	1131	742	392
Placebo	1766	1736	1682	1605	1516	1408	1048	660	354

Cumulative incidence estimates are based on time from randomization to first composite renal event with non-CV and non-renal death modelled as competing risk. The x-axis is truncated at 52 months where approximately 5% of the population was in the trial. Sustained was defined as having 2 consecutive measurements ≥28 days apart fulfilling the criteria.

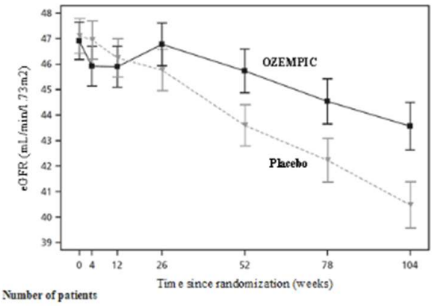
Figure 7. Cumulative incidence: Time to First Occurrence of MACE in FLOW Trial



Patients at risk

OZEMPIC	1767	1725	1672	1622	1575	1515	1176	793	430
Placebo	1766	1721	1663	1583	1535	1478	1133	731	418

Figure 8. Observed Mean Plot: eGFR (mL/min/1.73m2) by Week in FLOW Trial



Number of patients

OZEMPIC	1766	1591	1607	1522	1469
Placebo	1766	1573	1609	1490	1441

Observed data from the in-trial period until week 104. Error bars are +/- 1.96 *standard error of the mean eGFR, which was calculated using the CKD-EPI 2009 formula.

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, eGFR: estimated glomerular filtration rate.

Paediatric population

The MHRA has deferred the obligation to submit the results of studies with Ozempic in one or more subsets of the paediatric population in type 2 diabetes (see section 4.2 for information on paediatric use).

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

Maximum concentration was reached 1 to 3 days post dose. Steady state exposure was achieved following 4–5 weeks of once weekly

administration. In patients with type 2 diabetes, the mean steady state concentrations following subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively. In the trial comparing semaglutide 1 mg and 2 mg, the mean steady state concentrations were 27 nmol/L and 54 nmol/L, respectively. Semaglutide exposure increased in a dose proportional manner for doses of 0.5 mg, 1 mg and 2 mg. Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. Absolute bioavailability of subcutaneous semaglutide was 89%.

Distribution

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

Biotransformation

Prior to excretion, semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

Elimination

In a trial with a single subcutaneous dose of radiolabelled semaglutide, it was found that the primary excretion routes of semaglutide-related material were via urine and faeces; approximately 2/3 of semaglutide-related material were excreted in urine and approximately 1/3 in faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine. In patients with type 2 diabetes clearance of semaglutide was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Special population

Elderly

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a studies including patients of 20–86 years of age.

Gender, 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 has an effect on the exposure of semaglutide. Higher body weight results in lower exposure; a 20% difference in body weight between individuals will result in an approximate 16% difference in exposure. Semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure over a body weight range of 40–198 kg.

Renal impairment

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with subjects with normal renal function. This was also shown for subjects with type 2

diabetes and with renal impairment based on data from phase 3a studies, although the experience in patients with end-stage renal disease was limited.

Hepatic impairment

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

Paediatric population

Semaglutide has not been studied in paediatric patients.

Immunogenicity

Development of anti-semaglutide antibodies when treated with semaglutide 1 mg and 2.4 mg occurred infrequently (see section 4.8) and the response did not appear to influence semaglutide pharmacokinetics.

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 hydrogen phosphate dihydrate
Propylene Glycol
Propylene Glycol
Hydrochloric acid
Sodium Hydroxide
Water for Injection

6.2 Incompatibilities

NA

6.3 Shelf-Life

12 months

6.4 Special Precautions for storage

Store Below 30°C

6.5 Nature and Content of container

Clear Glass cartridge (Type 1)

6.6 Special precautions for disposal and other handling

NA

7. Marketing Authorization Holder

Beximco Pharmaceuticals Ltd.
Address: 19 Dhanmondi R/A, Road No. 7, Dhaka-1205.
Country: Bangladesh
Telephone: +880 2 58611001-7
Telefax: +880 2 58613888
E-Mail: info@bpl.net
Website: www.beximcopharma.com

8. Marketing Authorization Number

H2024/CTD10866/24476

9. Date of first authorization/renewal of the authorization

2024 March 04

10. Date of revision of the text

2029 March 04