**Abbreviated prescribing information (and not full package insert)**

**Generic Name:** Semaglutide Tablets

**Brand Name:** Rybelsus® 3 mg tablets, Rybelsus® 7 mg tablets and Rybelsus®14 mg tablets.

**Presentation:** Rybelsus® 3 mg, 7 mg and 14 mg tablets for once-daily oral use. Each tablet contains 3, 7 or 14 mg semaglutide. Tablet for once daily oral use. **Indication:** RYBELSUS® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: • RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. [see section 4.4 Special Warnings and Precautions] •RYBELSUS® is not indicated for use in patients with type 1 diabetes mellitus. **Description:** The semaglutide drug products are white to light yellow oval shaped tablets. The primary packaging is a blister card composed of coloured forming foil and non-coloured lid foil. The colour of the forming foil is unique for each tablet strength: green for 3 mg tablets, red for 7 mg tablets and blue for 14 mg tablets. The blister card contains 10 identical cavities, each containing 1 tablet. Batch specific information is printed on each blister card. The secondary packaging consists of an outer sales carton. **Dosing and administration: Posology** The starting dose of Rybelsus® is 3 mg once daily. After 1 month, the dose should be increased to a maintenance dose of 7 mg once daily. If additional benefits are needed after at least one month on the 7 mg dose, the dose can be increased to a maintenance dose of 14 mg once daily. Rybelsus® can be used as monotherapy or in combination with one or more glucose-lowering medicinal products. When Rybelsus® is used in combination with metformin and/or a sodium-glucose co-transporter 2 inhibitor (SGLT2i) or thiazolidinedione, the current dose of metformin and/or SGLT2i/thiazolidinedione can be continued. When Rybelsus® is used in combination with a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. Missed dose: If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day. **Method of administration:** Rybelsus® is a tablet for once-daily oral use. Rybelsus® should be taken on an empty stomach. Rybelsus® should be swallowed whole with up to half a glass of water equivalent to 120 ml. Do not split, crush or chew the tablet. Wait at least 30 minutes before the first meal or drink of the day or taking other oral medicinal products. Waiting less than 30 minutes may decrease the absorption of semaglutide. **Special Population:** Elderly (≥65 years old): No dose adjustment is required based on age. Gender: No dose adjustment is required based on gender. Race and ethnicity: No dose adjustment is required based on race and ethnicity. Patients with hepatic impairment: No dose adjustment is required for patients with hepatic impairment. Patients with renal impairment: No dose adjustment is required for patients with renal impairment. Children and adolescents: The safety and efficacy of Rybelsus® in children and adolescents below 18 years have not been studied. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** Rybelsus® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Gastrointestinal effects: Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions that can cause dehydration, which in rare cases can lead to a deterioration of renal function. Acute pancreatitis: Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Rybelsus® should be discontinued; if confirmed, Rybelsus® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis. Hypoglycaemia: Insulin and sulfonylurea are known to cause hypoglycaemia. 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. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with Rybelsus®. Diabetic retinopathy: Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines. Heart failure: There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV. **Pregnancy and lactation:** Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, Rybelsus® should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with Rybelsus®. If a patient wishes to become pregnant, or pregnancy occurs, Rybelsus® should be discontinued. Rybelsus® should be discontinued at least 2 months before a planned pregnancy due to the long half-life. In lactating rats, semaglutide, salcaprozate sodium and/or its metabolites were excreted in milk. As a risk to a breast-fed child cannot be excluded, Rybelsus® should not be used during breast-feeding. **Drug Interaction:** Interaction with other medicines: In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters. Semaglutide delays gastric emptying which may influence the absorption of other oral medicinal products. No clinically relevant drug-drug interaction with semaglutide was observed based on the evaluated medicinal products. Therefore, no dose adjustment is required for medicinal products when taken with Rybelsus®. Effects of Rybelsus® on other medicinal products: Total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single dose of levothyroxine. Maximum exposure (Cmax) was unchanged. Monitoring of thyroid parameters should be considered when treating patients with semaglutide at the same time as levothyroxine. No clinically relevant change in AUC or Cmax of warfarin, digoxin, oral contraceptives (containing ethinylestradiol and levonorgestrel), metformin, furosemide or rosuvastatin was observed when concurrently administered with semaglutide. Effects of other medicinal products on semaglutide: No clinically relevant change in AUC or Cmax of semaglutide was observed when taken with omeprazole. Interaction with food: Concomitant intake of food reduces the exposure of semaglutide. **Undesirable Effects:** In 10 phase 3a trials, 5,707 patients were exposed to Rybelsus® alone or in combination with other glucose-lowering medicinal products. The duration of the treatment ranged from 26 weeks to 78 weeks. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration. Other undesirable effects being delayed gastric emptying, dysgeusia and dizziness **Shelf life:** 3 mg: 24 months; 7 mg: 30 months; 14 mg: 30 months. **Storage** Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month. Do not store above 30°C. Store in the original package to protect from moisture and light. Keep the tablet in the blister until you are ready to take it. Removing it too soon can prevent it from working as planned. Do not use this medicine if you notice that the package is damaged or shows signs of being open.

**Disclaimer:** The abbreviated package insert is updated from the CDSCO approved package insert (F. No.- 4-40/Novo Nordisk/PAC-R-Semaglutide/2023-BD dated 22 July 2024). Rybelsus® is a registered trademark owned by Novo Nordisk A/S and registered in Denmark. Imported by: Novo Nordisk India Private Limited, Bangalore

*The full prescribing information can be obtained at no cost from Novo Nordisk. For full prescribing information please contact +91-080-40303200 or write to us at INAgree@novonordisk.com or reach us at Novo Nordisk India Private Limited, NXT Tower -2,

Floor 1 & 2, Embassy Manyata Business Park, Nagavara Village, Kasaba Hobli, Bangalore-560045).

Note: For detailed information on this product, please refer to full package insert*.

RYBELSUS® and the Apis bull logo are registered trademarks of Novo Nordisk A/S. Please refer latest summary of product characteristics for more details. To get information on the updated package insert please contact +91 80 4030 3200 or write to us at inagree@novonordisk.com.

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RYBELSUS® semaglutide tablets

This content is strictly for healthcare professionals practicing in India.

# LET YOUR PATIENTS WAKE UP TO NEW POSSIBILITIES

RYBELSUS®
semaglutide tablets

**A GAME CHANGER. A LIFE CHANGER.**

**PRODUCT MONOGRAPH**

**For adults with type 2 diabetes**

**• A dosing guide to get patients started on once-daily oral RYBELSUS**

RYBELSUS® semaglutide tablets

novo nordisk®

# INDEX

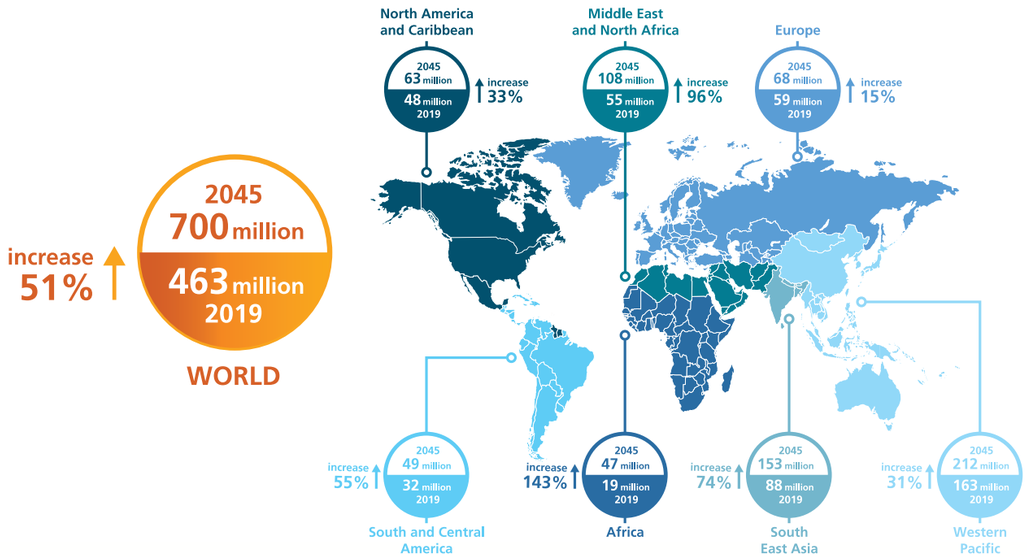
# TYPE 2 DIABETES: CLINICAL BACKGROUND

This chapter provides an overview of the epidemiology and pathophysiology of T2D and summarises current management strategies and unmet treatment needs.

## 1.1 The global burden of T2D[1]

In 2019, the global prevalence of diabetes was estimated to be 463 million adults (20–79 years), and is expected to rise to 700 million by 2045 (Figure 1)[1]

**Figure 1. The global burden of diabetes**




- T2D is a complex and progressive disease associated with significant morbidity and mortality
  - Four million deaths worldwide are attributable to diabetes, with half of the 4 million deaths in people aged under 60 years[1]
  - The risk of death among people with diabetes (aged 20–59 years) is at least double that in those without diabetes[2]
- The cost of managing the condition and its complications is substantial
  - It is estimated that the total global healthcare expenditure on diabetes in 2019 will be US $760 billion[1]
- It has been estimated that as many as 232 million people or half of all people aged 20–79 years with diabetes worldwide are unaware of their disease as symptoms may not be apparent for many years[1]
- However, diagnosis and treatment should occur as early as possible to prevent serious and costly complications[1]
- Risk factors for diabetes include genetic predisposition, sedentary lifestyle, smoking and alcohol consumption[3]
- A key factor underlying the global rise in diabetes is the increasing prevalence of obesity, which is a significant risk factor for diabetes
  - 11% of men and 15% of women worldwide were classified as having obesity in 2014, while 38% of men and 40% of women were classified as overweight[4]
  - A BMI of >35 kg/m$^2$ is associated with an increased risk of diabetes of >40-fold in men and >70-fold in women[5]

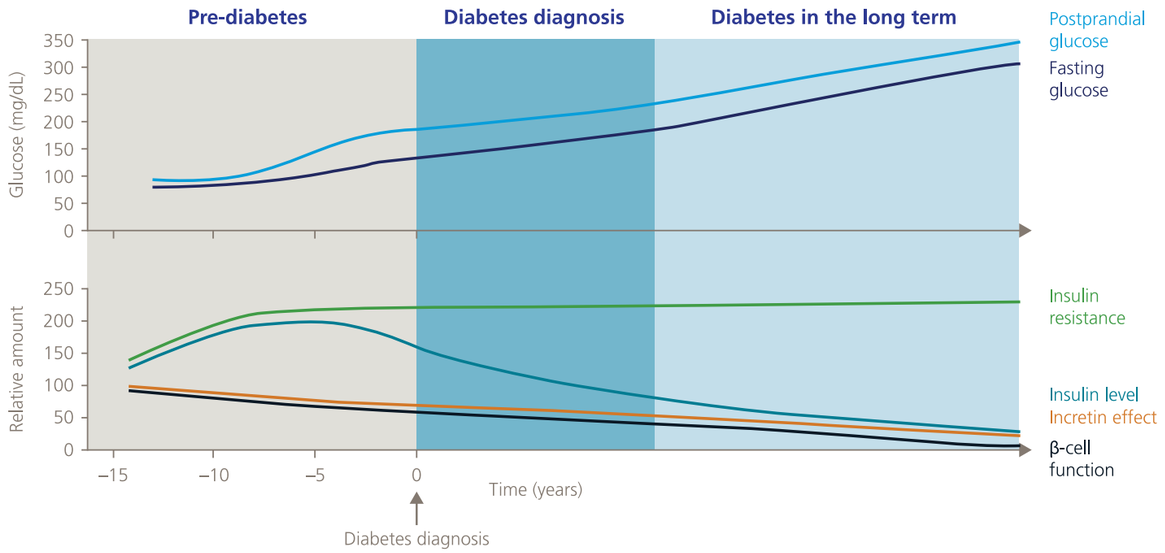
  When combined with overweight/obesity, the risks of serious long-term complications and overall mortality associated with diabetes are further increased

## 1.2 The pathophysiology of T2D

- The pathophysiology of T2D is progressive and involves multiple defects that contribute to chronic hyperglycaemia[6,7] (Figure 2)
- At least eight distinct pathophysiological abnormalities contribute to impaired glucose homeostasis (Figure 3) and are present early in the natural history of T2D[7]

# TYPE 2 DIABETES: CLINICAL BACKGROUND

**Figure 2. T2D is a progressive disease[7-9]**

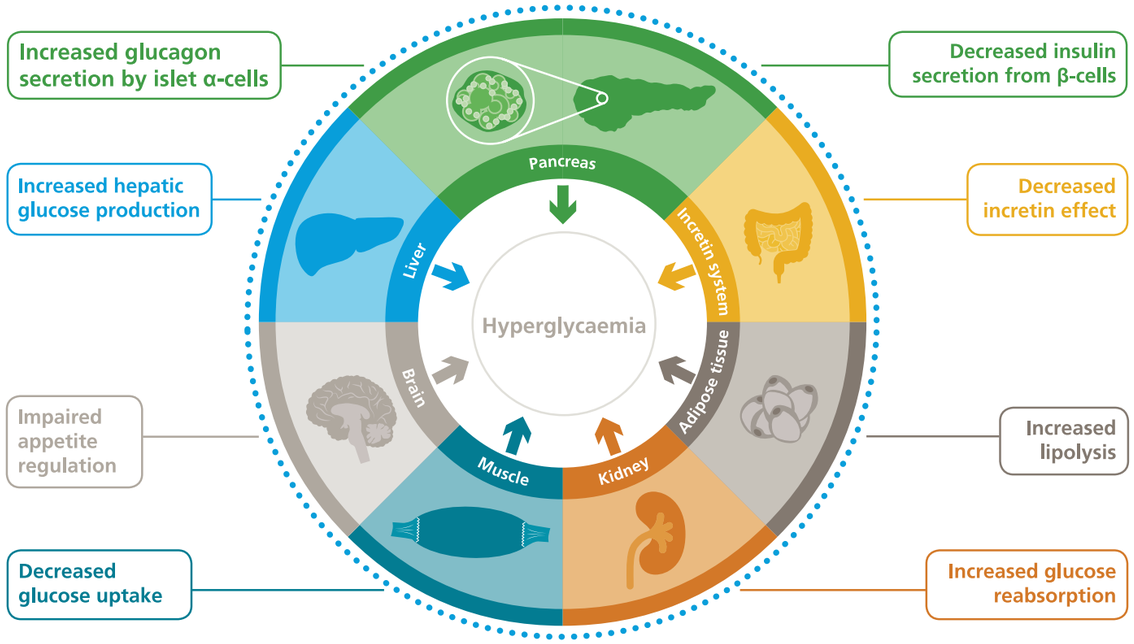



| Pre-diabetes | Diabetes diagnosis | Diabetes in the long term |
|---|---|---|
| During pre-diabetes, insulin resistance and insulin levels begin to increase, in parallel with a gradual decline in the incretin effect and β-cell function. Consequently, postprandial and fasting glucose levels then begin to rise. | By the time that diabetes is diagnosed, as much as 50% of β-cell function may already have been lost. | As the disease progresses, there is further deterioration of the incretin effect, and a decline in β-cell function and insulin levels occurs, causing post-meal and fasting glucose levels to increase even further. |





**Figure 3. The 'ominous octet': multiple pathophysiological abnormalities contribute to hyperglycaemia[6,7]**




- Decreased insulin secretion by pancreatic β-cells and insulin resistance in muscle and the liver are core defects in T2D[6,7]
- A decreased incretin effect has also been shown to play an important role in the progressive β-cell failure of T2D[6,7]
  - β-cell resistance to GLP-1 contributes to progressive failure in the function of β-cells[6,7]
- Increased glucagon secretion by islet α-cells and enhanced hepatic sensitivity to glucagon contribute to increased hepatic glucose production while muscle glucose uptake is impaired[6,7]
- Insulin resistance in adipocytes results in increased lipolysis and increased plasma free fatty acid levels, both of which aggravate insulin resistance in muscle and the liver and contribute to β-cell failure[6,7]

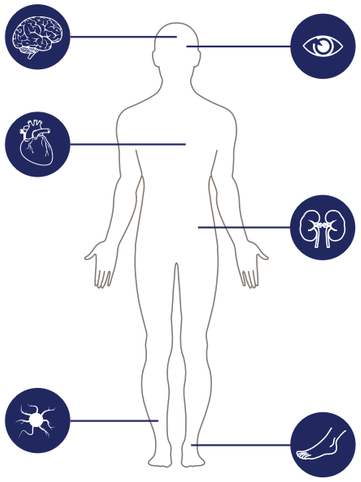
# TYPE 2 DIABETES: CLINICAL BACKGROUND

- Increased renal glucose reabsorption by the SGLT2 and the increased threshold for glucose spillage in the urine contribute to the maintenance of hyperglycaemia[6,7]
- Resistance to the appetite- suppressive effects of insulin and neurotransmitters, as well as low brain dopamine and increased brain serotonin levels, contribute to impaired appetite regulation and weight gain, which exacerbate the underlying resistance[6,7]
- Treatments are needed for T2D that address as many of these pathophysiological abnormalities as possible to maintain normoglycaemia[6,7]

## 1.3 Micro- and macrovascular complications

- Over time, uncontrolled hyperglycaemia can lead to micro- and macrovascular complications (Figure 4)[1]
- These complications are key drivers of the morbidity, mortality and cost of diabetes[10]
- Timely diagnosis, early appropriate treatment and maintaining BG levels around the normal range can reduce the risk of complications and death[1]

**Figure 4. Micro- and macrovascular complications of T2D[1]**



**CVD**
- Is 2 to 3 times more common in people with diabetes than without diabetes
- Responsible for between one-third and one-half of all deaths in diabetes
- Includes MI, stroke, peripheral artery disease and HF
- Risk factors include high BP and cholesterol levels

**Macrovascular**

**Diabetic retinopathy**
- Affects over one-third of all people with diabetes
- Is one of the leading causes of blindness in the working-age population

**Kidney disease**
- T2D is among the leading cause of kidney failure
- The prevalence of end-stage renal disease is up to 10 times higher in people with diabetes than without diabetes

**Microvascular**

**Neuropathy and diabetic foot**
- Neuropathy can lead to ulceration* and amputation
- Amputation in people with diabetes is 10 to 20 times more common compared with people without diabetes
- Every 30 seconds, a lower limb or part of a lower limb is lost to amputation as a consequence of diabetes

*Ulceration can also be a macrovascular complication.





## 1.3.1 Microvascular complications

- In the UKPDS, people with T2D (n=3867) who received intensive glucose-lowering therapy had a 25% lower risk of microvascular complications than those receiving conventional therapy after 10 years' follow-up (p=0.01)11 and continued reduction (24%; p=0.001) in microvascular risk was observed after an additional 10 years' non-interventional follow-up[12]
  - Similar reductions in microvascular complications were also observed in other large-scale interventional trials[13-15]

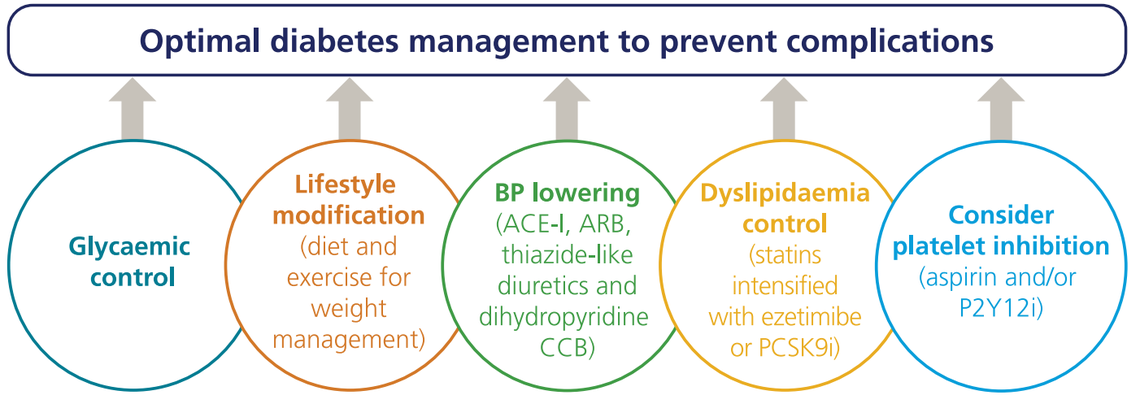
## 1.3.2 Macrovascular complications

- The risk of CVD mortality in people with T2D is more than double that of people without diabetes, and CVD remains the major cause of death and disability in people with T2D[1]

  In UKPDS, intensive glucose lowering was associated with a non-significant 16% reduction in MI versus conventional treatment[11], with a significant 15% reduction (p=0.01) observed after additional follow-up[12]
  - Other large-scale interventional studies have not shown a significant reduction in CV events with intensive glucose lowering[13-15]
- The effect of intensive multifactorial interventions on CV outcomes was investigated in the STENO-2 trial in 160 people with T2D; achievement of multitargets related to $HbA_{1c}$, total cholesterol, triglycerides and BP was studied versus conventional therapy[16]
  - Intensive multifactorial intervention reduced the risk of CV events (59%, p<0.001), CV death (57%, p=0.04) and all-cause mortality (46%, p=0.02)[16]
  - It is recommended that CV risk factors are systematically assessed at least annually in all people with diabetes and that modifiable abnormal risk factors are treated (Figure 5)[17]

# TYPE 2 DIABETES: CLINICAL BACKGROUND

**Figure 5. A multifactorial approach to T2D is recommended to reduce complications[17–20]**




- Results from landmark studies indicate that diabetes management should involve timely normalisation of glucose levels to achieve targeted $HbA_{1c}$ levels and prevent complications, with multifactorial control of CV risk factors[17,20]
  - Cardiometabolic benefits, including improvements in BP, lipids and CV biomarkers, as well as reduced CV mortality[26-31]

## 1.4 Obesity in T2D

- Approximately 80% of people with T2D are overweight or have obesity[21]
- Obesity carries a significant mortality risk[22]
  - For every 5 kg/m$^2$ increase in BMI above the normal range, there is a ~30% increase in overall risk of mortality
- Obesity, and in particular central obesity, is associated with increased insulin resistance and disturbances in glucose metabolism
- Weight loss is associated with significant health benefits related to diabetes:
  - Glycaemic benefits, including improvements in HbA1c and FPG[23-25]
  - Even modest, sustained weight loss of 3–5% can produce clinically meaningful health benefits, and greater weight losses can produce greater benefits[32]
- In people with T2D who are overweight or have obesity, a 5–10% reduction in body weight is associated with clinically relevant reductions in HbA1c and a reduced need for diabetes medications[32]
- People with T2D and obesity often struggle to lose weight[33]. This is in part because several classes of anti-hyperglycaemic medications are associated with weight gain[34]
- The impact on body weight should be taken into account when selecting glucose-lowering medications[34]





## 1.5 Recommendations for the management of T2D

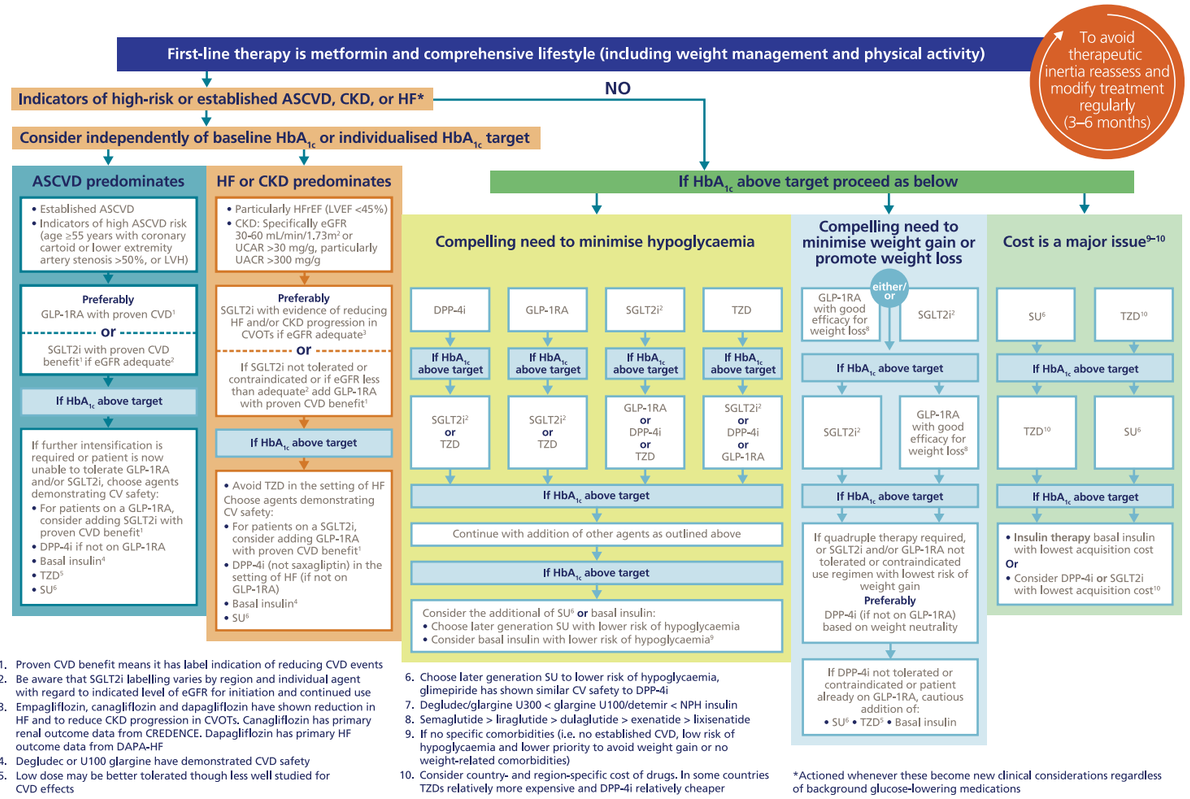
- Current treatment guidelines recommend an HbA1c target of <7% (ADA and EASD) or 6.5% (American Association of Clinical Endocrinologists), with the understanding that targets are individualised based on the person and their disease features[34,35]
  - Personalisation is necessary to balance the benefit of glycaemic control with its potential risks, taking into account the adverse effects of glucose-lowering medications (eg. hypoglycaemia and weight gain), and the person's age and health status, among other concerns
- Guidelines for patients with T2D also highlight the importance of managing CV risk factors, including body weight, lipids and BP[17]
- Lifestyle changes, including diabetes education, dietary intervention, exercise and weight control, are recommended as an essential part of T2D management[34]
- However, lifestyle changes alone are often insufficient to reduce BG to normal levels, and many people with T2D also require pharmacotherapy
- Different drug classes with varying modes of action are recommended:[36]
  - Biguanides
  - SUs
  - TZDs
  - DPP-4is
  - SGLT2is
  - GLP-1RAs
  - Basal insulin analogues
- The drug classes have different properties, varying in their efficacy, hypoglycaemia risk, effects on body weight, CV and renal effects and routes of administration (Table 1)[36]
- Metformin monotherapy is the usual first-line pharmacotherapy for T2D[36]
- In a consensus approach from the ADA and EASD, it is recommended that selection of medication added to metformin is based on the individuals' preference and clinical characteristics[34]
- Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk of specific adverse medication effects, particularly hypoglycaemia and weight gain, as well as safety, tolerability and cost (Figure 6)[36]
- A GLP-1RA or SGLT2i with proven CV benefit are recommended in people with T2D and established ASCVD[36]
- A SGLT2i with proven benefit is recommended in people with T2D and CKD or clinical HF. If a SGLT2i is not tolerated or contraindicated, or if eGFR is less than adequate, addition of a GLP-1RA with proven CV benefit is recommended[36]
- GLP-1RAs are generally recommended as the first injectable medication[36]

# TYPE 2 DIABETES: CLINICAL BACKGROUND

## Table 1. Properties of different classes of glucose-lowering agents[36]

| | Efficacy | Hypoglycaemia | Weight change | CV effects | | Renal | Route |
|---|---|---|---|---|---|---|---|
| | | | | ASCVD | CHF | | |
| **Metformin** | High | No | Neutral (potential for modest loss) | Potential benefit | Neutral | Neutral | Oral |
| **SGLT2i** | Intermediate | No | Loss | Benefit: canagliflozin, empagliflozin | Benefit: empagliflozin, canagliflozin, dapagliflozin | Benefit: empagliflozin, canagliflozin, dapagliflozin | Oral |
| **GLP-1RA** | High | No | Loss | Neutral: lixisenatide<br>Potential benefit: dulaglutide[37]<br>Benefit: liraglutide[38], semaglutide[39] | Neutral | Benefit: liraglutide | s.c.<br>Oral |
| **DPP-4i** | Intermediate | No | Neutral | Neutral | Potential risk: saxagliptin | Neutral | Oral |
| **TZD** | High | No | Gain | Potential benefit: pioglitazone | Increased risk | Neutral | Oral |
| **SU** | High | Yes | Gain | Neutral | Neutral | Neutral | Oral |
| **Insulin** | Highest | Yes | Gain | Neutral | Neutral | Neutral | s.c. |

## Figure 6. Overall approach to glucose-lowering medication in T2D from the ADA Standards of Medical Care in Diabetes - 2024[36]




1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary HF outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycaemia, glimepiride has shown similar CV safety to DPP-4i
7. Degludec/glargine U300 < glargine U100/detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

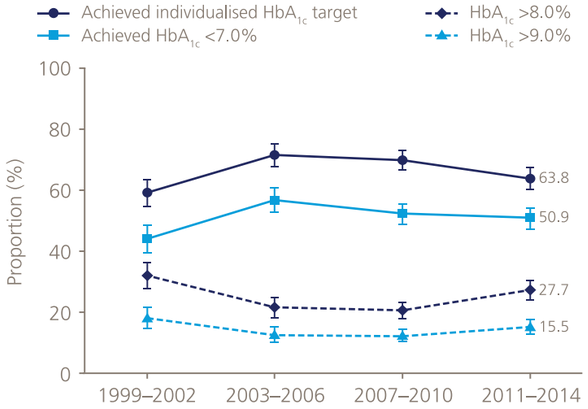
*Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications

# TYPE 2 DIABETES: CLINICAL BACKGROUND

## 1.6 Glycaemic target achievement

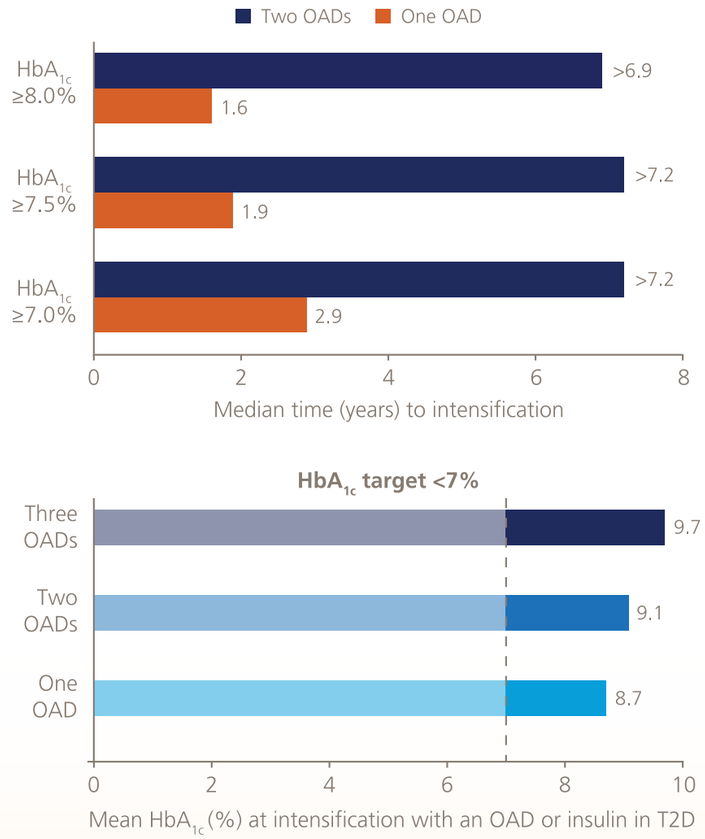
- Despite the range of pharmacotherapies currently available, many people with T2D have suboptimal glycaemic control and there has been little improvement over the past two decades (Figure 7)[40,41]
  - Over one-third of people with T2D are not achieving their individualised $HbA_{1c}$ target and only one-half have $HbA_{1c}$ <7%[41]
  - Furthermore, over one-quarter have $HbA_{1c}$ >8%[41]

**Figure 7. HbA1c target achievement in US adults with T2D[41]**




- Despite recommendations advocating treatment intensification if $HbA_{1c}$ targets are not achieved after 3 months, many of those with poor glycaemic control do not receive timely and appropriate intensification of therapy[42]
- In recent studies, the median time to treatment intensification was more than 1 year among those in whom metformin monotherapy has failed[43]
- In a US study of 5239 people with T2D treated with metformin monotherapy for ≥3 months, 28% did not receive intensification within 6 months of HbA1c >8%[43]
- Importantly, time to $HbA_{1c}$ goal attainment was shorter among those who received early intensification[43]
- Failure to initiate or intensify therapy in a timely manner is known as clinical inertia[42,43]
- Clinical inertia may contribute to people with T2D living with suboptimal glycaemic control for many years, with consequences for the person in terms of quality of life, morbidity and mortality, and for public health because of the huge costs associated with uncontrolled T2D[42]
- In a large UK study (n=105,477), 22% of people with newly diagnosed T2D had poor glycaemic control for 2 years, and 26% did not have their treatment intensified during this time[43]
  - When compared with those whose treatment was intensified within 1 year of diagnosis, delayed intensification together with poor glycaemic control (HbA1c ≥7.0%) significantly increased the risk of MI, HF or stroke by 62% ($p<0.01$) over 5.3 years' follow-up[44]
- In a retrospective UK cohort study (n=81,573), median time from above $HbA_{1c}$ cut-off (≥7.0, ≥7.5 or ≥8.0%) to intensification with an additional OAD was 1.6 to 2.9 years, respectively, for those taking one OAD and exceeded the maximum follow-up time for those taking two OADs (Figure 8)[45]
  - Mean $HbA_{1c}$ at intensification with an OAD or insulin for people taking one, two or three OADs was 8.7, 9.1 and 9.7%
  - In those intensified with only an additional OAD, mean HbA1c was 8.7% in those previously taking one OAD and 8.8% in those previously taking two OADs

**Figure 8. Years of delay and average HbA1c at intensification[45]**



# TYPE 2 DIABETES: CLINICAL BACKGROUND

- Both physician- and person-related factors can contribute to clinical inertia[42]
  - Physician-related factors include time and resource constraints, concerns relating to avoidance of treatment-related AEs and underestimation of the person's need
  - Person-related factors include AEs, inability to follow complex treatment regimens, lack of acknowledgment of disease severity, poor communication between the person and the physician, and low health literacy
- Low rates of adherence and persistence are common in people with T2D and may be associated with poor glycaemic control and outcomes[41,46]
  - Prospective analyses of adherence using electronic monitoring indicated that individuals took 61–85% of oral glucose-lowering drugs as prescribed[46]
  - In a study of electronic records for various medications in people with T2D, only 40% were persistent after 24 months[46]
- Factors affecting adherence and persistence include treatment side effects, hypoglycaemia, weight gain, inconvenience or perceived complexity of treatment administration, fear of needles or painful injections, poor efficacy and cost[41,46,47]

## 1.7 Hypoglycaemia

- Lowering BG levels must be balanced with minimising the risk of hypoglycaemia[48]
- Glucose-lowering medications that increase circulating insulin in a glucose-independent manner, such as insulin and SU therapy, are the most common cause of hypoglycaemia[49]
- Hypoglycaemia is associated with acute short-term symptoms related to either counterregulation, such as tachycardia and sweating, or to neuroglycopenia, such as confusion, and in severe cases, coma and even death[49]
- There are also long-term consequences of hypoglycaemia such as reduced working capacity, loss of self-confidence and reduced quality of life[49]
- Other serious long-term consequences include weight gain, caused by increased eating in self-defence against hypoglycaemia, and an association with increased risk of CVD with severe hypoglycaemia[49]
- Risk of hypoglycaemia is also an important factor underlying clinical inertia. Fear of hypoglycaemia may prevent healthcare providers from suggesting intensification of glucose-lowering therapy
  - In a survey of physicians (n=1250), most (75.5%) reported that they would treat more aggressively if not for concern about hypoglycaemia[50]
- Fear of hypoglycaemia may also diminish the desire of individuals to adhere to therapy[49]
- As such, hypoglycaemia carries a high cost for the person with T2D, for the healthcare system and for society at large[49]
- Appropriate selection of glucose-lowering medication is an important strategy to mitigate the risk of hypoglycaemia[49]

## 1.8 Optimising the management of diabetes

- To improve glycaemic control, there is a need for pharmacotherapies to:
  - Address as many underlying pathophysiological defects as possible
  - Effectively lower BG while minimising (or eliminating) the risk of hypoglycaemia
  - Provide clinically relevant reductions in body weight
  - Help to minimise CV risk
  - Have an acceptable safety profile
  - Offer a simple, convenient treatment regimen to improve acceptance and adherence

## 1.9 Summary

- The incidence of diabetes is increasing globally, closely linked to the rise in obesity
- The pathophysiology of T2D involves progressive pancreatic b-cell failure with consequently reduced insulin secretion and insulin resistance, leading to chronic hyperglycaemia
- There is a need for early multifactorial management of T2D to prevent hyperglycaemia and reduce the risk of serious, burdensome and costly complications
- Current treatment guidelines recommend an HbA1c target of <7% or 6.5%, together with management of other CV risk factors (body weight, lipids and BP)
- Despite the range of therapies currently available, many people with T2D still have inadequate glycaemic control and there is a delay in intensification to achieve HbA1c targets
- A person-centred approach is required to ensure timely individualised care and optimal adherence; this includes new, convenient treatment options that lower BG and reduce body weight, and have acceptable safety profiles with a low risk of hypoglycaemia and no increase in CV risk

# TYPE 2 DIABETES: CLINICAL BACKGROUND

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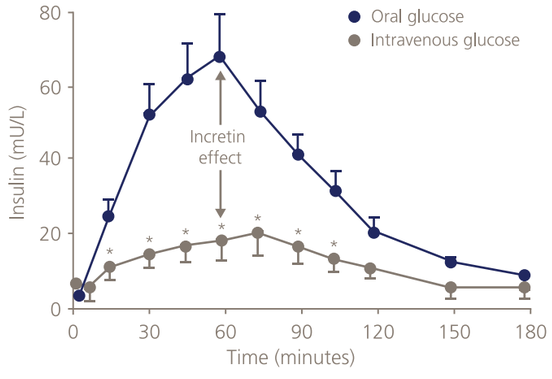
# INCRETIN EFFECT AND GLP-1 THERAPY

In the early part of the 20th century, Bayliss and Starling were the first to describe the connection between the pancreas, the gut and incretin hormones in their landmark publication 'The Mechanism of Pancreatic Secretion'. This chapter describes the physiological effects of incretin hormones in both healthy individuals and people with T2D. It also provides an overview of incretin-based therapies for T2D, with a focus on GLP-1RAs.

## 2.1 Incretin effect and GLP-1

- The peptide hormones GLP-1 and GIP, also known as incretins, are secreted from the GI tract into the circulation in response to nutrient ingestion
  - In the human gut, GLP-1 is a product of the proglucagon gene, expressed by enteroendocrine L cells that are predominantly distributed in the ileum and colon[1]. GLP-1 is also secreted in the nucleus tractus solitaries of the brain[2]
  - GIP is mainly produced by enteroendocrine K cells, which are largely located in the duodenum and jejunum[3]
- The main effect of GLP-1 and GIP is the glucose-dependent secretion of insulin in response to nutrient intake, known as the incretin effect[4]
  - Up to 70% of insulin secretion is caused by the release of incretin hormones
  - Studies have shown that exogenous GLP-1, but not GIP, can lower BG in people with T2D[5]
- The incretin effect was elucidated following the observation that oral administration of glucose results in a far greater rise in plasma insulin than with intravenous administration of glucose, despite matching BG profiles (Figure 1)[4]
- The result of the incretin effect is the reduction of plasma glucose levels, thus making incretins an attractive target in the management of diabetes
- The first phase of GLP-1 secretion occurs within 10–30 minutes of food ingestion, as a result of neural and endocrine stimulation. A second and longer (30–60 minutes) phase of release follows this, which is the result of direct contact between ingested nutrients and the GLP-1-secreting L cells of the intestinal mucosa[4,6]

**Figure 1. The incretin effect in healthy subjects**




*Significant difference (p≤0.05) to the respective value after the oral load.





## 2.2 Physiological mechanisms of GLP-1

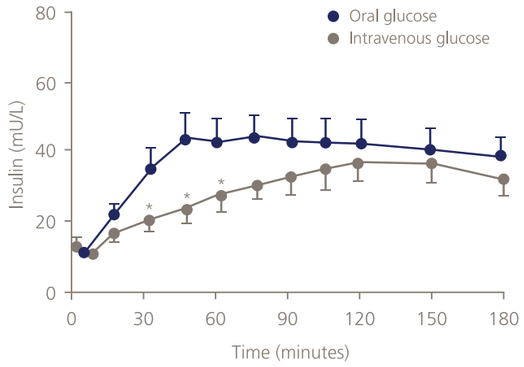
- GLP-1 mediates its effects via receptors belonging to the G protein-coupled receptor family; these receptors are found in pancreatic islets and also various other tissues throughout the body, including the brain, kidney, liver, GI and CV system[8]
- Through activation of these receptors, GLP-1 mediates numerous effects in the body including:
  - **Pancreas:** the binding of GLP-1 to GLP-1 receptors on β-cells results in the activation of signalling cascades, leading to increased cAMP and potentiation of insulin secretion in a glucose-dependent manner[5,9,10]. In *vitro* and animal model studies have shown that other effects of GLP-1 on β-cells are to improve function[11,12], stimulate neogenesis[13,14] , suppress apoptosis[11,15] and confer glucose sensitivity to glucose-resistant β-cells[16] Improved glucose sensitivity and -cell function has also been shown in humans[17]. In addition, GLP-1 has been shown to suppress glucagon secretion in pancreatic α-cells in a glucose-dependent manner, although the mechanisms remain unknown.
  - **Brain:** GLP-1 is produced by preproglucagon neurons in the lower brainstem, predominantly those in the caudal nucleus tractus solitaries and the intermediate reticular nucleus: areas involved in the regulation of food intake, with the GLP-1 receptor involved in this process[2,18-20]. Release of GLP-1 from the nucleus tractus solitaries can then activate GLP-1 receptors in the hypothalamic region of the brain, promoting satiety[21]. These regions may contribute to both appetite regulation and glucose homeostasis[21], although further studies are required to fully elucidate the relative contributions and precise mechanisms.
  - **CV system:** GLP-1 has been shown to reduce systolic BP and improve endothelial function, potentially mediated via increased natriuresis and diuresis[22,23]. GLP-1 treatment has also been associated with improved ventricular function, functional status and quality of life in those with severe HF[24]. Atherosclerosis is a complex pathological process associated with multiple inflammatory reactions. GLP-1 has anti-inflammatory effects and reduces the levels of several biomarkers associated with CVD[25].
  - **Liver:** GLP-1 has been shown to inhibit hepatic glucose production[26]; this is a result of its suppressive effect on glucagon secretion[4] , although further studies are required to clarify the exact mechanism. The existence of functional GLP-1 receptors in human liver remains controversial[5]

# INCRETIN EFFECT AND GLP-1 THERAPY

## 2.3 Reduced incretin effect in T2D

- The incretin effect is significantly impaired in people with T2D, greatly reducing the capacity for insulin release in response to food intake (Figure 2)[7,27]
- Potential mechanisms for this reduction are thought to involve defective β-cell receptor expression or post-receptor defects, defective β-cell function in general resulting in a diminished incretin effect, or genetic factors contributing to incretin hormone resistance. However, the precise mechanism is unclear, with conflicting evidence regarding a reduction in GLP-1 secretory responses in people with T2D[28]
  - Analyses of clinical studies investigating GLP-1 secretion suggest that, in general, people with T2D do not exhibit reduced GLP-1 secretion in response to an oral glucose tolerance or meal test, thus supporting the idea that deterioration in GLP-1 effect, rather than GLP-1 secretion, contributes to the reduced incretin effect in these individuals[29]
- A factor that has been shown to contribute to reduced insulin secretion is a markedly impaired β-cell response to physiological levels of GLP-1[26,27]

**Figure 2. The incretin effect in people with T2D[7]**




*Significant difference (p≤0.05) to the respective value after the oral load.

## 2.4 GLP-1 therapy in T2D

- The insulin secretory response in T2D can be restored with pharmacological levels of native GLP-1[30]
- While this demonstrates the potential of GLP-1 as an attractive treatment target, the short $t_{½}$ of native GLP-1 limits its therapeutic use: immediately after secretion, it is rapidly degraded by the enzyme DPP-4, resulting in a $t_{½}$ of around 1.5 minutes and low (10–15%) concentration in the systemic circulation in intact form[31]
- Therefore, there has been a focus on developing GLP-1RAs that have enhanced protein binding and a slower degradation by DPP-4 compared with physiological GLP-1, and thus a prolonged $t_{½}$

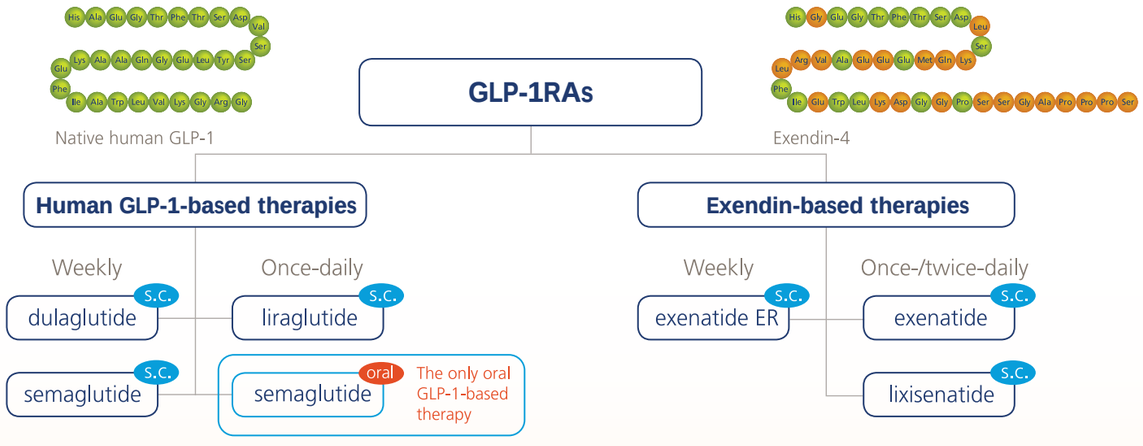
## 2.5 Incretin-based therapies

- Incretin-based therapies work either by preventing enzymatic degradation of GLP-1, thus maintaining plasma levels of endogenous GLP-1 (DPP-4is)[32,33] or by directly activating GLP-1 receptors and mimicking the action of native GLP-1 (GLP-1RAs)[34,35]
- DPP-4is (e.g. saxagliptin, sitagliptin, linagliptin, alogliptin) are oral agents given once daily (vildagliptin is available in the EU but not US and is given twice daily)
- DPP-4is provide moderate improvements in glycaemic control and are weight neutral[34]

## 2.6 GLP-1 receptor agonists

- There are two types of GLP-1RAs (Figure 3):
  - Human-based GLP-1RAs are based on the human GLP-1 amino-acid sequence and include once-daily liraglutide and once-weekly semaglutide or dulaglutide, which are administered by s.c. injection, and once-daily semaglutide, which is administered orally
    - Oral semaglutide was approved by the FDA in September 2019[36]
  - Exendin-based therapies are based on exendin-4, a 39-amino acid peptide from the saliva of the lizard Heloderma suspectum[37] and are structurally less similar to native human GLP-1
    - Exenatide and lixisenatide are administered by s.c. injection once/twice daily; exenatide ER can be administered s.c. once weekly

**Figure 3. GLP-1-based therapies for the treatment of T2D[37]**

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# INCRETIN EFFECT AND GLP-1 THERAPY

- In addition to differences in the backbone (human or exendin), there are other structural modifications (amino acid substitution, acylation) that differ between the GLP-1RAs. These structural differences confer differences in the properties of the therapies, such as the $t_{½}$ and PD[35,37]
- Like native GLP-1, GLP-1RAs have a glucose-dependent mechanism of action[38] and offer a number of beneficial effects in people with T2D[8]
- At least eight distinct pathophysiological abnormalities, comprising the 'ominous octet', contribute to impaired glucose homeostasis[39]
- At pharmacological levels, GLP-1RAs have numerous direct and indirect effects that address these defects (Figure 4)
- Effects of GLP-1RAs include improvement in glycaemic control, lowering of body weight and reductions in CV risk with some agents[25]. There is also evidence of neuroprotective and neuroregenerative effects[16]

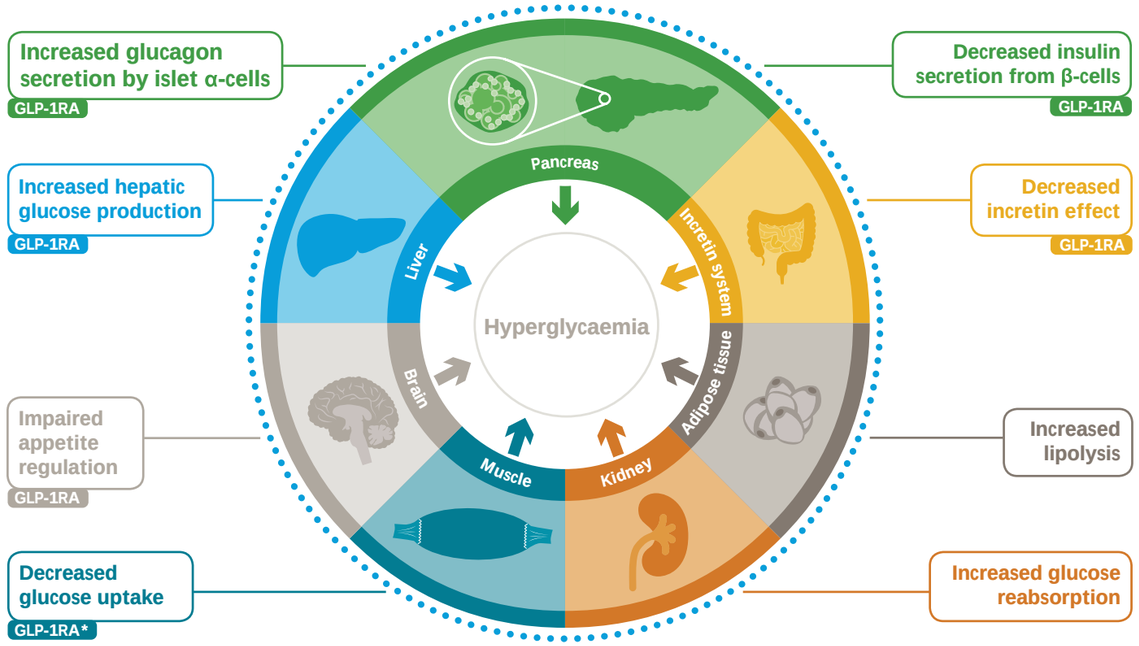
## 2.6.1 Improving glycaemic control, with a low risk for hypoglycaemia

- In the pancreas, GLP-1RAs increase insulin secretion and inhibit glucagon secretion in a glucose-dependent manner. GLP-1RAs also increase insulin synthesis, stimulate the proliferation and formation of new β-cells (neogenesis) and inhibit β-cell apoptosis in preclinical studies[16]
- In the liver, GLP-1RAs inhibit hepatic glucose production and reduce hepatic lipid content[16,40,41]
- The direct and indirect effects of GLP-1RAs at therapeutic levels in the pancreas, and indirect effects in the liver, result in the reduction of hyperglycaemia
- The glucose-dependent mechanism of action protects against hypoglycaemia as effects on insulin and glucagon secretion are lost in the absence of elevated BG concentrations[5,38]
  - It has been demonstrated that the glucagonostatic effect of GLP-1RA does not compromise glucagon secretion during the counter-regulatory response to hypoglycaemia[42]
- Substantial $HbA_{1c}$ reductions from baseline have been observed with liraglutide administered s.c. once daily in the LEAD (Liraglutide Effect and Action in Diabetes) phase 3 clinical trial programme, with superior $HbA_{1c}$ reductions versus a range of comparators[43-46]
- Similarly, substantial $HbA_{1c}$ reductions have also been observed with semaglutide administered both s.c. once weekly in the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) phase 3 clinical trial programme (Chapter 3), and as oral semaglutide once daily in the PIONEER (Peptide InnOvatioN for Early diabEtes tReatment) phase 3 clinical trial programme (Chapter 7)





**Figure 4. GLP-1RAs address multiple pathophysiological defects in T2D[39]**




*Indirectly, weight loss enhances both muscle and hepatic sensitivity to insulin.

## 2.6.2 Multifactorial effects beyond glycaemic control

- GLP-1RAs have numerous effects, both direct and indirect, beyond glycaemic control, including effects on the brain, heart, liver, pancreas and stomach[16,20,40,41,47-53] (Figure 5)

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# INCRETIN EFFECT AND GLP-1 THERAPY

**Figure 5. GLP-1RAs provide multiple benefits[16,20,40,41,47-53]**

**Pancreas**
- ↑ β-cell function
- ↓ β-cell apoptosis
- ↑ Insulin biosynthesis
- ↑ Glucose-dependent insulin secretion
- ↓ Glucose-dependent glucagon secretion

**Heart**
- ↓ CV risk
- ↓ Fatty acid metabolism
- ↑ Cardiac function
- ↓ BP
- ↓ Inflammation
- ↓ Atherosclerotic plaque progression

**Brain**
Body weight
Food intake
Satiety

**Incretin system**
Replacement of deficient GLP-1 response

**Liver**
Endogenous glucose production
Hepatic insulin sensitivity
De novo Lipotoxicity
Steatosis

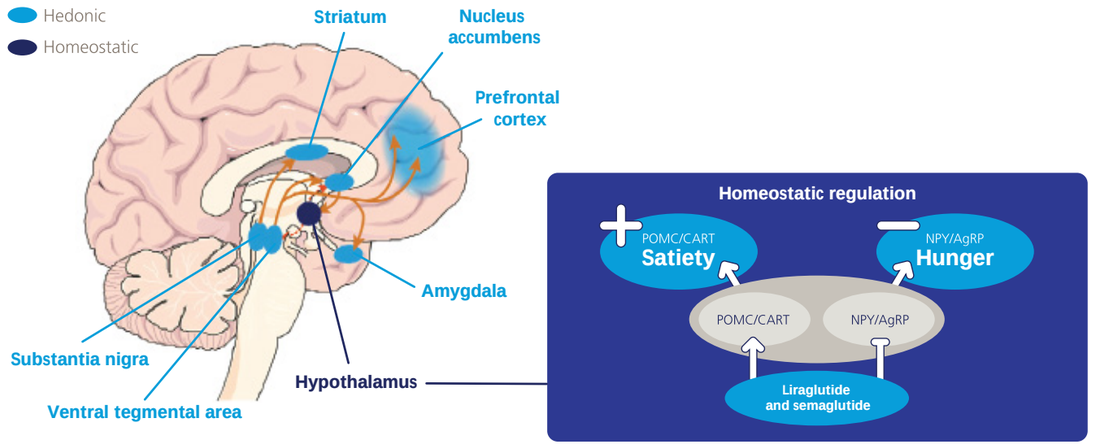
## Lowering body weight

- GLP-1RAs have access to selected parts of the brain and bind to GLP-1 receptors on arcuate nucleus neurons in the hypothalamus, which control calorie intake and energy expenditure
  - Evidence from animal studies indicates that liraglutide and semaglutide directly activate POMC/CART-producing neurons within the arcuate nucleus of the hypothalamus to increase feelings of satiety, and indirectly inhibits NPY/AgRP-producing neurons to reduce feelings of hunger (Figure 6)[21,54]
- Clinical trials have demonstrated the effects of GLP-1RAs at therapeutic dose levels in achieving clinically meaningful body weight reduction in subjects who are overweight or have obesity, with or without T2D[55]
- Across the LEAD programme, liraglutide was associated with significantly greater weight loss than a range of comparators[43-46]
- Significant weight loss has also been demonstrated with once-weekly s.c. semaglutide, and once-daily oral semaglutide, versus comparators in the SUSTAIN (Chapter 3) and PIONEER (Chapter 7) programmes





**Figure 6. Liraglutide and semaglutide regulate hedonic and homeostatic aspects of appetite[21,54,56,57]**




## Reducing CV risk

- GLP-1RAs provide CV benefits via multiple effects, including reduction in fasting and postprandial hyperglycaemia, loss of body weight and improvements in lipids and BP. GLP-1RAs have also been shown to exert anti-inflammatory effects, which may explain some of their vasoprotective properties[58,59]
- Several preclinical models of CV dysfunction have indicated that GLP-1RAs have cardioprotective /anti-atherosclerotic actions[58]
- To ensure CV safety and to meet regulatory requirements, GLP-1RAs have been investigated in large-scale CVOTs in people with T2D at high CV risk, with varying results:
  - Lixisenatide and exenatide ER demonstrated a neutral CV effect[60,61]
  - Liraglutide, dulaglutide and albiglutide demonstrated beneficial effects on CV outcomes versus placebo in the LEADER[47], REWIND[62] and HARMONY-OUTCOMES[63] trials, respectively
  - Once-weekly s.c. semaglutide demonstrated a 26% reduction in MACE versus placebo in the SUSTAIN 6 trial and is discussed further in Chapter 3[64]
  - The PIONEER 6 trial showed CV safety of oral semaglutide with a non-significant 21% reduction in risk of MACE versus placebo and is discussed in Chapter 7[65]
  - A neutral effect on CV safety has been observed with the DPP-4is, saxagliptin, alogliptin, sitagliptin and linagliptin[66-69]
  - Regarding other oral agents, a beneficial effect on CV outcomes has been observed with the SGLT2is, empagliflozin and canagliflozin (ASCVD and CHF) and dapagliflozin (CHF only)[70-72]

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# INCRETIN EFFECT AND GLP-1 THERAPY

### Beneficial hepatic effects

- In addition to inhibiting hepatic glucose production, GLP-1RAs decrease hepatic steatosis (fatty liver) and concentrations of liver enzymes in murine models of fatty liver disease[16,40,41,73]
- The Liraglutide Efficacy and Action in NASH (LEAN) study assessed the efficacy and safety of liraglutide versus placebo in 52 people with T2D and NASH41
  - The primary outcome measure of histological resolution of NASH with no worsening in fibrosis over 48 weeks was met in nine (39%) of 23 patients treated with liraglutide, which was well tolerated.
- GLP-1RAs exert effects on six out of the eight core pathophysiological defects in T2D
- Direct activation by GLP-1RAs has been shown widely to increase insulin and decrease glucagon secretion in a glucose-dependent manner, resulting in reduced blood-glucose levels combined with low risk of hypoglycaemia
- GLP-1RAs also have a series of beneficial multifactorial effects beyond glycaemic control that include reduction of body weight, and improvement of CV outcomes by some GLP-1R
- As such, GLP-1RAs are recommended early and across the continuum of diabetes management[74]

## 2.7 Summary

- GLP-1 is a peptide hormone primarily secreted in the GI tract in response to nutrient intake, which acts via receptors expressed on various tissues to mediate several important physiological effects
- The main action of GLP-1, known as the incretin effect, is to increase postprandial insulin secretion in a glucose-dependent manner
- The incretin effect is reduced in people with T2D; however, it can be restored using pharmacological doses of GLP-1
- Therapies have been developed that either increase the t½ of native GLP-1 by inhibiting DPP-4 or directly activate GLP-1 receptors





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# SEMAGLUTIDE STRUCTURE

This chapter further describes the GLP-1RA, semaglutide, ovides an overview of phase 3 studies conducted with the once-weekly s.c. formulation.

## 3.1 The structure of semaglutide

- Semaglutide was designed as a potent, long-acting GLP-1 analogue that could be administered s.c. once weekly, rather than s.c. once daily, to improve convenience and potentially adherence
- Semaglutide has 94% sequence homology with native GLP-1 and three key structural differences that provide extended PK (Figure 1)[1,2]

1. Substitution of Ala at peptide position 8 with Aib

- This modification disrupts the cleavage site of DPP-4, thus inhibiting the degradation of semaglutide and extending its systemic $t_{½}$ compared with native GLP-1 and liraglutide

2. Attachment of a linker and C18 di-acid chain at position[26]

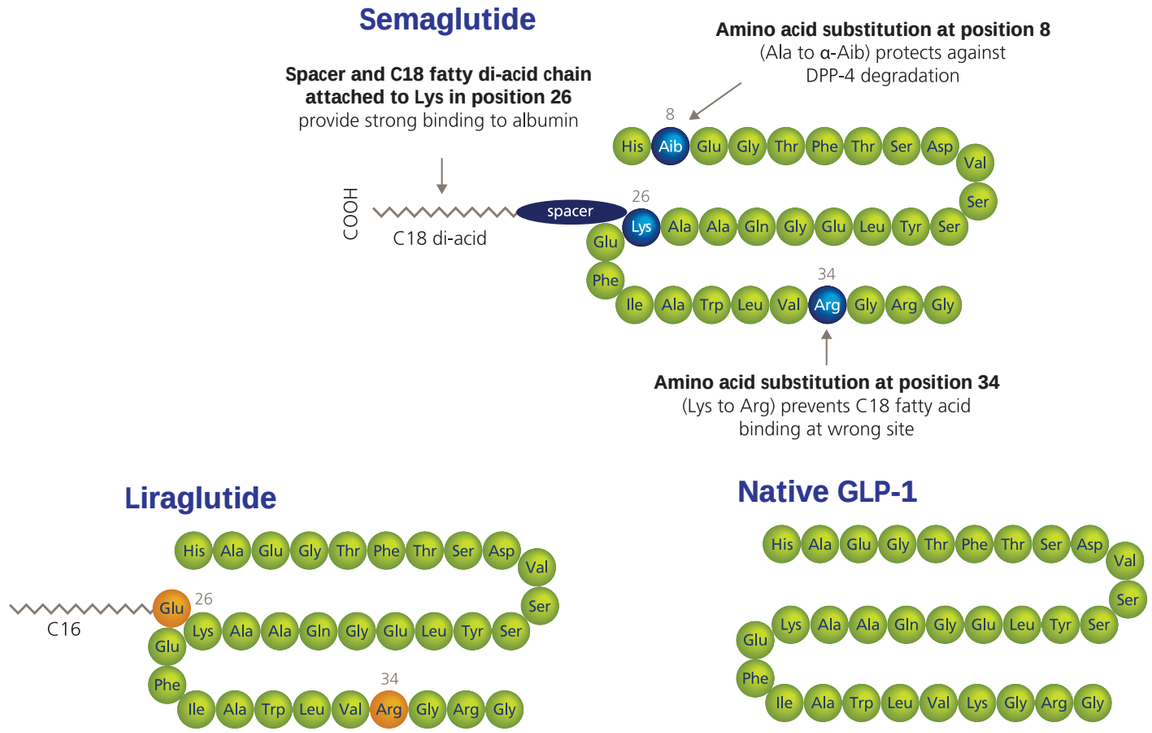
- Longer fatty di-acid chains are associated with higher binding affinity for albumin. This gives semaglutide 5.6-fold higher albumin affinity than liraglutide, which has a shorter C16 chain
- The linker structure has a significant impact on affinity to the GLP-1 receptor. For semaglutide, the γ-Glu-2xOEG was found to optimally balance binding affinity for albumin and the GLP-1 receptor, extending its $t_{½}$ without reducing its potency[1]

3. Substitution of Lys at position 34 with Arg in the GLP-1 peptide backbone (also present in liraglutide)

- The substitution of Lys[34] in GLP-1 to Arg in semaglutide ensures that, during manufacture, acylation occurs only at the correct position of Lys[26]



**Figure 1. Structures of semaglutide, liraglutide and native GLP-1**




- Together, these structural changes confer improved albumin affinity and resistance to DPP-4 degradation compared with liraglutide, and extend the t½ of semaglutide to approximately 1 week, without compromisingGLP-1 receptor binding[1,3] (Table 1)

**Table 1. Summary of PK characteristics of GLP-1RAs[2,4-9]**

| Agent | $t_{1/2}$ | $t_{max}$ |
|---|---|---|
| **Exenatide BID** | 2.4 h | 0.6 h |
| **Lixisenatide OD** | 3 h | 1–3.5 h |
| **Liraglutide OD** | 13 h | 8–12 h |
| **Dulaglutide OW** | ~4 days | 24–48 h |
| **Exenatide OW** | 7–14 days | 6–7 weeks |
| **Semaglutide OW** | ~7 days | 1–3 days |

Subcutaneous Semaglutide once weekly injection is not approved/marketed in India

# SEMAGLUTIDE STRUCTURE

## 3.2 Summary

- Structural modifications to GLP-1 led to the development of semaglutide, a potent long-acting GLP-1 analogue,which has an extended t½ without compromised GLP-1 receptor binding



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20. Marso SP, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375: 311-22.

# ORAL SEMAGLUTIDE INVESTIGATIONS

## Why do we need an oral GLP-1RA?

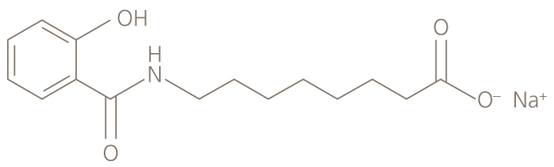
- Timely treatment of T2D is needed to reduce the risk of T2D complications[1] and yet many patients do not achieve current $HbA_{1c}$ targets with the treatment options available
- GLP-1RAs provide effective glycaemic control with weight reduction and a low risk of hypoglycaemia
- An oral GLP-1RA may lead to initiation of GLP-1RA treatment earlier in the continuum of the disease and may improve acceptance and adherence[2] for some patients compared with injectable formulations of GLP-1RA

## 4.1 Addressing the challenges of absorption of oral peptide-based drugs

- Oral protein-based drug absorption is limited due to:
  - Degradation in the stomach due to low pH and proteolytic enzymes
  - Limited permeability across the GI epithelium
- The bioavailability of GLP-1RAs administered orally alone is very low and in order to avoid degradation, the active molecule has to be protected and delivered through the GI epithelium and into the bloodstream
- Co-formulation of semaglutide with an absorption enhancer is necessary to achieve adequate bioavailability of semaglutide after oral administration
- The absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) (Figure 1), is a small fatty acid derivative that promotes absorption across the gastric epithelium3

**Figure 1. Structure of SNAC[3]**

**S**odium **N**-(8-[2-hydroxybenzoyl] **A**mino) **C**aprylate (SNAC)




- SNAC has previously been co-formulated with heparin, ibandronate and vitamin B12 to increase drug absorption[4-6]
  - SNAC (100 mg per tablet) co-formulated with vitamin B12 is currently available on prescription as a medical food for patients who have a medically diagnosed vitamin B12 deficiency
- Following the development of the oral formulation of semaglutide, an extensive series of non-clinical and clinical studies have been conducted to characterise its properties, primarily relating to mode of absorption, dosing conditions and PK (Figure 2)





**Figure 2. Overview of clinical studies designed to characterise the properties of oral semaglutide**

**Mode of absorption**
**3957:** Pharmacoscintigraphic investigation
**3794:** Optimal dosing conditions
**4154:** Food effect on PK

**Drug–drug interactions**
**4065:** Lisinopril and warfarin
**4141:** Omeprazole
**4145:** Metformin and digoxin
**4249:** Ethinylestradiol and levonorgestrel
**4250:** Furosemide and rosuvastatin
**4279:** Levothyroxine and co-administered tablets

**PK in special populations**
**4079:** PK/tolerability in subjects withrenal impairment
**4082:** PK/tolerability in subjects withhepatic impairment
**4267:** Effect of upper GI disease on PK
**[4140:** Safety/tolerability/PK in Japanese andCaucasian subjects (dose escalation)]
**[4303:** PK/tolerability in Chinese subjects]

**Dose equivalence, metabolites and safety**
**3691:** Safety (single dose)
**3692:** Safety, tolerability, PK/PD (multiple dose)
**3991:** Safety, tolerability,PK/PD (multiple dose)
**[4247:** QTc]
**4248:** PD effect

Studies in brackets are not included in this synopsis as they had not been presented at congress at the time of writing.

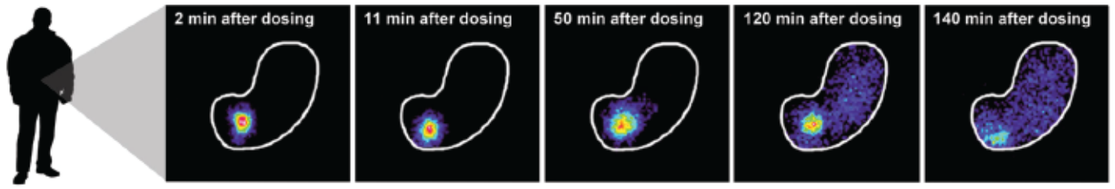
## 4.2 Mode of absorption

### Data from a pharmacoscintigraphic study indicate early systemic absorption from the stomach[3]

- Gamma scintigraphy was used to investigate the anatomical site of tablet erosion and erosion kinetics in healthy males
  - Methods: a randomised, open-label crossover study (Study 3957; NCT01619345) was conducted in 26 healthy males in a fasting state who received a single dose of 10 mg oral semaglutide containing $^{111}$In labelled ion exchange resin
- Complete tablet erosion occurred in the stomach. Representative scintigraphic images (Figure 3) show that, in this individual, no erosion had occurred 2 minutes after dosing, whereas no intact tablet core remained after 140 minutes
- Measurement of semaglutide plasma concentrations confirmed early systemic absorption and an apparently slow elimination phase once present in the systemic circulation (Figure 4)

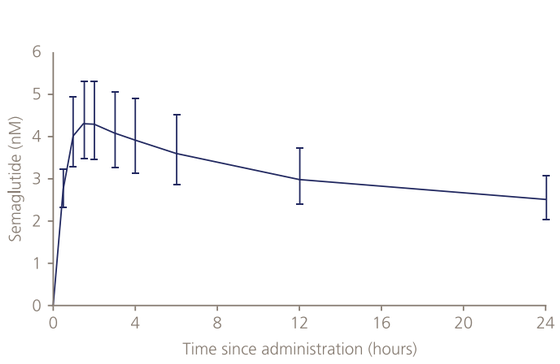
# ORAL SEMAGLUTIDE INVESTIGATIONS

**Figure 3. Gamma scintigraphic imaging of tablet erosion in the stomach after a single dose of oral semaglutide 10 mg in a representative healthy subject[3]**




The intense colours within the stomach (e.g. red/yellow/green/blue) represent the tablet core and released radioactivity.

**Figure 4. Estimated mean semaglutide plasma concentration–time profile after a single dose of oral semaglutide 10 mg[3]**




Error bars show ± standard error of the mean calculated on a log-scale and back-transformed to the original scale.

## Preclinical studies have confirmed the gastric absorption of oral semaglutide[3]

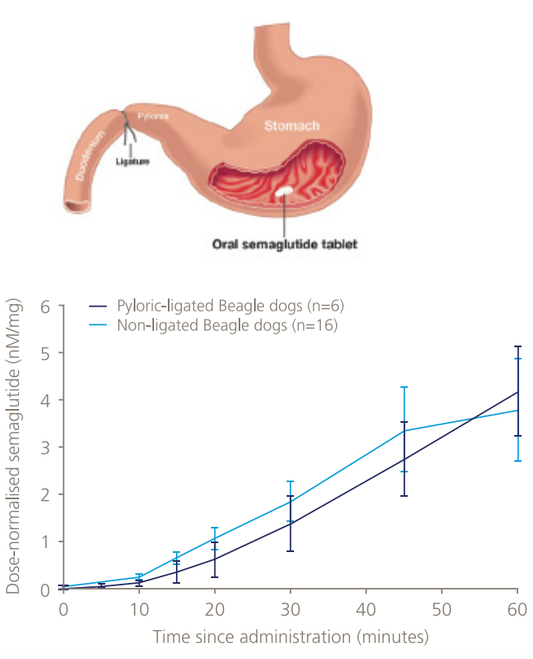
- A preclinical study in dogs examined local concentrations of semaglutide and SNAC in gastric fluid
  - Methods: Beagle dogs received a single dose of oral semaglutide (9.4–12.7 mg/300 mg SNAC). Semaglutide exposure was compared between six anaesthetised, pyloric-ligated dogs (to avoid exit of the tablet from the stomach, thereby preventing intestinal absorption) receiving intragastric dosing and 16 awake, non-ligated dogs receiving oral dosing
- Prevention of intestinal absorption by pyloric ligation resulted in similar semaglutide plasma concentrations as seen in non-ligated dogs (Figure 5), indicating that absorption can occur in the stomach
- In another preclinical study, semaglutide exposure was compared between the splenic vein (draining the gastric cavity) and the portal vein (draining the GI system) after intragastric dosing in non-ligated dogs
  - Methods: a single intragastric dose of oral semaglutide (10 mg/300 mg SNAC) was administered to seven anaesthetised, non-ligated dogs





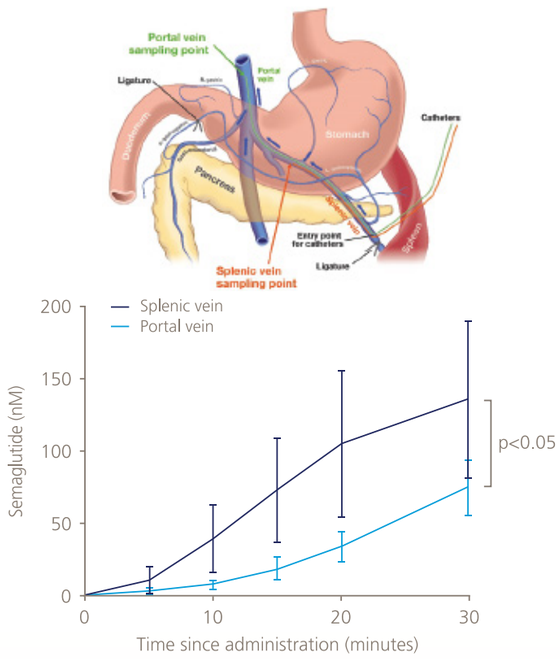
- Plasma concentrations of semaglutide were higher in the splenic vein (draining the gastric cavity) than in the portal vein (draining the GI system) (Figure 6)
- The ratio of $AUC_{0–30}$ min between the splenic and portal veins was 1.94 [95% CI 1.15, 2.74] ($p<0.05$), confirming the stomach as the predominant site of absorption
- Collectively, non-clinical data using pyloric ligation, splenic versus portal vein sampling and gastric fluid aspiration suggest that oral semaglutide is absorbed in the stomach

**Figure 5. Mean dose-normalised semaglutide plasma concentration–time profiles after a single dose of oral semaglutide in pyloric-ligated and non-ligated dogs[3]**




Error bars are ± standard error of the mean.

**Figure 6. Mean semaglutide plasma concentration–time profiles in the splenic vein and portal vein after a single dose of oral semaglutide in dogs[3]**



# ORAL SEMAGLUTIDE INVESTIGATIONS

### SNAC promotes absorption of semaglutide in a concentration-dependent manner via effects on transcellular pathways, which are transient and fully reversible[3]

- A series of in vitro studies were conducted to investigate the mechanism via which SNAC enhances the absorption of semaglutide
  - Methods: the trans-epithelial transport of semaglutide was examined in cell monolayers of gastric epithelium (NCI-N87) with and without SNAC exposure
- The absorption-enhancing action of SNAC on semaglutide was found to require concentrations in the mM range, as reflected by a significant increase in the apparent permeability coefficient of semaglutide across gastric epithelial cell monolayers in the presence of 80 mM SNAC
- There was a substantial increase in intracellular uptake of semaglutide by gastric epithelial cells with SNAC exposure compared with control, which was not apparent with EDTA, a modulator of tight junction function
- These divergent patterns indicate that SNAC mediates absorption via the transcellular route

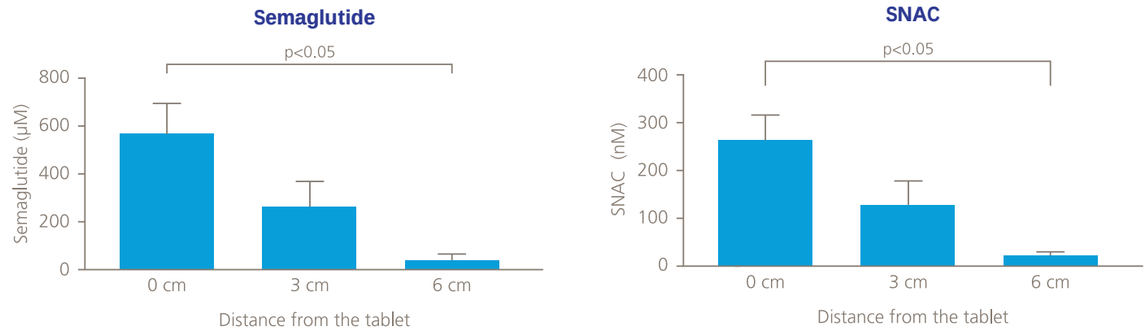
### SNAC-mediated semaglutide absorption is highly localised3

- A preclinical study in dogs examined local concentrations of semaglutide and SNAC in gastric fluid
  - Methods: a single intragastric dose of oral semaglutide (10 mg/300 mg SNAC) was administered to eight anaesthetised dogs. Liquid from underneath an oral semaglutide tablet at 0 cm and at 3 cm and 6 cm from the tablet was aspirated and assayed for semaglutide and SNAC
- High concentrations of semaglutide and SNAC in the gastric fluid were restricted to areas close to the tablet (Figure 7), indicating that semaglutide absorption occurs in a localised environment and depends on the spatial proximity of semaglutide and SNAC





**Figure 7. Mean concentrations of semaglutide and SNAC in gastric fluid aspirated from under and around the tablet 30 minutes after dosing in dogs[3]**



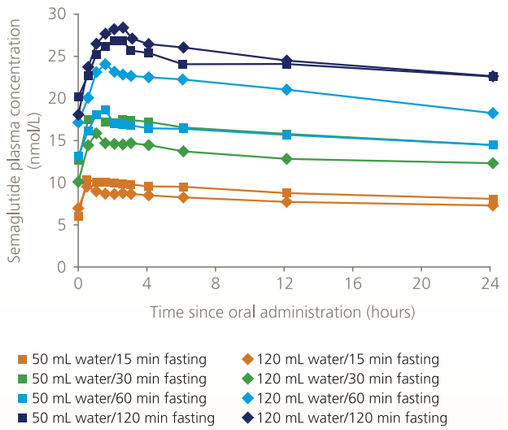

Error bars show ± standard error of the mean.

## 4.3 Optimal dosing conditions

### Administration of oral semaglutide in the fasting state, a post-dose fasting period of at least 30 minutes, and with up to 120 mL water results in clinically relevant semaglutide exposure[7]

- A phase 1 trial evaluated oral semaglutide administration under different dosing conditions in order to identify the minimum dosing requirements needed to ensure clinically relevant semaglutide exposure and an acceptable safety profile
  - Methods: in an open-label, randomised trial (Study 3794; NCT01572753), 158 healthy males were exposed to once-daily oral semaglutide 10 mg for 10 days in combination with different water volumes when dosing (50/120 mL) and with different durations of post-dose fasting (15/30/60/120 minutes)
- Semaglutide exposure ($AUC_{0–24h}$ and $C_{max}$) and tmax after 10 consecutive doses increased with longer post-dose fasting periods but there was no apparent effect on t½
- Semaglutide exposure ($AUC_{0–24h}$ and $C_{max}$), tmax and t½ were unaffected by water volume (50 mL vs 120 mL) (Figure 8)

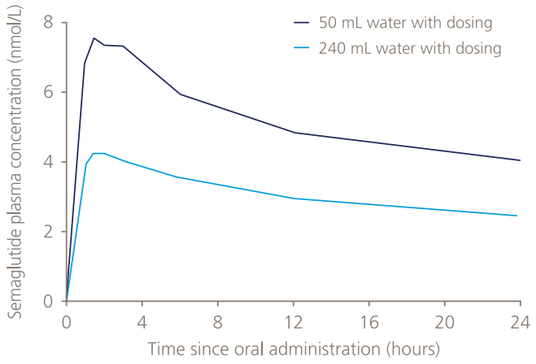
**Figure 8. Geometric mean semaglutide plasma concentration–time profiles after the 10th dosing of oral semaglutide under different dosing conditions[7]**



# ORAL SEMAGLUTIDE INVESTIGATIONS

- In the pharmacoscintigraphic study, lower semaglutide exposure levels were observed with 240 versus 50 mL water volume (Figure 9)[8], indicating that excess water should be avoided

**Figure 9. Estimated mean semaglutide plasma concentration–time profiles after a single dose of 10 mg oral semaglutide with 50 or 240 mL water in healthy male subjects[8]**




- A water volume of 120 mL was selected as the optimal water volume to accompany administration of oral semaglutide

**Therapeutic levels of semaglutide are achieved when oral semaglutide is administered in the fasting state[7,9]**

- The effect of food versus fasting on the PK of oral semaglutide was investigated

- Methods: an open-label, randomised trial (Study 4154; NCT02172313) was conducted in which 78 healthy subjects received once-daily oral semaglutide (5 mg for 5 days followed by 10 mg for 5 days) under three dosing conditions:

  - Fed: high-calorie, high-fat breakfast 30 minutes pre-dose; 240 mL water with dosing; 4 hours post-dose fasting

  - Fasting: fasting overnight; 240 mL water with dosing; 4 hours post-dose fasting

  - Reference: fasting overnight; 120 mL water with dosing; 30 minutes post-dose fasting (reflects the dosing conditions used in phase 2 and 3 trials)

- Sufficient semaglutide plasma exposure was achieved when oral semaglutide was administered in the fasting state; however, limited semaglutide exposure (11 of 25 subjects) or no exposure (14 of 25 patients) was observed in the fed arm (Figure 10)

- Semaglutide exposure after the 10th dose appeared to be ~40% greater under fasting versus reference conditions, which reflect the phase 2 and 3 dosing conditions, although this was not statistically significant (Figure 11)





**Figure 10. Individual semaglutide 24-hour profiles after the 10th dosing of oral semaglutide[7,9]**

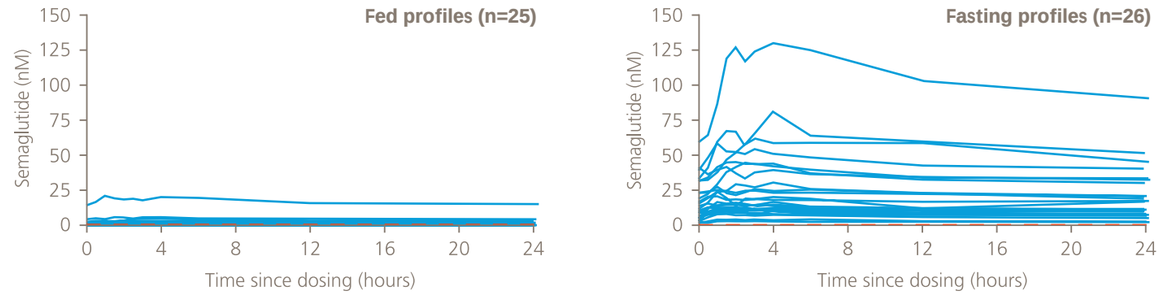
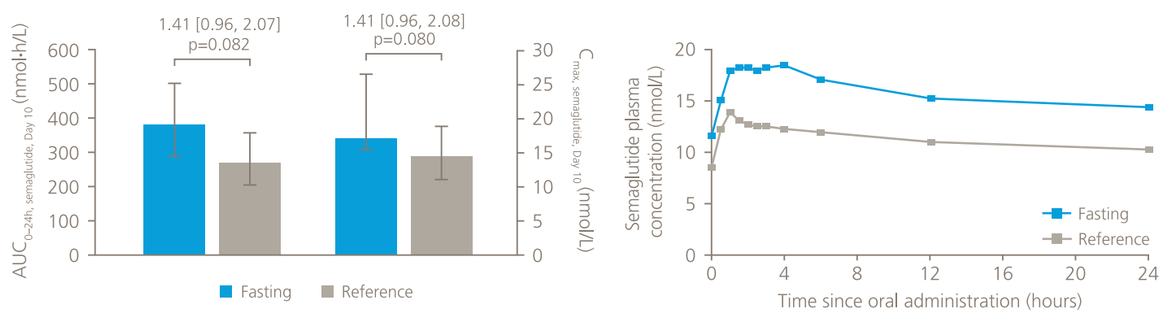



**Figure 11. Estimated mean semaglutide plasma concentration–time profile and estimated means and ratios [95% CI] for AUC and $C_{max}$ for plasma semaglutide concentrations after the 10th dosing of oral semaglutide[9]**




Error bars show 95% CIs.

- After the 10th dosing, there was no apparent difference in $t_{½}$ (160 hours vs 152 hours, respectively)

- Administration of oral semaglutide in a fasting state with up to 120 mL water and a post-dose fasting period of at least 30 minutes resulted in clinically relevant semaglutide exposure[8,9] and are used in the phase 2 trial and in the phase 3a PIONEER programme (Figure 12). These conditions are expected to be acceptable by patients

# ORAL SEMAGLUTIDE INVESTIGATIONS

**Figure 12. Dosing instructions for oral semaglutide used in the phase 2 dose-finding trial and phase 3a PIONEER programme**


## 4.4 Investigations characterising the properties of oral semaglutide

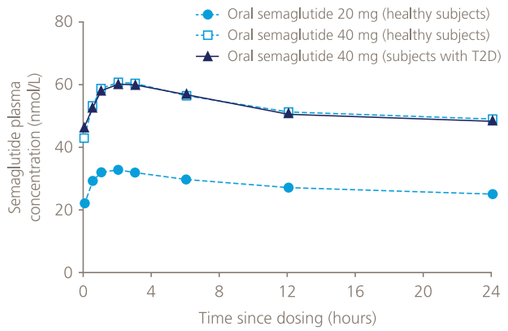
### Safety, tolerability and PK in the first-in-human phase 1 trial of oral semaglutide[7,10]

- The first-in-human phase 1 trial of oral semaglutide investigated the safety, tolerability and PK of different combinations of doses of semaglutide with SNAC
  - Methods: a randomised, double-blind, placebo-controlled, single-dose, dose-escalation trial (Study 3691; NCT01037582) was conducted in healthy males who received oral semaglutide (n=112; 2, 5, 10, 15 or 20 mg semaglutide in different combinations with 150, 300, 450 or 600 mg SNAC) or placebo with SNAC (n=23; 150–600 mg)
  - Trial products were administered in the morning after an overnight fast
- The proportion of subjects with measurable semaglutide plasma concentrations appeared to increase with increasing dose of oral semaglutide from 2 to 10 mg at a fixed amount of 300 mg SNAC
- Following dosing of oral semaglutide with 150 to 600 mg SNAC, semaglutide exposure levels suggested that 300 mg is the optimal amount of SNAC to enhance absorption of semaglutide
- No safety or tolerability concerns were detected
- There were no SAEs and no subjects were withdrawn due to AEs

### PK studies in healthy volunteers and subjects with T2D indicated that oral semaglutide is suitable for once-daily dosing10

- Methods: in a randomised, double-blind, placebo- controlled, 10-week trial (Study 3991; NCT01686945), healthy males received once-daily oral semaglutide 20 mg (n=16; placebo n=6; placebo with SNAC n=6) or 40 mg (n=32; n=12; n=12) and males with T2D received oral semaglutide 40 mg (n=11; n=6; n=6), all with dose escalation over 2–4 weeks
  - Trial products were administered in the morning after an overnight fast
- The safety profile was as expected for the GLP-1RA drug class with no new safety concerns
- Semaglutide plasma exposure ($AUC_{0–24h}$) and $C_{max}$ at steady state were approximately 2-fold higher in healthy males receiving 40-mg versus 20-mg dosing (Figure 13)
- Semaglutide $AUC_{0–24h}$ and $C_{max}$ were similar in healthy males and males with T2D receiving the 40-mg dose (Figure 13)
- $t_{½}$ was comparable between groups with geometric means of 153, 161 and 158 hours in the healthy 20-mg, healthy 40-mg and subjects with T2D 40-mg arms, respectively

**Figure 13. Geometric mean plasma concentration–time profiles for oral semaglutide at steady state in healthy subjects and subjects with T2D[10]**



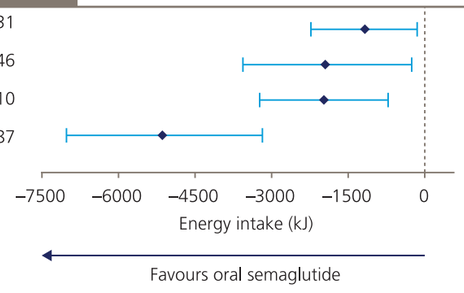

Geometric means of the last 3 days of once-daily semaglutide treatment for10 weeks.

# ORAL SEMAGLUTIDE INVESTIGATIONS

- Gastric emptying was significantly delayed by oral semaglutide during the first postprandial hour, but there was no significant effect on overall gastric emptying during the 5-hour postprandial period studied
- Total daily *ad libitum* energy intake was 39% lower with oral semaglutide treatment compared with placebo (Figure 15)
- Hunger was reduced while satiety and fullness were increased during treatment with oral semaglutide versus placebo after a fat-rich breakfast, whereas there was no difference in appetite after a standard breakfast
- Control of eating was improved during treatment with oral semaglutide compared with placebo. This did not appear to be related to palatability or food aversion
- AEs were more common in patients receiving oral semaglutide versus placebo and GI AEs were most frequently reported

**Figure 15. Ad libitum energy intake was reduced with oral semaglutide treatment versus placebo**

| Energy intake, kJ | Oral semaglutide 14 mg | Placebo | ETD [95% CI] | Relative difference | p value |
|---|---|---|---|---|---|
| Lunch meal | 2133 | 3331 | | –35.9% | 0.0257 |
| Evening meal | 2620 | 4546 | | –42.4% | 0.0263 |
| Snackbox | 3237 | 5210 | | –37.9% | 0.0058 |
| Total daily intake | 7991 | 13087 | | –38.9% | 0.0001 |






## Similar efficacy and GI tolerability versus exposure for oral and S.C. semaglutide[13]

- An exposure–response analysis was conducted to determine whether there were any differences in efficacy and tolerability of semaglutide when administered orally versus s.c.
  - Methods: population PK and exposure–response analyses were based on average semaglutide concentrations at steady-state. Response data from four trials (SUSTAIN 1, 2, 3 and SUSTAIN-Japan) of once-weekly s.c. semaglutide 0.5 and 1.0 mg over 30 weeks (n=1,552) were compared with data from six trials (PIONEER 1, 2, 3, 5, 8 and 9) of once-daily oral semaglutide 3, 7 or 14 mg over 26 weeks (n=3,003). Propensity score matching was used to help ensure that differences between trial populations did not influence the exposure–response evaluation. After matching, both datasets contained 1,551 patients with well-matched characteristics. Using graphical and model-based techniques, exposure–response relationships were investigated for changes from baseline in HbA1c and body weight, and the proportion of patients reporting GI AEs of nausea or vomiting at any time during treatment
- Population PK analysis indicated dose-proportional PK profiles for both oral and s.c. semaglutide, with body weight the main factor influencing exposure
- The exposure range was wider with oral versus s.c. administration, but with considerable overlap between oral semaglutide 7 and 14 mg, and s.c. semaglutide 0.5 and 1.0 mg
- Increasing semaglutide exposure was associated with greater efficacy and an increased proportion of patients reporting GI AEs
- Oral and s.c. semaglutide have consistent efficacy and GI safety profiles versus exposure regardless of the route of administration (Figure 16)

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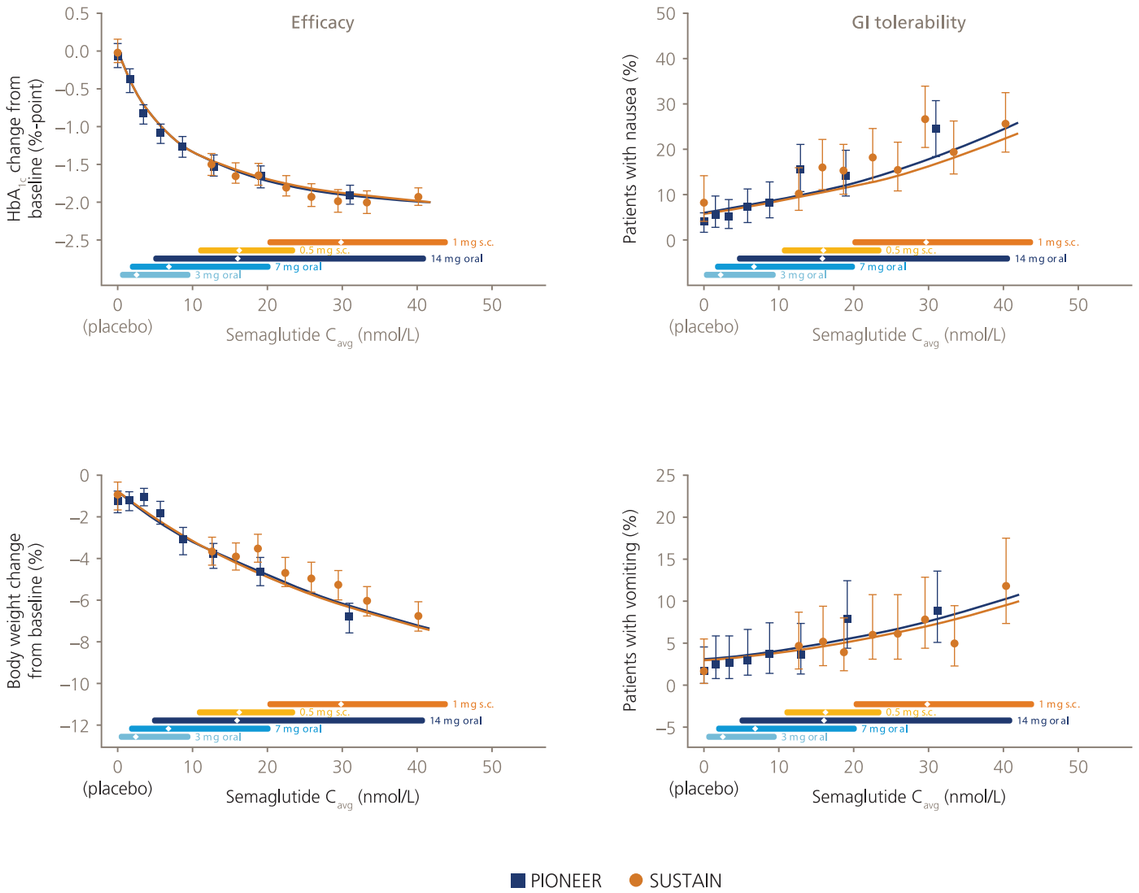
# ORAL SEMAGLUTIDE INVESTIGATIONS

**Figure 16. Similar glycaemic efficacy and GI tolerability between oral semaglutide and s.c. semaglutide (propensity score matched populations)**

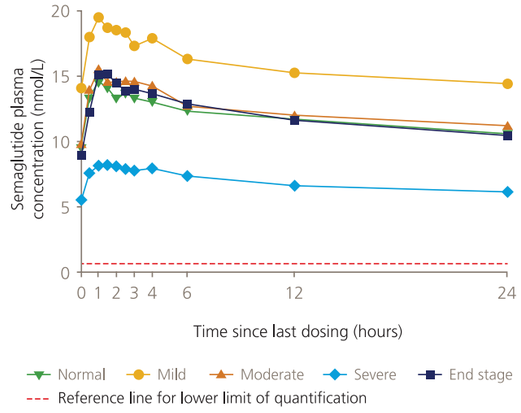



## 4.4.1 PK in special populations

### Renal impairment did not appear to impact the PK properties or tolerability of oral semaglutide[14]

- Renal impairment is a frequent comorbidity in patients with T2D and can affect the metabolism and excretion of antidiabetic medications[15]
- As semaglutide is a peptide-based drug and is not cleared by one specific organ, the impact of renal impairment on PK is expected to be limited; however, the effect of renal impairment on the PK of SNAC is unknown
  - Methods: a multicentre, open-label, multiple-dose trial (Study 4079; NCT02014259) was conducted in 71 subjects classified into five groups based on creatinine clearance using the Cockcroft-Gault formula (normal renal function [n=24]; mild [n=12], moderate [n=12] or severe [n=12] renal impairment; end-stage renal disease requiring haemodialysis [n=11]) who received once-daily oral semaglutide (5 mg for 5 days followed by 10 mg for 5 days)
- There was no consistent pattern of increase or decrease in semaglutide exposure ($AUC_{0–24h}$ and $C_{max}$) by renal function group after 10 consecutive once-daily doses (Figure 17)
- There was no effect on PK in subjects with end-stage renal disease undergoing haemodialysis
- No safety concerns were identified
- These results indicate that adjusted dosing for oral semaglutide may not be required for patients with impaired renal function

**Figure 17. Geometric mean concentration–time profilesof semaglutide after the 10th dose by degree of renalimpairment[14]**

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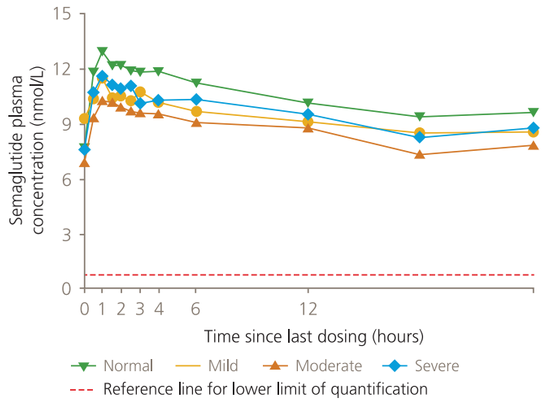
# ORAL SEMAGLUTIDE INVESTIGATIONS

## There was no apparent effect of hepatic impairment on the PK and tolerability of oral semaglutide[16]

- GLP-1RAs are thought to be primarily metabolised throughout the body with multiple organ/tissue clearance and hepatic impairment is not expected to lead to altered exposure; however, this needed to be confirmed for oral semaglutide
  - Methods: in a multicentre, open-label, multiple-dose trial (Study 4082; NCT02016911), 56 subjects were classified into four groups having normal hepatic function (n=24), or mild (n=12), moderate (n=12) or severe (n=8) hepatic impairment according to Child-Pugh criteria, and received once-daily oral semaglutide (5 mg for 5 days followed by 10 mg for 5 days)
- Semaglutide exposure ($AUC_{0–24h}$ and $C_{max}$) after 10 consecutive once-daily oral doses appeared similar across the hepatic function groups with no apparent effect of impairment, regardless of severity (Figure 18)
- The safety profile of oral semaglutide was as expected for the GLP-1RA drug class, independent of the degree of hepatic impairment
- These results indicate that adjusted dosing for oral semaglutide may not be required for patients with impaired hepatic function

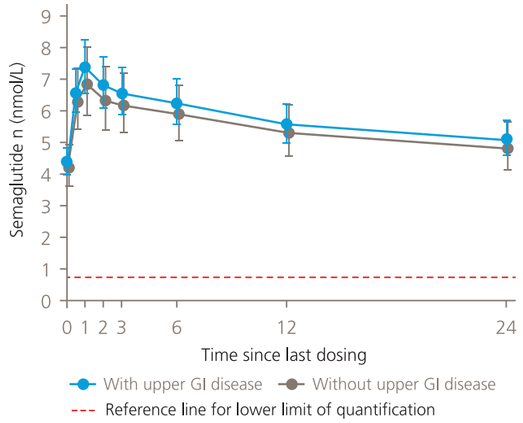
**Figure 18. Geometric mean concentration–time profilesof semaglutide after the 10th dose by degree of hepatic impairment[16]**




## There was no significant difference in exposure to oral semaglutide in patients with upper GI disease[17]

- Since oral semaglutide is absorbed in the stomach, the effect of upper GI disease (chronic gastritis and gastroesophageal reflux disease) on exposure to oral semaglutide was investigated
  - Methods: an open-label, parallel-group trial (Study 4267; NCT02877355) conducted in patients with T2D and upper GI disease (n=36) or without upper GI disease (n=19); all patients received oral semaglutide 3 mg once daily for 5 days followed by oral semaglutide 7 mg once daily for 5 days
- Semaglutide exposure was not statistically significantly different in patients with or without upper GI disease when measured after the 10th dosing (Figure 19). The estimated group ratio for patients with versus without upper GI disease for AUC0–24h was 1.18 [95% CI 0.80, 1.75] and for Cmax was 1.16 [95% CI 0.77, 1.76]
- $t_{max}$ and $t_{½}$ of semaglutide were similar in patients with and without upper GI disease
- All AEs were mild or moderate with no withdrawals due to AEs
- Based on these results, no dose adjustment for oral semaglutide is expected to be required for patients with upper GI disease

**Figure 19. Mean semaglutide exposure after 10th dose in patients with and without upper GI disease[17]**




Error bars are ± standard error of the mean.

# ORAL SEMAGLUTIDE INVESTIGATIONS

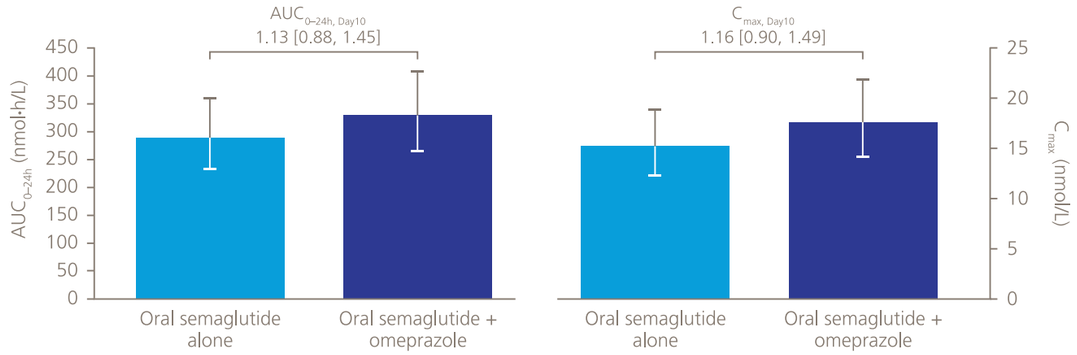
## 4.4.2 Drug–drug interactions

- Given that many patients with T2D are likely to be taking additional medications to control their diabetes or to manage comorbidities, it is important to understand potential drug–drug interactions with oral semaglutide

  **There was no clinically relevant effect on PK when oral semaglutide was administered with omeprazole[18]**

- Omeprazole is a proton pump inhibitor that increases gastric pH and could potentially affect the absorption-enhancing effects of SNAC
- A phase 1 trial investigated if omeprazole influences the PK of oral semaglutide and assessed the safety and tolerability of oral semaglutide administered in combination with omeprazole
  - Methods: a randomised, open-label trial (Study 4141; NCT02249871) was conducted in 54 healthy subjects who received once-daily oral semaglutide (5 mg for 5 days followed by 10 mg for 5 days) with or without concomitant administration of once-daily oral omeprazole 40 mg
  - Oral semaglutide was administered once daily after an overnight fast and the subjects continued fasting for 30 minutes post dose
  - Omeprazole was taken 2 hours before oral semaglutide to ensure maximum effect on gastric pH during semaglutide absorption
- Exposure of semaglutide appeared to be slightly increased when administered with omeprazole compared to oral semaglutide alone (Figure 20)
- The slight increase was considered non-clinically relevant and, as such, no dose adjustment of oral semaglutide is likely to be required when administered with omeprazole
- No effect of concomitant omeprazole administration on semaglutide $t_{max}$ or $t_{½}$ was observed
- The safety profile was as expected for the GLP-1RA drug class and did not appear to be influenced by concomitant use of omeprazole

**Figure 20. Estimated means and ratios of $AUC_{0–24h}$ and $C_{max}$ for plasma semaglutide concentrations with and without omeprazole after the 10th dose[18]**

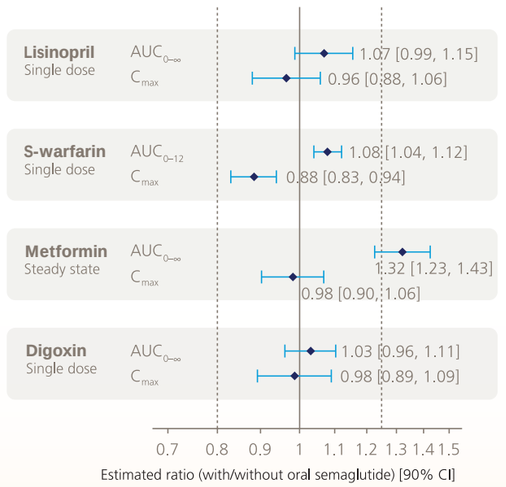



Bars are estimated means and 95% CIs. Treatment comparisons show estimated treatment ratios and 90% CIs.

### Exposure of lisinopril, S-warfarin and R-warfarin following a single dose were unaffected by oral semaglutide co-administration[6,19]

- Lisinopril is a representative of the BCS class III, with high solubility and low permeability
- Warfarin is a representative of the BCS class I/II, with poor-to-high solubility and high permeability, and has a narrow therapeutic index
  - Methods: an open-label, one-sequence, crossover trial (Study 4065; NCT02070510) was conducted in which 52 healthy subjects received single doses of lisinopril 20 mg or warfarin 25 mg alone or co-administered with oral semaglutide (20 mg once daily at steady state)
- Exposure of lisinopril, S-warfarin and R-warfarin were unaffected when a single dose of oral semaglutide was co-administered (Figure 21)

**Figure 21. Estimated AUC and $C_{max}$ ratios for lisinopril, warfarin, metformin and digoxin with and without oral semaglutide[6,19]**



# ORAL SEMAGLUTIDE INVESTIGATIONS

- Oral semaglutide had no influence on the international normalised ratio response to warfarin
- The safety profile was as expected for the GLP-1RA drug class and was not affected by lisinopril or warfarin co-administration

**Oral semaglutide had no clinically relevant effect on the exposure of metformin or digoxin[19]**

- Metformin is a representative of the BCS class III, with high solubility and low permeability and is very commonly used by patients with T2D
- Digoxin has low solubility with incomplete absorption and a narrow therapeutic index
  - Methods: in an open-label, one-sequence, crossover trial (Study 4145; NCT02249910), 32 healthy subjects received metformin (850 mg twice daily for 4 days) or digoxin (500-µg single dose) alone, and subsequently with SNAC (300-mg single dose) and with oral semaglutide (20 mg once daily at steady state)
- The AUC of metformin was increased by 32% with oral semaglutide co-administration, while $C_{max}$ was unaffected (Figure 21); however, based on the wide therapeutic index of metformin, the increased exposure to metformin was not considered clinically relevant
- SNAC alone did not affect the AUC or $C_{max}$ of metformin, indicating that the increase in the AUC of metformin observed with oral semaglutide was not due to any absorption-enhancing effect of SNAC on metformin
- No effect on AUC or $C_{max}$ was observed when metformin was co-administered with s.c. semaglutide20; however, multiple doses of dulaglutide co-administered with steady-state metformin increased AUC by up to 15%21. The exact mechanism responsible for the higher AUC of metformin with oral semaglutide and dulaglutide is unknown but may relate to a delay in gastric emptying or differences in study design. Metformin is primarily absorbed in the small intestine and delayed gastric emptying with GLP-1RAs might result in slower and more prolonged absorption[22]
- The AUC and Cmax of digoxin were unaffected (Figure 21)
- The safety profile of oral semaglutide was not affected by metformin or digoxin co-administration

**No clinically relevant effect on PK when oral semaglutide was administered with furosemide or rosuvastatin[23]**

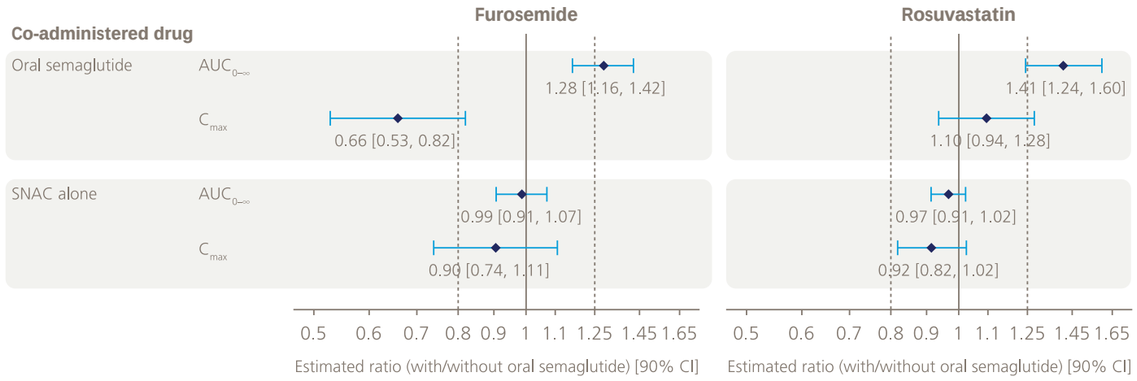
- In vitro assessments have indicated that SNAC may inhibit drug transporters, such as the breast cancer resistance protein and OAT polypeptides OATP1B1 and OAT1/3, potentially leading to increased plasma levels of drugs that are transporter substrates





- A phase 1 trial investigated the effect of oral semaglutide and SNAC alone on the PK of furosemide and rosuvastatin, which are substrates for BRCP and OATP1B1 and OAT1 and/or OAT3 transporters
  - Methods: an open-label, one-sequence, cross-over trial (Study 4250; NCT03010475) was conducted in 41 healthy subjects who received single doses of furosemide 40 mg and rosuvastatin 20 mg alone, co-administered with SNAC 300 mg, and co-administered with oral semaglutide (dose escalated to steady state at week 6: 1 week at 3-mg dose, 1 week at 7-mg dose, 4 weeks at 14-mg dose)
- Co-administration of steady-state oral semaglutide with single-dose furosemide resulted in a 28% increase in total furosemide exposure ($AUC_{0-\infty}$) and a 34% decrease in maximum furosemide Cmax (Figure 22). When co-administered with SNAC alone, there was no effect on the $AUC_{0-\infty}$ of single-dose furosemide while $C_{max}$ decreased by 10%
- Co-administration of steady-state oral semaglutide with single-dose rosuvastatin resulted in increases in both $AUC_{0-\infty}$ (41%) and $C_{max}$ (10%) (Figure 22). $AUC_{0-\infty}$ and $C_{max}$ of rosuvastatin were not affected by co-administration of SNAC alone

**Figure 22. Estimated AUC and Cmax ratios for furosemide and rosuvastatin with and without semaglutide[23]**

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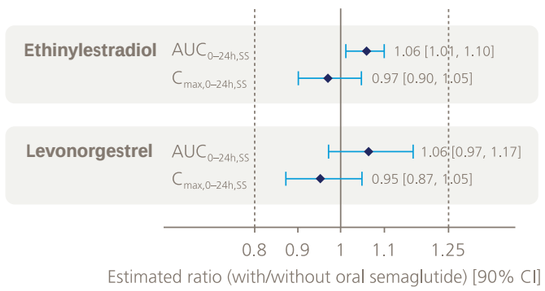
# ORAL SEMAGLUTIDE INVESTIGATIONS

- Changes in exposure of furosemide and rosuvastatin when co-administered with oral semaglutide may be related to the known gastric emptying delaying effect of the GLP-1 component, which may influence both the rate and the extent of absorption of co-administered drugs
- The safety profile was as expected for the GLP-1RA drug class and did not appear to be influenced by concomitant use of furosemide or rosuvastatin
- These data indicate that the SNAC component of oral semaglutide does not inhibit the transporters, BRCP, OATP1B1 or OAT1/3. The observed changes in furosemide and rosuvastatin exposure are not expected to be clinically relevant

### Oral semaglutide did not affect the exposure of the combined oral contraceptive, ethinylestradiol / levonorgestrel[24]

- The effect of oral semaglutide on the PK of the combined oral contraceptive ethinylestradiol (0.03 mg)/levonorgestrel (0.15 mg) was assessed in an open-label, one-sequence crossover trial
  - Methods: healthy post-menopausal females (n=25) received 8 days of oral contraceptive alone and 8 days of oral contraceptive with oral semaglutide (dose escalated to steady state at week 6: 1 week at 3-mg dose, 1 week at 7-mg dose, 4 weeks at 14-mg dose)
- Steady-state $AUC_{0–24h}$ and $C_{max}$ of ethinylestradiol and levonorgestrel appeared similar with or without oral semaglutide co-administration (Figure 23)

**Figure 23. Estimated AUC and Cmax ratios for ethinylestradiol and levonorgestrel with and without semaglutide[24]**




- AEs reported were consistent with expected GLP-1RA effects and well-known effects of hormone replacement therapy in postmenopausal women
- These data indicate that oral semaglutide does not affect the exposure of ethinylestradiol and levonorgestrel, which supports that oral semaglutide is suitable for use with concomitant oral contraceptives



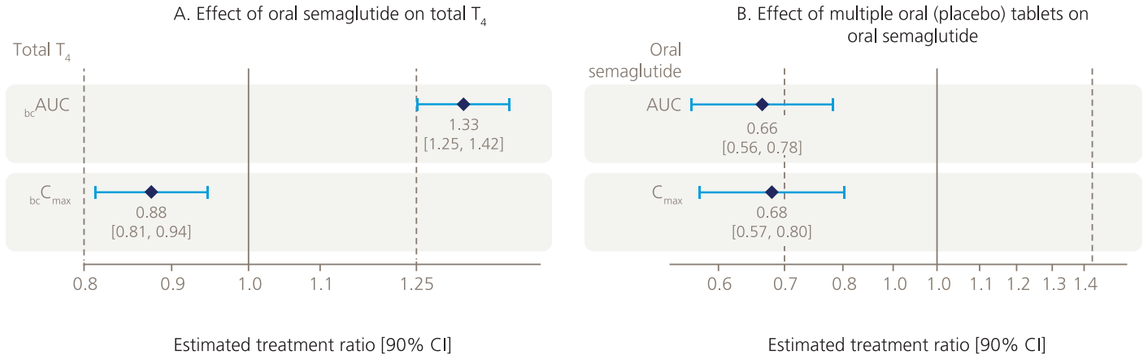


### No clinically relevant effect on PK when oral semaglutide was administered with levothyroxine. PK of semaglutide was affected by the presence of multiple placebo tablets in the stomach[25]

- Levothyroxine is a frequently used oral thyroid hormone replacement therapy with similar dosing conditions to oral semaglutide
- Many patients with T2D take several different medications leading to the presence of multiple tablets in the stomach
- A phase 1, two-part trial investigated the effect of oral semaglutide and SNAC alone on the PK of thyroxine, and whether multiple placebo tablets had an effect on the PK of oral semaglutide
  - Methods: an open-label, one-sequence, cross-over trial (Study 4279; NCT02920385) was conducted in 45 healthy subjects
    - Part A: subjects received a single dose of levothyroxine 600 µg either alone, with SNAC 300 mg or with steady-state oral semaglutide 14 mg
    - Part B: subjects received once daily co-administration of 5 placebo tablets with or without oral semaglutide 14 mg (at steady-state) for 5 weeks
- Total exposure ($AUC_{0–48h}$) of thyroxine (T4; adjusted for endogenous levels [$_{bc}AUC$]) was increased by 33% following administration of a single dose of levothyroxine 600 µg co-administered with semaglutide; maximum exposure ($_{bc}C_{max}$) was unchanged (Figure 24A)
- Co-administration of levothyroxine with SNAC alone did not increase exposure of total $T_4$
- Co-administration of oral semaglutide with five placebo tablets resulted in decreased semaglutide $AUC_{0–24h}$ (34%) and $C_{max}$ (32%) (Figure 24B)
- The safety profile of oral semaglutide was as expected for the GLP-1RA drug class
- This trial was designed according to FDA guidelines for drug–drug interaction studies. The use of single doses and healthy subjects should be taken into consideration when interpreting results. Monitoring of thyroid parameters should be considered when treating patients with oral semaglutide and levothyroxine concomitantly. No obvious effect on levothyroxine PK was seen with SNAC alone, therefore increased levothyroxine exposure may be due to the delay in gastric emptying caused by the GLP-1 component of oral semaglutide. Absorption of oral semaglutide is affected by co-administration with five placebo tablets, and this is reflected in the dosing conditions for oral semaglutide

# ORAL SEMAGLUTIDE INVESTIGATIONS

**Figure 24. Estimated AUC and $C_{max}$ ratios for (A) total thyroxine ($T_4$) with and without semaglutide and (B) oral semaglutide with and without multiple placebo tablets[25]**




No effect confirmed if the 90% CI is entirely within the pre-defined interval of 0.80–1.25 for thyroxine and 0.7000–1.4286 for oral semaglutide (wider interval because oral semaglutide has a broad therapeutic window). All endpoints were analysed using an ANOVA model with the log-transformed endpoint as dependent variable and subject and treatment (two levels) as fixed effects. Two subjects withdrew after starting trial product administration and therefore did not contribute to the PK analysis.

## 4.5 Summary

- SNAC promotes the absorption of semaglutide in a concentration-dependent manner via effects on transcellular pathways[6]
- Semaglutide absorption occurs in a localised gastric environment and depends on the spatial proximity of semaglutide and SNAC[6,8]
- Administration of oral semaglutide in a fasting state with up to 120 mL water and a post-dose fasting period of at least 30 minutes resulted in clinically relevant semaglutide exposure[7,9]
- Oral semaglutide was well tolerated and found suitable for once-daily dosing in healthy volunteers and subjects with T2D[10]
- There was no apparent effect of renal impairment, hepatic impairment or upper GI disease on the PK and tolerability of oral semaglutide suggesting dose adjustment is not necessary in these special populations[14,16,17]
- There was a slight increase in semaglutide exposure not considered clinically relevant when oral semaglutide was administered with omeprazole at the time of maximum anti-secretory effect[18]
- When co-administered, oral semaglutide had no clinically relevant effect on the exposure of lisinopril, warfarin, digoxin and metformin, which are all commonly used in patients with T2D[19]
- Observed changes in furosemide and rosuvastatin exposure with oral semaglutide are not expected to be clinically relevant and may be due to the delayed gastric emptying with GLP-1RAs since there was no effect with SNAC alone[23]
- Oral semaglutide did not affect the exposure of ethinylestradiol and levonorgestrel[24]
- Observed changes in thyroxine exposure suggest that thyroid parameters should be monitored when treating patients with oral semaglutide and levothyroxine concomitantly[25]
- Changes in oral semaglutide PK when co-administered with multiple tablets is addressed in the dosing conditions for oral semaglutide[25]

# ORAL SEMAGLUTIDE INVESTIGATIONS

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# PHASE 2 DOSE-FINDING TRIAL

This chapter summarises findings from a phase 2 trial that assessed the dose–response relationship of five doses of oral semaglutide compared with placebo (primary objective) and once-weekly s.c. semaglutide (secondary objective) in terms of glycaemic control in subjects with T2D (NCT01923181).[1]

The phase 2 trial was designed with the aim of establishing the optimal dose regimen to be taken forward into the phase 3 clinical development programme.

## 5.1 Trial design

- This was a 26-week, randomised, parallel-group, phase 2, dose-finding trial (Figure 1) conducted in 14 countries
- Five oral semaglutide dosage groups (2.5, 5, 10, 20 and 40 mg) and an oral placebo group received a double-blind once-daily dose with a standard 4-week interval dose escalation (oral semaglutide groups 5, 10, 20 and 40 mg)
- Two additional double-blind once-daily oral semaglutide 40-mg dose groups were included to evaluate 8-week (slow) and 2-week (fast) dose escalation versus standard 4-weekly escalation (data not shown here)
- One group received once-weekly s.c. semaglutide 1 mg in an open-label manner to limit unnecessary injections

**Figure 1. Trial design**

### 632 patients with T2D

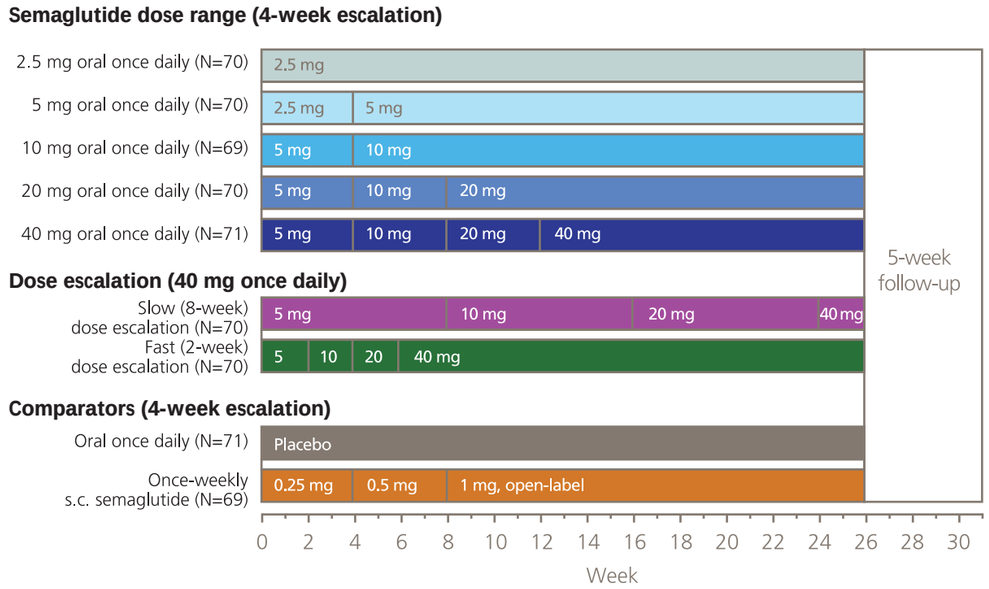
- Age ≥18 years
- HbA1c 7.0–9.5%
- BMI 25–40 kg/m$^2$

Treated with diet and exercise alone or a stable dose of metformin for 30 days prior to screening

### Trial information

- Phase 2, randomised, parallel-group, dose-finding, multinational trial
- Stratification according to background metformin






### Trial objectives

- Primary: to assess the dose–response relationship on glycaemic control of five doses (2.5, 5, 10, 20 or 40 mg) of once-daily oral semaglutide compared with placebo in a double-blind design
- Secondary: to assess the efficacy (glycaemic control) of oral semaglutide with open-label once-weekly s.c. semaglutide

### Key endpoints

- Primary efficacy: change from baseline in $HbA_{1c}$ at week 26
- Secondary efficacy: at week 26, proportion of patients achieving $HbA_{1c}$ <7.0%, change from baseline in FPG and body weight
- Safety: number of treatment-emergent AEs and hypoglycaemic episodes from baseline to week 31

# PHASE 2 DOSE-FINDING TRIAL

## 5.2 Results

### 5.2.1 Baseline characteristics

- Overall, 632 subjects were randomised and baseline characteristics were similar in the nine groups (Table 1)

**Table 1. Baseline characteristics**

| | Placebo n=71 | Oral semaglutide 4-week escalation: 2.5 mg n=70 | 5 mg n=70 | 10 mg n=69 | 20 mg n=70 | 40 mg n=71 | Oral semaglutide 8-week escalation: 40 mg n=70 | Oral semaglutide 2-week escalation: 40 mg n=70 | s.c. semaglutide 1 mg n=69 |
|---|---|---|---|---|---|---|---|---|---|
| Male, % of patients | 56. | 364. | 367. | 162. | 362. | 960. | 658. | 662. | 969.6 |
| Age, years | 58.9 (10.3) | 56.7 (9.9) | 55.7 (11.0) | 56.5 (10.1) | 58.3 (10.4) | 56.5 (10.2) | 57.1 (10.5) | 57.7 (10.8) | 56.8 (11.8) |
| Duration of diabetes, years | 6.7 (5.1) | 6.1 (6.0) | 5.3 (4.7) | 5.8 (4.8) | 7.0 (5.3) | 7.7 (5.9) | 6.6 (4.9) | 5.6 (4.7) | 5.6 (5.0) |
| $HbA_{1c}$, % | 8.0 (0.8) | 8.0 (0.7) | 7.8 (0.6) | 7.8 (0.7) | 7.9 (0.7) | 8.0 (0.7) | 8.0 (0.7) | 7.8 (0.8) | 7.8 (0.7) |
| FPG, mmol/L | 9.5 (2.7) | 9.5 (2.2) | 9.6 (2.6) | 9.2 (2.0) | 9.2 (2.1) | 9.9 (2.7) | 9.6 (2.4) | 8.9 (1.7) | 9.6 (2.5) |
| Body weight, kg | 93.8 (18.1) | 93.6 (15.6) | 93.1 (19.0) | 91.8 (14.0) | 93.8 (17.9) | 90.8 (16.5) | 93.3 (18.8) | 92.0 (15.4) | 88.8 (15.4) |
| BMI, $kg/m^2$ | 32.6 (4.5) | 31.7 (4.1) | 31.6 (4.9) | 31.9 (4.4) | 32.0 (4.5) | 31.1 (4.1) | 32.3 (4.5) | 31.7 (3.8) | 30.7 (4.0) |
| Metformin use, % of patients | 81.7 | 87.1 | 85.7 | 84.1 | 84.3 | 85.9 | 85.7 | 85.7 | 84.1 |

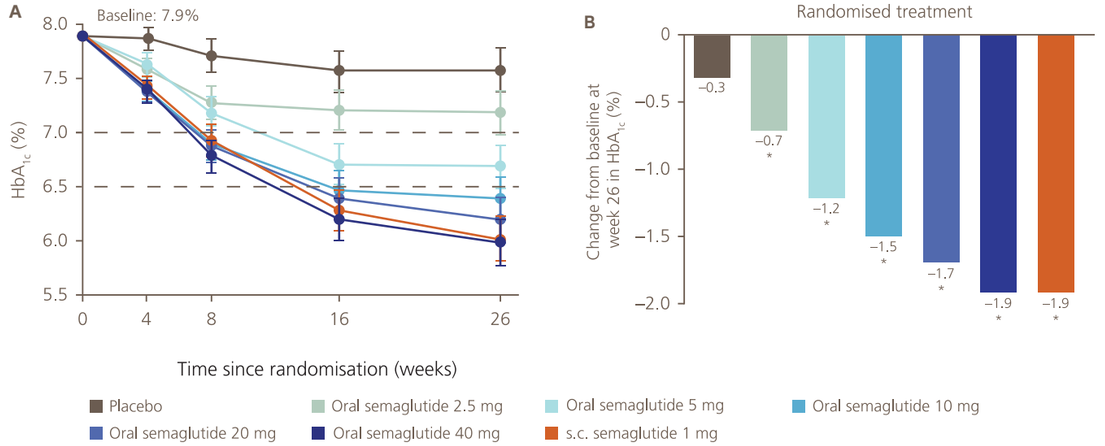
All values are mean (SD) unless otherwise stated.



### 5.2.2 Glycaemic control

- $HbA_{1c}$ level decreased from baseline to week 26 in a dosage-dependent manner with oral semaglutide (Figure 2A and 2B)
- Oral semaglutide $HbA_{1c}$ reductions were significant versus placebo (dosage-dependent estimated treatment difference range for oral semaglutide vs placebo, –0.4% to –1.6%; p<0 .01 for 2.5 mg, p<0.001 for all other dosages)
- With the exception of the 2.5-mg group, almost 100% of patients experienced a reduction in $HbA_{1c}$ versus 74% in the placebo group
- For the oral and s.c. semaglutide groups, most subjects achieved glycaemic targets (Figure 3)

**Figure 2. Change in $HbA_{1c}$ over time and at week 26**




Values are estimated means for on-treatment without rescue medication data (all randomised patients), analysed using a mixed model for repeated measurements.
*p<0.05 vs placebo.

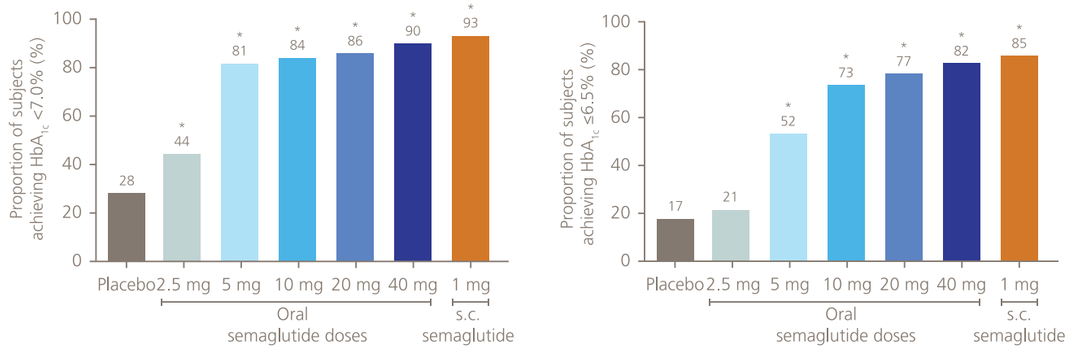
Subcutaneous Semaglutide once weekly injection is not approved/marketed in India

RYBELSUS® semaglutide tablets

novo nordisk®

# PHASE 2 DOSE-FINDING TRIAL

### Figure 3. Proportion of subjects achieving glycaemic targets at week 26



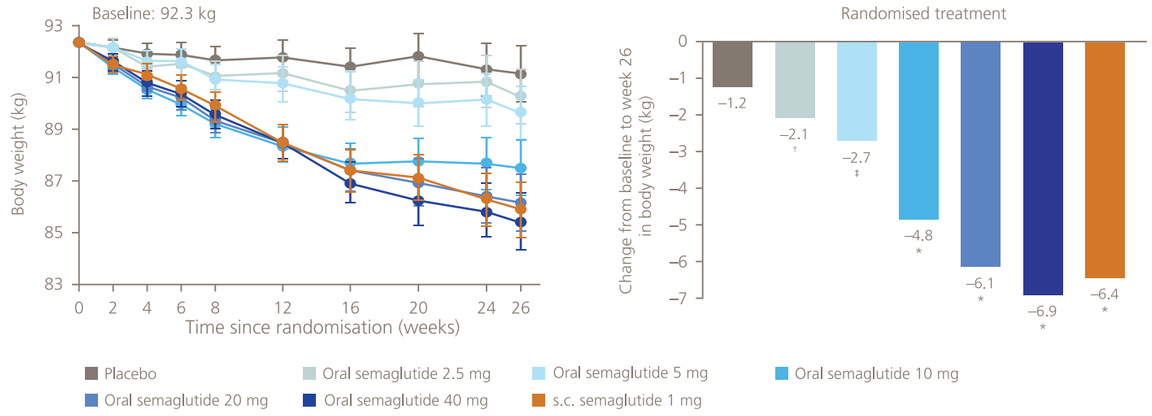

On-treatment without rescue medication data, analysed using a logistic regression model.
*p<0.05 vs placebo.

## 5.2.3 Body weight

- At week 26, the decrease from baseline in mean body weight in the oral semaglutide groups was dose dependent (Figure 4) and greater than with placebo
  - Estimated treatment difference: 2.5-mg group, –0.9 kg; 5-mg group, –1.5 kg; 10-mg group, –3.6 kg; 20-mg group, –5.0 kg; 40-mg standard escalation group, –5.7 kg(significant vs placebo in the ≥10-mg dosage groups [p<0.001])
- Clinically relevant (5% or more) weight loss was achieved in up to 71% of patients receiving oral semaglutide
- The proportion of patients achieving 5% weight loss was significantly greater than placebo for oral semaglutide dosage groups of 10 mg and higher (p<0.001)



### Figure 4. Change in body weight over time and at week 26




Values are estimated means for on-treatment without rescue medication data (all randomised patients), analysed using a mixed model for repeated measurements. *p<0.05; †p=0.25; ‡p=0.06 vs placebo. Error bars are 95% CIs.

## 5.2.4 Safety

- AEs were reported by 63% to 86% of patients in the oral semaglutide groups, 81% in the s.c. semaglutide group and 68% in the placebo group (Table 2)
- There were no fatal events
- The number of SAEs was low (31 events reported in 21 patients), with no grouping of events
- The most common AEs were GI, which were mostly mild to moderate in severity with oral semaglutide
- The proportion of patients reporting GI events was higher with oral semaglutide (31–77%) and s.c. semaglutide (54%) than with placebo (28%)
- Overall, similar proportions of patients reported GI related AEs in the three 40-mg dose escalation groups (2, 4 and 8 weeks)

Subcutaneous Semaglutide once weekly injection is not approved/marketed in India

# PHASE 2 DOSE-FINDING TRIAL

**Table 2. Treatment-emergent AEs**

| | Placebo | Oral semaglutide 4-week escalation | | | | | | | | | Oral semaglutide 8-week escalation | | | Oral semaglutide 2-week escalation | | | s.c. semaglutide 1 mg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2.5 mg | | 5 mg | | | 10 mg | | | 20 mg | | | 40 mg | | | 40 mg | | | 40 mg | | | | | |
| | N | (%) | E | N | (%) | E | N | (%) | E | N | (%) | E | N | (%) | E | N | (%) | E | N | (%) | E | N | (%) | E |
| Subjects | 71 | | | 70 | | | 70 | | | 69 | | | 70 | | | 71 | | | 70 | | | 70 | | | 69 | | |
| AEs | 48 | (68) | 127 | 47 | (67) | 142 | 44 | (63) | 169 | 52 | (75) | 233 | 57 | (81) | 289 | 56 | (79) | 230 | 55 | (79) | 233 | 60 | (86) | 245 | 56 | (81) | 218 |
| SAEs | 5 | (7) | 8 | 1 | (1) | 1 | 2 | (3) | 2 | 2 | (3) | 5 | - | | | 1 | (1) | 1 | 3 | (4) | 3 | 5 | (7) | 9 | 2 | (3) | 2 |
| AEs leading to premature trial product discontinuation | 1 | (1) | 2 | 6 | (9) | 7 | 4 | (6) | 6 | 8 | (12) | 16 | 19 | (27) | 42 | 16 | (23) | 30 | 10 | (14) | 22 | 18 | (26) | 35 | 10 | (14) | 20 |
| Any gastrointestinal AEs | 20 | (28) | 32 | 22 | (31) | 44 | 22 | (31) | 49 | 37 | (54) | 101 | 39 | (56) | 127 | 43 | (61) | 128 | 38 | (54) | 116 | 54 | (77) | 111 | 37 | (54) | 86 |

- Fewer nausea events were reported when patients started oral semaglutide treatment at a dose of 2.5 mg (2.5 and 5 mg groups), while all the other oral semaglutide dose groups started with 5 mg and had a higher frequency of nausea events in the first weeks
- The frequency of gastrointestinal AEs was highest during the dose-escalation period and decreased over time in the oral semaglutide groups
- Premature treatment discontinuation due to AEs was more frequent with oral (6–27%) and s.c. (14%) semaglutide than with placebo (1%) (Table 2), and was mostly due to GI AEs (4–21% with oral semaglutide vs 12% with s.c. semaglutide and none with placebo)
- The proportion of patients prematurely discontinuing treatment due to AEs was slightly lower with 40 mg slow escalation of oral semaglutide from a starting dose of 5 mg up to 40 mg (14%) compared with the other 40-mg groups (40-mg standard escalation, 23%; 40-mg fast escalation, 26%) and the 20-mg group (27%)
- The overall rate of severe or BG-confirmed (plasma glucose ≤3.9 mmol/L [70 mg/dL]) hypoglycaemia was low, with only 2 episodes of severe hypoglycaemia reported (s.c. semaglutide group, 1 patient; oral semaglutide 40-mg fast escalation group, 1 patient)
- Reductions in systolic and diastolic BP occurred in all treatment groups; systolic BP reductions were more pronounced with oral (–5.4 to –7.8 mmHg) and s.c. semaglutide (–5.7 mmHg) than with placebo (–2.7 mmHg)
- At week 26, change in mean heart rate ranged from –1.7 to 3.0 beats/min with oral semaglutide versus 2.6 beats/min with s.c. semaglutide and –4.0 beats/min with placebo
  - Changes in heart rate were significantly greater with oral semaglutide 5 mg or higher and s.c. semaglutide compared with placebo
- Six CV events in 5 patients were confirmed by adjudication (oral semaglutide: 10-mg group, 1 patient; 40-mg slow escalation group, 2 patients; placebo: 2 patients)
- Three mild-to-moderate events of pancreatitis in 3 patients were confirmed by adjudication (s.c. semaglutide group, 1 patient; oral semaglutide 20-mg group, 1 patient; 40-mg standard escalation group, 1 patient)

## 5.3 Summary

- Among patients with T2D, oral semaglutide resulted in better glycaemic control than placebo over 26 weeks, with clinically relevant weight loss in most patients with oral semaglutide ≥10 mg
- Improvements in glycaemic control and body weight with oral semaglutide were achieved with a low rate of hypoglycaemia
- The AE profile of oral semaglutide was comparable with s.c. semaglutide, with no unexpected safety findings
- GI AEs were observed in the oral semaglutide groups, consistent with the known AEs of GLP-1RAs
- Fewer and less severe nausea events were reported when patients started oral semaglutide treatment at a dose of 2.5 mg
- Findings from the phase 2 trial demonstrated that oral semaglutide has sufficient bioavailability to deliver therapeutically relevant semaglutide exposure and clinically relevant effects
- Phase 2 findings provided important information regarding appropriate dosing regimens and indicated that studies to assess longer-term efficacy and safety outcomes were warranted

## References

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# PIONEER TRIAL PROGRAMME

This chapter provides an introduction to the phase 3a PIONEER (Peptide InnOvatioN for Early diabEtes tReatment) programme, evaluating the efficacy and safety of oral semaglutide and clinical outcomes following treatment in a large and broad population of subjects with T2D.

## 6.1 Dosing of oral semaglutide in the PIONEER phase 3 programme

- Based on the findings of the phase 2 trial, three once-daily dose levels were selected for the phase 3a programme, which were expected to have the optimal benefit–risk profile: 3, 7 and 14 mg
- In each trial, oral semaglutide treatment was initiated with the lowest dose and 4-week dose escalation was used to reduce the risk of GI AEs
- Based on PK studies, subjects took oral semaglutide in the morning in a fasting state, with up to half a glass of water (approximately 120 mL), and at least 30 minutes before eating, drinking or taking any other oral medication

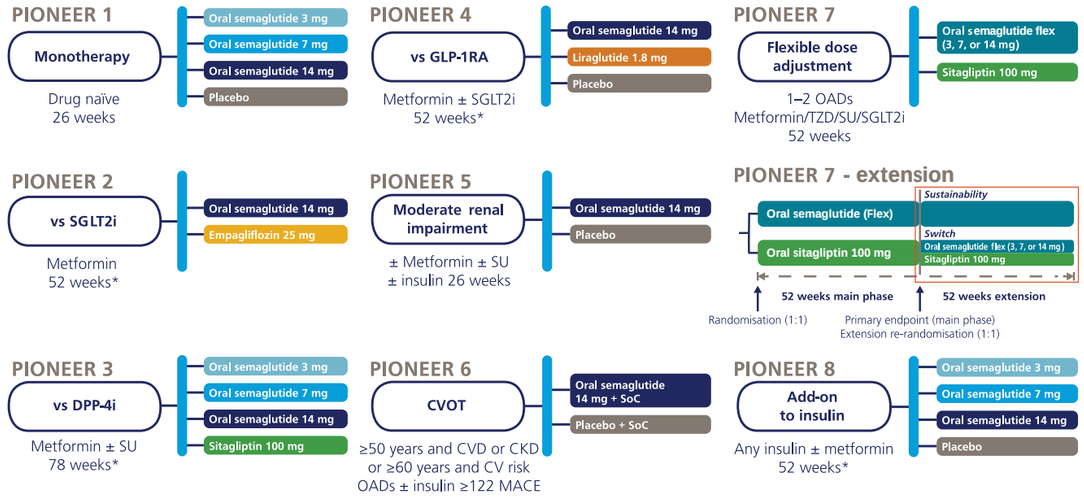
## 6.2 Overview of the PIONEER programme[1–10]

- The PIONEER programme for oral semaglutide was initiated in 2016 and the main treatment periods for all 10 trials completed in 2018
- The PIONEER programme enrolled 9,543 people with T2D
- PIONEER trials involved early and advanced disease, different background treatments (drug naïve, add-on to metformin, add-on to insulin, etc.), different comparators (placebo, empagliflozin, sitagliptin, liraglutide and dulaglutide) and subjects with complications (subjects with renal impairment and subjects at high CV risk)
- Eight global trials were conducted (Figure 1)[1-8]





**Figure 1. Overview of global trials in the PIONEER programme[1–8]**




*Time to primary endpoint: 26 weeks.

# PIONEER TRIAL PROGRAMME

## Key common eligibility criteria in PIONEER studies

### Inclusion

- Male or female adults (≥18 years or ≥20 years for Japanese patients)*
- Patients with T2D diagnosed ≥90 days prior to screening†
- $HbA_{1c}$ 7.0–10.5% or HbA1c 7.0–9.5% in studies with a placebo arm‡

### Exclusion

- Proliferative retinopathy or maculopathy requiring acute treatment
- Diabetes or obesity medication not permitted as per protocol 90 days prior to screening
- History of pancreatitis
- History of multiple endocrine neoplasia type 2 or medullary thyroid cancer
- History of major surgical procedures involving the stomach
- Known hypoglycaemic unawareness
- History or presence of malignant neoplasms within the last 5 years

*In PIONEER 6, ≥50 years and CVD or CKD or ≥60 years and CV risk
† In PIONEER 1, patients with T2D diagnosed ≥30 days were included;
‡ In PIONEER 7, patients with HbA1c of 7.5–9.5% were enrolled.

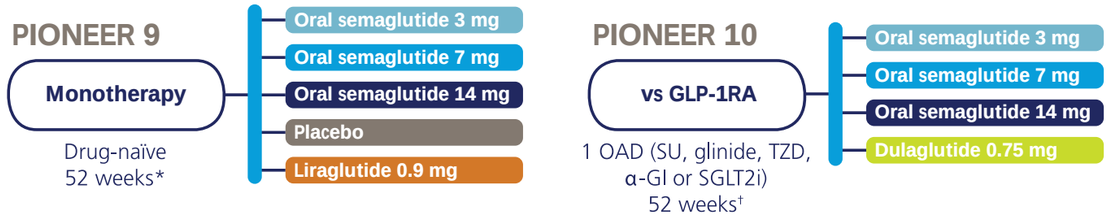
## Primary endpoints of the global PIONEER studies

| | |
|---|---|
| PIONEER 1 | Change in $HbA_{1c}$ at week 26 |
| PIONEER 2 | Change in $HbA_{1c}$ at week 26 |
| PIONEER 3 | Change in $HbA_{1c}$ at week 26 |
| PIONEER 4 | Change in $HbA_{1c}$ at week 26 |
| PIONEER 5 | Change in $HbA_{1c}$ at week 26 |
| PIONEER 6 | Time to first occurrence of MACE (CV death, non-fatal stroke or non-fatal MI) |
| PIONEER 7 | Proportion of patients who achieved $HbA_{1c}$ <7.0% at week 52 |
| PIONEER 8 | Change in $HbA_{1c}$ at week 26 |





**Figure 2. Overview of Japanese trials in the PIONEER programme[9,10]**




*Time to primary endpoint of 26 weeks; †time to primary endpoint of 57 weeks (52-week treatment period plus 5-week follow-up period).

- The two additional studies have been conducted in Japanese patients, which compare oral semaglutide with other GLP-1RAs (liraglutide and dulaglutide, dosed according to Japanese label) (Figure 2)
- Diabetic retinopathy was closely monitored across studies in the PIONEER programme
  - Patients with proliferative retinopathy or maculopathy requiring acute treatment were excluded from participation
  - Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation

## 6.3 Strategy and statistical analysis[11]

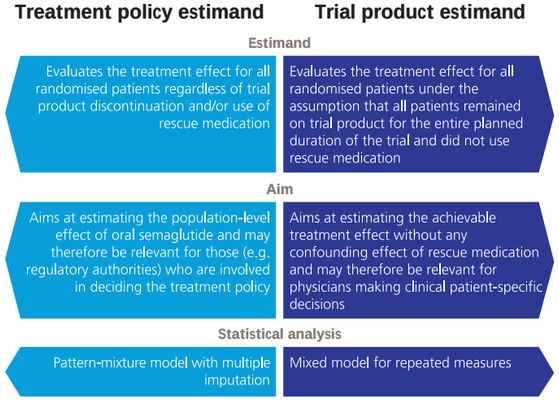
- In the PIONEER studies, the estimand concept was used to understand the treatment effects of oral semaglutide
  - An estimand reflects what is to be estimated to address the scientific question of interest posed by a trial
- The estimand prespecifies how intercurrent events will be handled, as well as describing the population and endpoint of interest, and population level summary, in order to align with the study objectives and allow better interpretation of treatment effects and how they may vary under different conditions
- In the PIONEER programme, two different scientific questions related to the efficacy objectives were addressed through the definition of two estimands: 'treatment policy' and 'trial product' (Figure 3). Both estimands were defined based on interactions with regulatory agencies
- The treatment policy estimand evaluates the treatment effect for all randomised patients regardless of trial product discontinuation and use of rescue medication. This estimand reflects the intention-to-treat

# PIONEER TRIAL PROGRAMME

principle as defined in International Conference on Harmonisation E912. The estimand reflects the effect of initiating treatment with oral semaglutide compared to initiating treatment with a comparator, both potentially followed by either discontinuation of trial product and/or addition of or switch to another glucose-lowering drug

- The treatment policy estimand is estimated by a pattern mixture model using multiple imputation to handle missing data

**Figure 3. Estimands in the PIONEER programme[11]**




Trial product discontinuation and initiation of rescue medication are accounted for by the treatment policy strategy for the treatment policy estimand and by the hypothetical strategy for the trial product estimand as defined in International Conference on Harmonisation E9 (R1).[12]

- The trial product estimand evaluates the treatment effect for all randomised patients under the assumption that all patients remained on trial product for the entire planned duration of the trial and did not use rescue medication. This estimand aims at reflecting the effect of oral semaglutide compared to comparator without the confounding effect of rescue medication
- The trial product estimand is estimated by a mixed model for repeated measures
- The statistical analysis that was applied to estimate this estimand is similar to how many phase 3a diabetes trials have been evaluated and results from such analyses are currently included in many product labels (US prescribing information and EU summary of product characteristics) for glucose-lowering drugs (e.g. Ozempic summary of product characteristics)[13]

## 6.4 Summary

- Oral semaglutide is the first oral GLP-1RA to complete phase 3 development
- The comprehensive nature of the PIONEER programme ensured that the efficacy and safety of oral semaglutide was fully evaluated against several comparators, across the continuum of T2D care and different background treatments, in the presence of complications and in global and national trials





## References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# Overview of results from the PIONEER programme

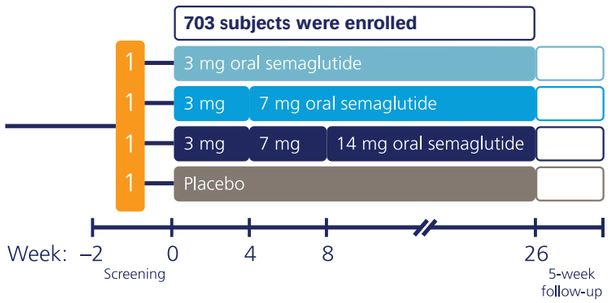
## 7.1 PIONEER 1: oral semaglutide as monotherapy[1]

- PIONEER 1 (NCT02906930) evaluated the efficacy and safety of three doses of oral semaglutide once daily versus placebo in patients with T2D treated with diet and exercise only (Figure 1)

**Figure 1. Trial design**

### Key inclusion criteria

- Age ≥18 years*
- T2D ≥30 days
- Diet and exercise for ≥30 days
- $HbA_{1c}$ 7.0–9.5% (53–80 mmol/mol)




### Trial information

- A 26-week multicentre, multinational, randomised, double-blind, placebo-controlled, phase 3a trial with four arms

*≥19 years in Algeria and ≥20 years in Japan.

### Primary endpoint

- Change from baseline at week 26 in $HbA_{1c}$

### Key secondary endpoints

- Change from baseline at week 26 in body weight
- Change in other parameters of efficacy, safety and tolerability





## 7.1.1 Baseline characteristics

- Baseline demographics and disease characteristics were similar between treatment groups (Table 1)

**Table 1. Baseline characteristics**

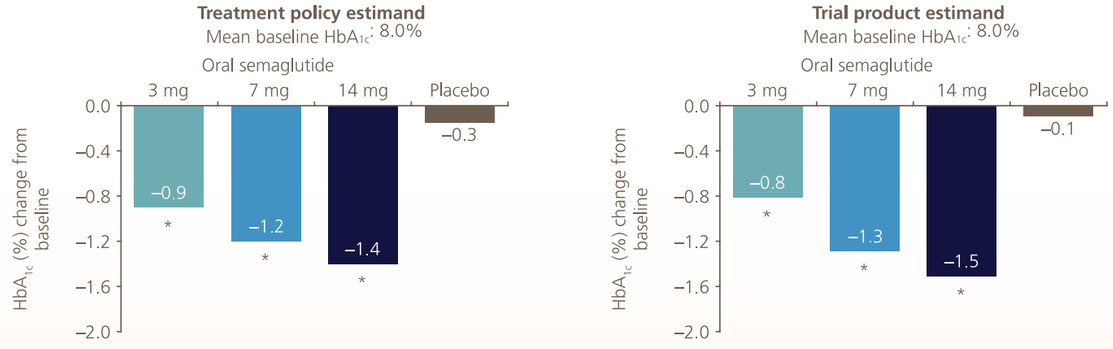
| | Oral semaglutide 3 mg n=175 | Oral semaglutide 7 mg n=175 | Oral semaglutide 14 mg n=175 | Placebo n=178 |
|---|---|---|---|---|
| **Age, years** | 55 (11) | 56 (11) | 54 (11) | 54 (11) |
| **Female, % of patients** | 49.1 | 46.9 | 50.9 | 50.0 |
| **White, % of patients** | 77.1 | 74.9 | 74.3 | 74.2 |
| **$HbA_{1c}$, %** | 7.9 (0.7) | 8.0 (0.6) | 8.0 (0.7) | 7.9 (0.7) |
| **Diabetes duration, years** | 3.8 (5.3) | 3.6 (5.1) | 3.4 (4.4) | 3.4 (4.6) |
| **FPG, mmol/L*** | 8.78 (2.35) | 8.98 (2.34) | 8.77 (2.17) | 8.88 (2.16) |
| **FPG, mg/dL*** | 158 (42) | 162 (42) | 158 (39) | 160 (39) |
| **Body weight, kg** | 86.9 (21.0) | 89.0 (21.8) | 88.1 (22.1) | 88.6 (23.4) |
| **BMI, kg/m²** | 31.8 (6.3) | 31.6 (6.4) | 31.7 (6.6) | 32.2 (6.9) |

Data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

## 7.1.2 Efficacy: change in $HbA_{1c}$ (primary endpoint)

- For the treatment policy estimand, superior and significant $HbA_{1c}$ reductions were seen with all doses of oral semaglutide versus placebo (Figure 2):
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.6% [–0.8, –0.4]; 7 mg, –0.9% [–1.1, –0.6]; 14 mg, –1.1% [–1.3, –0.9]; p<0.001 for all
- Similarly, significantly greater HbA1c reductions were seen with oral semaglutide versus placebo for the trial product estimand (Figure 2):
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.7% [–0.9, –0.5]; 7 mg, –1.2% [–1.5, –1.0]; 14 mg, –1.4% [–1.7, –1.2]; p<0.001 for all

**Figure 2. Estimated mean change from baseline in HbA1c at week 26**



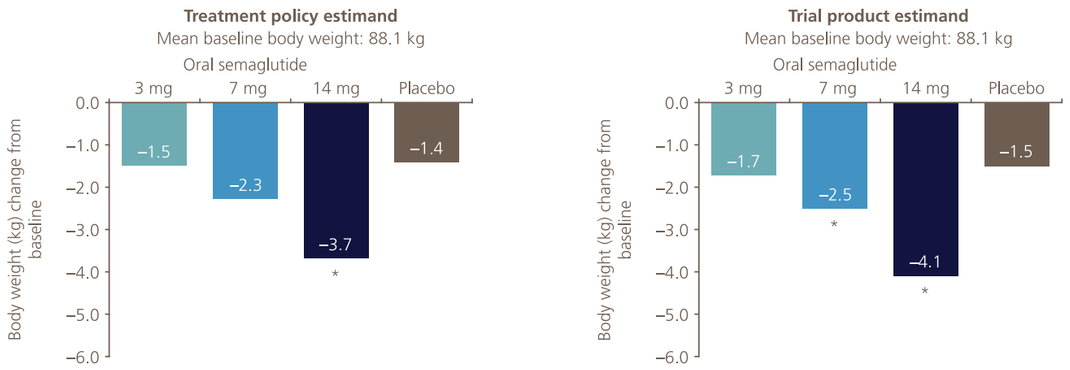

*p<0.05 vs placebo for the ETDs.

# Overview of results from the PIONEER programme

## 7.1.3 Efficacy: changes in body weight (confirmatory secondary endpoint)

- For the treatment policy estimand, superior and significant reductions in body weight were seen with oral semaglutide 14 mg versus placebo (Figure 3):
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.1 kg [–0.9, 0.8] (p=0.87); 7 mg, –0.9 kg [–1.9, 0.1] (p=0.09); 14 mg, –2.3 kg [–3.1, –1.5] (p<0.001)
- For the trial product estimand, significant reductions in body weight were seen with oral semaglutide 7 and 14 mg versus placebo at week 26 (Figure 3):
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.2 kg [–1.0, 0.6] (p=0.71); 7 mg, –1.0 kg [–1.8, –0.2] (p=0.01); 14 mg, –2.6 kg [–3.4, –1.8] (p<0.001)

**Figure 3. Estimated mean change from baseline in body weight at week 26**




*p<0.05 vs placebo for the ETDs.

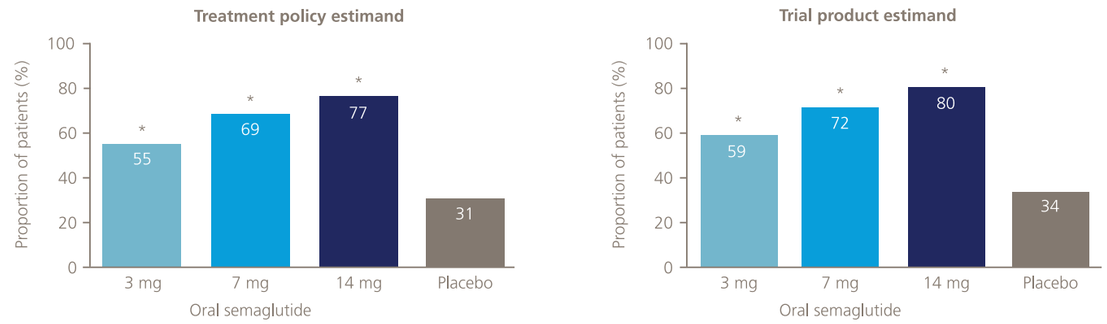




## 7.1.4 Efficacy: other secondary endpoints

- The odds of achieving $HbA_{1c}$ <7.0% were significantly greater with all oral semaglutide doses than with placebo (p<0.001, both estimands) (Figure 4)
- Compared with placebo, the odds of achieving ≥5% weight loss were significantly higher with oral semaglutide 7 mg (p<0.05) and 14 mg (p<0.001) compared with placebo for both estimands (no significant difference with oral semaglutide 3 mg)

**Figure 4. Observed proportions of patients achieving the target of HbA1c <7.0% at week 26**




*p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs placebo.

## 7.1.5 Safety

- AEs were reported by 58, 53 and 57% of patients with oral semaglutide 3, 7 and 14 mg, respectively, and 56% with placebo (Table 2)
- The incidence of SAEs was similar for oral semaglutide compared with placebo
- No deaths occurred while on trial product
- The most common class of AE with oral semaglutide was GI disorders, which were transient and generally mild or moderate in severity
- More patients discontinued treatment owing to AEs with oral semaglutide 7 and 14 mg than placebo; GI disorders were the most frequent cause of discontinuation due to AEs

# Overview of results from the PIONEER programme

### Table 2. Overview of on-treatment AEs

| | Oral semaglutide 3 mg n=175 | Oral semaglutide 7 mg n=175 | Oral semaglutide 14 mg n=175 | Placebo n=178 |
|---|---|---|---|---|
| AEs | 101 (57.7) | 93 (53.1) | 99 (56.6) | 99 (55.6) |
| SAEs | 5 (2.9) | 3 (1.7) | 2 (1.1) | 8 (4.5) |
| AEs leading to premature trial product discontinuation | 4 (2.3) | 7 (4.0) | 13 (7.4) | 4 (2.2) |
| AEs by severity | | | | |
| Mild | 89 (50.9) | 84 (48.0) | 81 (46.3) | 81 (45.5) |
| Moderate | 40 (22.9) | 29 (16.6) | 34 (19.4) | 47 (26.4) |
| Severe | 8 (4.6) | 1 (0.6) | 3 (1.7) | 5 (2.8) |
| GI disorder AEs | | | | |
| Nausea | 14 (8.0) | 9 (5.1) | 28 (16.0) | 10 (5.6) |
| Vomiting | 5 (2.9) | 8 (4.6) | 12 (6.9) | 4 (2.2) |
| Diarrhoea | 15 (8.6) | 9 (5.1) | 9 (5.1) | 4 (2.2) |
| Severe or BG-confirmed symptomatic hypoglycaemic events*†‡ | 5 (2.9) | 2 (1.1) | 1 (0.6) | 1 (0.6) |
| Severe hypoglycaemic episodes*† | 0 | 1 (0.6) | 0 | 0 |
| Deaths | 0 | 0 | 0§ | 0 |

Data are n (%) unless otherwise stated. The n number indicates the number of patients with at least one event. *Hypoglycaemic episodes were reported on a separate form to adverse events; †severe hypoglycaemia was defined according to the ADA classification (requires assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions). There was one case of severe nocturnal hypoglycaemia, which occurred in a patient in the oral semaglutide 7-mg group; ‡BG confirmation of symptomatic hypoglycaemia was based on a BG value (<56 mg/dL) with symptoms consistent with hypoglycaemia; §one patient died (cardiogenic shock with onset 42 days after discontinuing treatment due to other AEs [decreased appetite and weight loss].

## 7.1.6 Summary

- In PIONEER 1, oral semaglutide was superior to placebo in reducing $HbA_{1c}$ (all dose levels) and body weight (14 mg) at week 26 in patients with T2D treated with diet and exercise
- Oral semaglutide was well tolerated, and demonstrated a safety and tolerability profile consistent with that of other GLP1-RAs



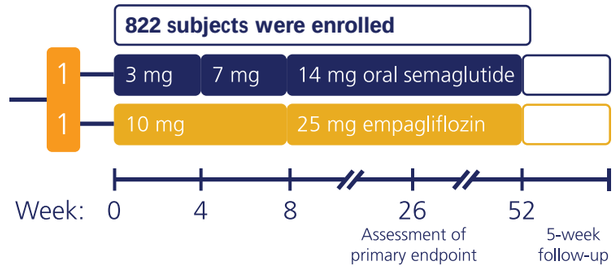


## 7.2 PIONEER 2: oral semaglutide versus empagliflozin (SGLT2i)[2]

- PIONEER 2 (NCT02863328) compared the efficacy and safety of oral semaglutide 14 mg once daily with the SGLT2i empagliflozin 25 mg once daily in patients with T2D who were uncontrolled on metformin (Figure 5)

### Figure 5. Trial design

**Key inclusion criteria**
- Age ≥18 years
- T2D ≥90 days
- Stable doses of metformin for ≥90 days
- $HbA_{1c}$ 7.0–10.5% (53–91 mmol/mol)




**Trial information**
- A 52-week randomised, open-label, active-controlled, parallel group, multinational, multicentre phase 3a trial with two arms

**Primary endpoint**
- Change from baseline to week 26 in $HbA_{1c}$

**Key secondary endpoints**
- Change from baseline to week 26 in body weight
- Change from baseline to week 52 in $HbA_{1c}$ and body weight
- Change in other parameters of efficacy, safety and tolerability

# Overview of results from the PIONEER programme

## 7.2.1 Baseline characteristics

- Baseline demographics and disease characteristics were similar between treatment groups (Table 3)

**Table 3. Baseline characteristics**

| | Oral semaglutide 14 mg n=411 | Empagliflozin 25 mg n=410 |
|---|---|---|
| **Age, years** | 57 (10) | 58 (10) |
| **Female, % of patients** | 49.9 | 49.0 |
| **White, % of patients** | 86.4 | 86.1 |
| **$HbA_{1c}$, %** | 8.1 (0.9) | 8.1 (0.9) |
| **Diabetes duration, years** | 7.2 (5.8) | 7.7 (6.3) |
| **FPG, mmol/L*** | 9.5 (2.3) | 9.7 (2.5) |
| **FPG, mg/dL*** | 171.5 (41.8) | 174.0 (45.2) |
| **Body weight, kg** | 91.9 (20.5) | 91.3 (20.1) |
| **BMI, kg/m²** | 32.9 (6.3) | 32.8 (5.9) |

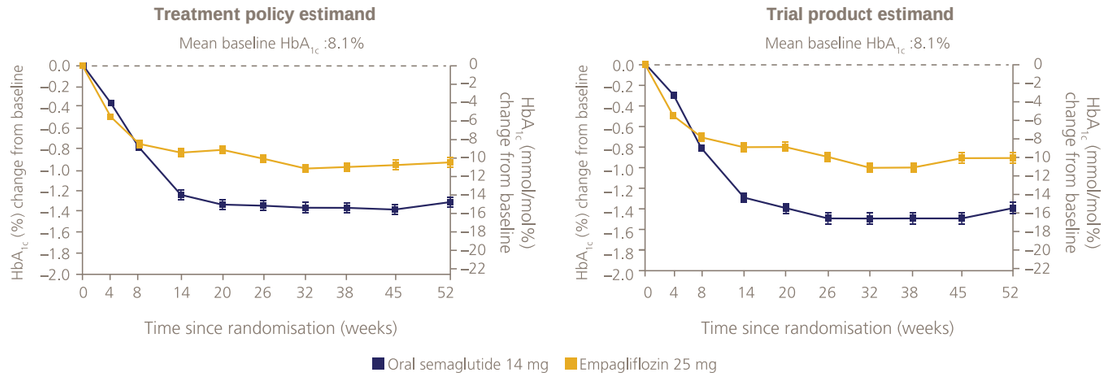
Data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

## 7.2.2 Efficacy: change in $HbA_{1c}$ (primary endpoint)

- For both estimands, an initial reduction in $HbA_{1c}$ was seen in both treatment groups. Separation of the curves indicated greater reductions for oral semaglutide versus empagliflozin after week 8. Reductions in $HbA_{1c}$ were sustained until week 52 in both treatment groups (Figure 6)
- For the treatment policy estimand, superior and significant $HbA_{1c}$ reductions were seen at week 26 for oral semaglutide versus empagliflozin (Figure 7)
  - The ETD [95% CI] for oral semaglutide 14 mg versus empagliflozin 25 mg at week 26 was –0.4% [–0.6, –0.3] (p<0.001 for superiority)
  - The effect of oral semaglutide over empagliflozin was conserved at the end of treatment (week 52)
- Findings were similar for the trial product estimand (Figure 7)
  - The ETD [95% CI] for oral semaglutide 14 mg versus empagliflozin 25 mg at week 26 was –0.5% [–0.7, –0.4] (p<0.001)
  - The effect of oral semaglutide over empagliflozin was conserved at the end of treatment (week 52)

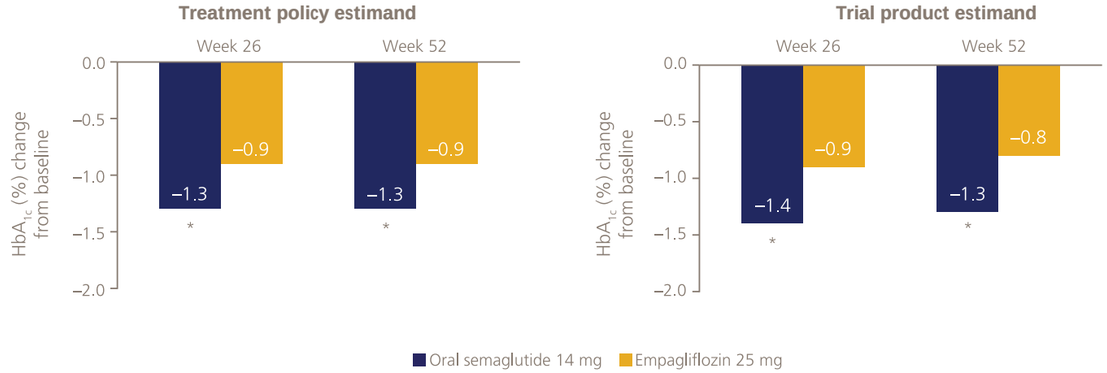


**Figure 6. Observed mean change from baseline in HbA1c to week 52**




Error bars are +/- SE

**Figure 7. Estimated mean change from baseline in HbA1c at weeks 26 and 52**




*p<0.05 vs empagliflozin for the ETDs.

RYBELSUS® semaglutide tablets

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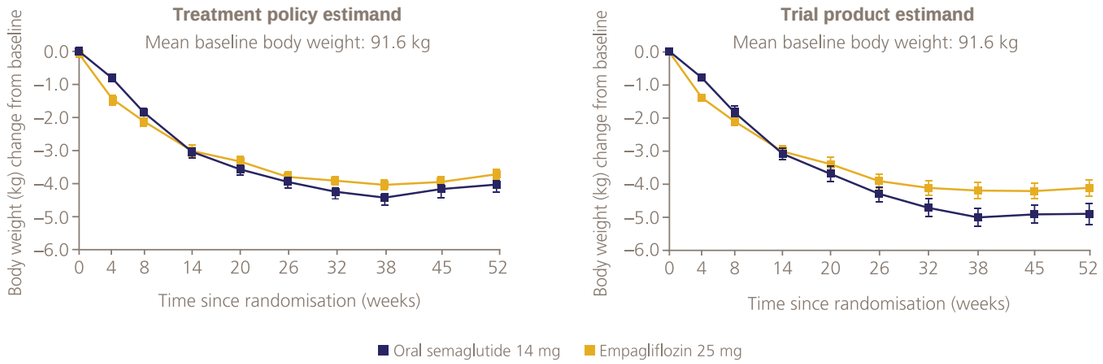
# Overview of results from the PIONEER programme

## 7.2.3 Efficacy: changes in body weight (confirmatory secondary endpoint)

- For both estimands, mean body weight gradually decreased from baseline in both treatment groups, with the largest reductions seen at week 38 (Figure 8)

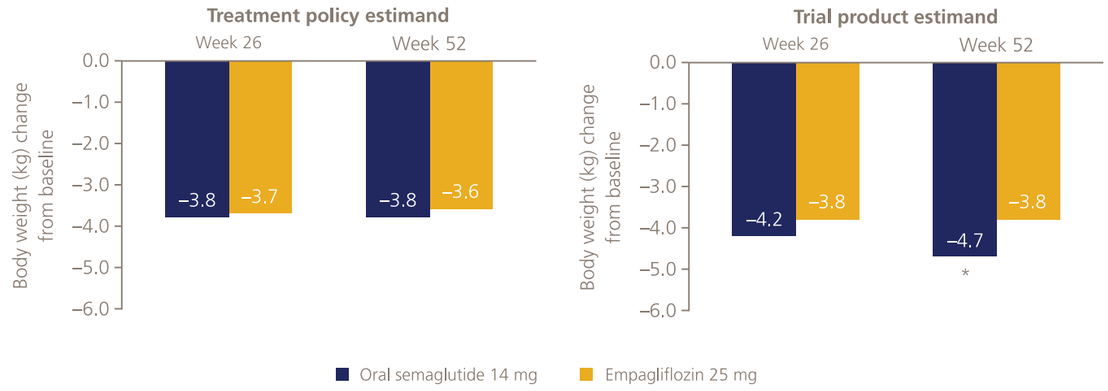
**Figure 8. Observed mean change from baseline in body weight to week 52**




- For the treatment policy estimand, body weight loss with oral semaglutide was not superior to empagliflozin at week 26 or week 52 (Figure 9):
  - ETDs for oral semaglutide 14 mg versus empagliflozin 25 mg at week 26 and 52 were –0.1 kg [95% CI –0.7, 0.5] (p=0.76) and –0.2 kg [95% CI –0.9, 0.5] (p=0.62), respectively
- For the trial product estimand, body weight loss with oral semaglutide was not significantly greater than with empagliflozin at week 26, but the difference reached statistical significance at week 52 (Figure 9):
  - ETDs for oral semaglutide 14 mg versus empagliflozin 25 mg at week 26 and 52 were –0.4 kg [95% CI –1.0, 0.1] (p=0.14) and –0.9 kg [95% CI –1.6, –0.2] (p<0.05), respectively



**Figure 9. Estimated mean change from baseline in body weight at weeks 26 and 52**



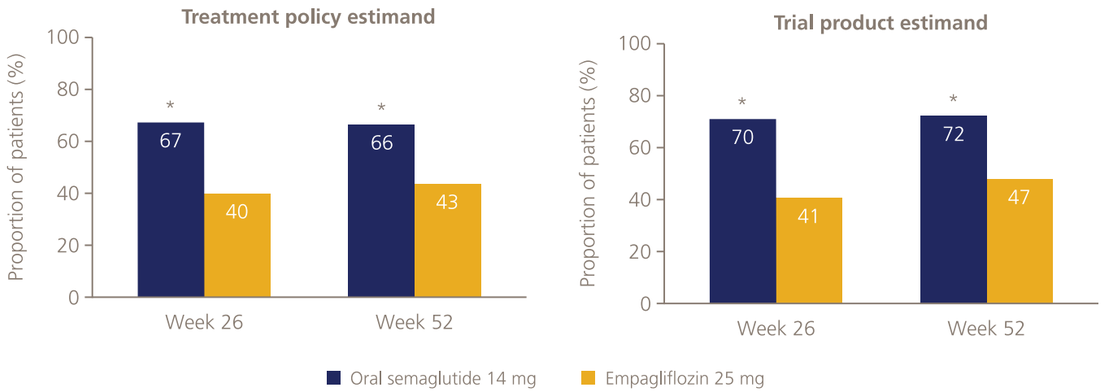

*p<0.05 vs empagliflozin.

## 7.2.4 Efficacy: other secondary endpoints

- The odds of achieving $HbA_{1c}$ <7.0% were significantly greater with oral semaglutide than with empagliflozin at both weeks 26 and 52 (p<0.001, both estimands) (Figure 10)
- The odds of achieving body weight reduction ≥5% were significantly greater for oral semaglutide 14 mg versus empagliflozin 25 mg at week 26 for the trial product estimand (p<0.05), but not at week 52 (no significant difference at either timepoint for treatment policy estimand)

# Overview of results from the PIONEER programme

## Figure 10. Observed proportions of patients achieving the target of HbA1c <7.0% at weeks 26 and 52




*p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs empagliflozin.

## 7.2.5 Safety

- The proportion of patients who reported AEs was similar between oral semaglutide and empagliflozin (Table 4)
- There were fewer SAEs with oral semaglutide than empagliflozin
- One death occurred in the empagliflozin group (undetermined cause)
- The most common class of AE with oral semaglutide was GI disorders, which were generally transient and mild or moderate in severity
- Genital mycotic infections of mild-to-moderate severity were more common with empagliflozin than oral semaglutide
- More patients discontinued treatment owing to AEs with oral semaglutide than empagliflozin; GI disorders were the most frequent cause of discontinuation due to AEs with oral semaglutide





## Table 4. Overview of on-treatment AEs

| | Oral semaglutide 14 mg n=410 | Empagliflozin 25 mg n=409 |
|---|---|---|
| AEs | 289 (70.5) | 283 (69.2) |
| SAEs | 27 (6.6) | 37 (9.0) |
| AEs leading to premature trial product discontinuation | 44 (10.7) | 18 (4.4) |
| AEs by severity | | |
| Mild | 242 (59.0) | 240 (58.7) |
| Moderate | 140 (34.1) | 118 (28.9) |
| Severe | 24 (5.9) | 23 (5.6) |
| Most frequent AEs (≥5% in either group) | | |
| Nausea | 81 (19.8) | 10 (2.4) |
| Diarrhoea | 38 (9.3) | 13 (3.2) |
| Vomiting | 30 (7.3) | 7 (1.7) |
| Decreased appetite | 21 (5.1) | 2 (0.5) |
| Influenza | 8 (2.0) | 21 (5.1) |
| Severe or BG-confirmed symptomatic hypoglycaemic episode*†‡ | 7 (1.7) | 8 (2.0) |
| Severe hypoglycaemic episode*† | 1 (0.2) | 1 (0.2) |
| Genital mycotic infections and increased urination§ | | |
| Genital mycotic infection | | |
| Female | 4 (2.0) | 17 (8.5) |
| Male | 0 | 14 (6.7) |
| Increased urination | 3 (0.7) | 26 (6.4) |
| Deaths | 0 | 1 (0.2) |

All data are n (%) unless otherwise stated.*Hypoglycaemic episodes were reported on a separate form to AEs; †requiring assistance of another person to actively administer carbohydrate or glucagon, or take other corrective actions; ‡based on a BG value (<56 mg/dL) with symptoms consistent with hypoglycaemia; §as defined post hoc based on the empagliflozin FDA label.

## 7.2.6 Summary

- Oral semaglutide provided superior reductions compared with empagliflozin in $HbA_{1c}$ but not body weight at week 26, and significant reductions in $HbA_{1c}$ and body weight (trial product estimand) at week 52
- Oral semaglutide was well tolerated, with a safety profile consistent with that of GLP-1RAs

# Overview of results from the PIONEER programme

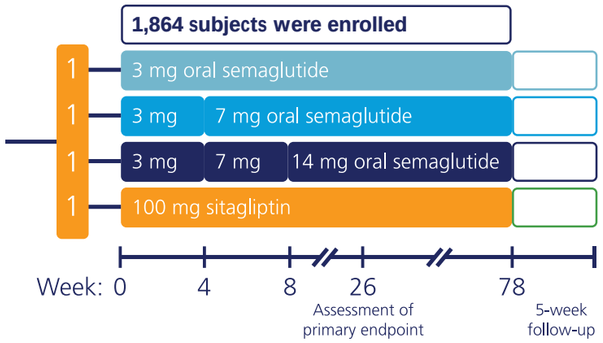
## 7.3 PIONEER 3: oral semaglutide versus sitagliptin (DPP-4i)[3]

- PIONEER 3 (NCT02607865) compared the efficacy, long-term safety and tolerability of oral semaglutide once daily with sitagliptin, a DPP-4i, once daily added on to metformin ± SU in patients with T2D (Figure 11)

**Figure 11. Trial design**

**Key inclusion criteria**

- Age ≥18 years*
- T2D ≥90 days
- Stable dose of metformin ± SU for ≥90 days
- $HbA_{1c}$ 7.0–10.5% (53–91 mmol/mol)




**Trial information**

- A 78-week randomised, double-blind, double-dummy, active-controlled, parallel-group, multicentre, multinational phase 3a trial with four arms

*≥20 years in Japan.

**Primary endpoint**

- Change from baseline to week 26 in $HbA_{1c}$

**Key secondary endpoints**

- Change from baseline to week 26 in body weight
- Change from baseline to week 78 in $HbA_{1c}$ and body weight
- Change in other parameters of efficacy, safety and tolerability





### 7.3.1 Baseline characteristics

- Demographics and baseline characteristics were balanced across the treatment groups (Table 5)

**Table 5. Baseline characteristics**

| | Oral semaglutide 3 mg n=466 | Oral semaglutide 7 mg n=465* | Oral semaglutide 14 mg n=465 | Sitagliptin 100 mg n=467 |
|---|---|---|---|---|
| **Age, years** | 58 (10.0) | 58 (10.0) | 57 (10.0) | 58 (10.0) |
| **Female, % of patients** | 45.5 | 47.3 | 46.9 | 49.0 |
| **White, % of patients** | 73.8 | 71.0 | 68.2 | 71.3 |
| **$HbA_{1c}$, %** | 8.3 (1.0) | 8.4 (1.0) | 8.3 (0.9) | 8.3 (0.9) |
| **Diabetes duration, years** | 8.4 (6.1) | 8.3 (5.8) | 8.7 (6.1) | 8.8 (6.0) |
| **FPG, mmol/L†** | 9.7 (2.8) | 9.5 (2.4) | 9.3 (2.5) | 9.5 (2.3) |
| **FPG, mg/dL†** | 174.2 (50.5) | 170.3 (42.9) | 167.9 (45.1) | 171.8 (41.9) |
| **Body weight, kg** | 91.6 (22.0) | 91.3 (20.8) | 91.2 (21.7) | 90.9 (21.0) |
| **BMI, kg/m²** | 32.6 (6.7) | 32.6 (6.4) | 32.3 (6.3) | 32.5 (6.2) |
| **Background medication, n (%)** | | | | |
| **Metformin alone** | 246 (52.8) | 247 (53.1) | 245 (52.7) | 248 (53.1) |
| **Metformin + SU** | 220 (47.2) | 218 (46.9) | 220 (47.3) | 219 (46.9) |

Data are mean (SD) unless otherwise stated.
*One patient was randomised in error; no assessments were done after screening; †FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

### 7.3.2 Efficacy: change in $HbA_{1c}$ (primary endpoint)

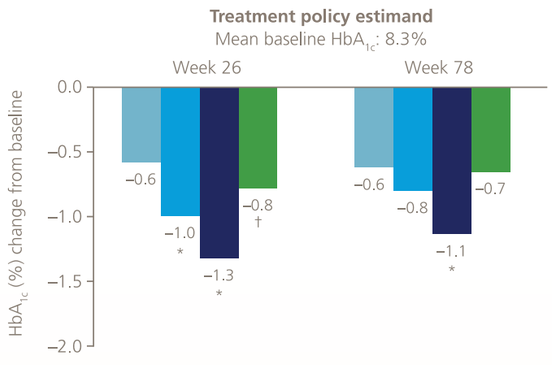
- For the treatment policy estimand at week 26, there were superior and significant HbA1c reductions with oral semaglutide 7 and 14 mg versus sitagliptin, but non-inferiority could not be demonstrated for oral semaglutide 3 mg (Figure 12):
  - ETDs [95% CI] versus sitagliptin at week 26 were –0.3% [–0.4, –0.1] for the oral semaglutide 7-mg dose and –0.5% [–0.6, –0.4] for the 14-mg dose (both p<0.001). For the 3-mg dose versus sitagliptin, the ETD was 0.2% [95% CI 0.0, 0.3] (p=0.008 in favour of sitagliptin)

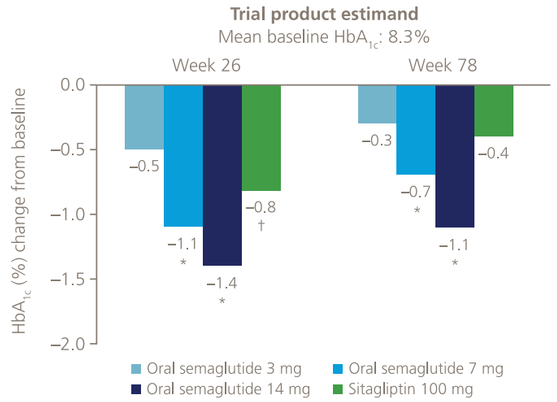
# Overview of results from the PIONEER programme

- The significant reductions in $HbA_{1c}$ versus sitagliptin were maintained to week 78 for the 14-mg dose of oral semaglutide

- Similar results were found for the trial product estimand (Figure 12):
  - ETDs [95% CI] versus sitagliptin at week 26 were –0.3% [–0.4, –0.2] for oral semaglutide 7 mg and –0.6% [–0.7, –0.5] for oral semaglutide 14 mg (both p<0.001). For oral semaglutide 3 mg versus sitagliptin, the ETD was 0.2% [95% CI 0.1, 0.4] (p<0.001 in favour of sitagliptin)
  - The effect of oral semaglutide 7 and 14 mg over sitagliptin was conserved up to week 78

**Figure 12. Estimated mean change from baseline in $HbA_{1c}$ at weeks 26 and 78[3]**




*p<0.05 vs sitagliptin; †p<0.05 vs oral semaglutide 3 mg for the ETDs.

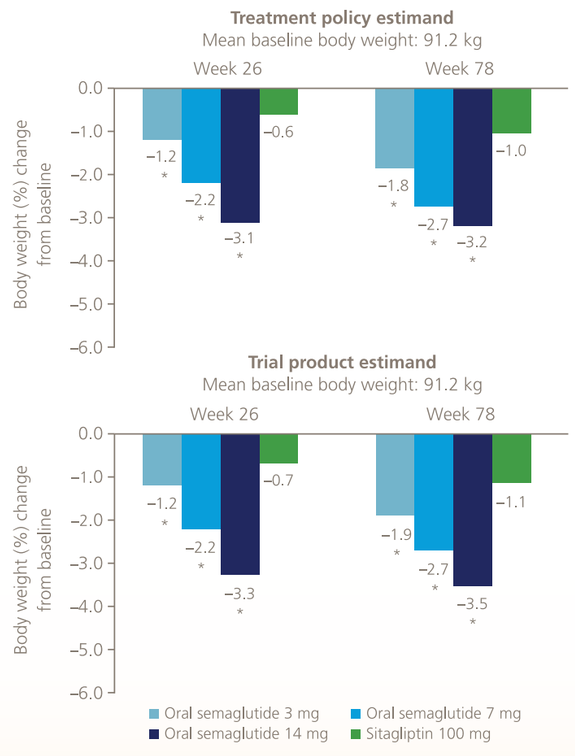
## 7.3.3 Efficacy: changes in body weight (key secondary endpoint)

- For the treatment policy estimand, oral semaglutide reduced body weight versus sitagliptin at week 26(Figure 13), with superiority confirmed for the 7- and 14-mg doses (3-mg superiority not tested in accordance with testing strategy)
  - ETDs [95% CI] versus sitagliptin at week 26 were –1.6 kg [–2.0, –1.1] for oral semaglutide 7 mg, and –2.5 kg [–3.0, –2.0] for oral semaglutide 14 mg (both p<0.001). For oral semaglutide 3 mg versus sitagliptin, the ETD was –0.6 kg [95% CI –1.1, –0.1] (p=0.02)
  - The effect of all three doses of oral semaglutide over sitagliptin was conserved at week 78



- Similar results were found for the trial product estimand (Figure 13)
  - ETDs [95% CI] versus sitagliptin at week 26 were –1.5 kg [–2.0, –1.1] for oral semaglutide 7 mg, and –2.6 kg [–3.1, –2.1] for oral semaglutide 14 mg (both p<0.001). For oral semaglutide 3 mg versus sitagliptin, the ETD was –0.5 kg [95% CI –1.0, –0.1] (p=0.03)
  - The effect of all three doses of oral semaglutide over sitagliptin was conserved at week 78

**Figure 13. Estimated change from baseline in body weight at weeks 26 and 78[3]**




*p<0.05 vs sitagliptin for the ETD.

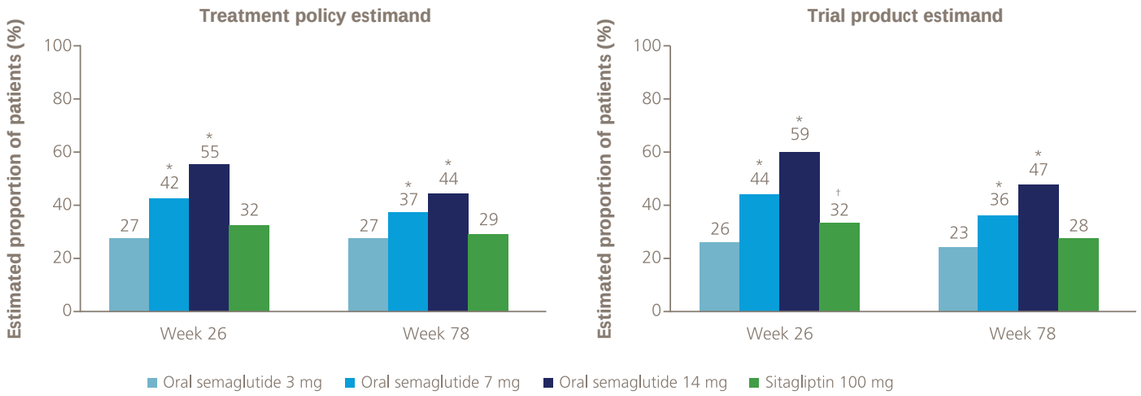
## 7.3.4 Efficacy: other secondary endpoints

- The estimated proportions of patients achieving $HbA^{1c}$ <7.0% were significantly greater with oral semaglutide 7 and 14 mg than with sitagliptin at weeks 26 and 78 (p<0.05 for all, both estimands), and significantly greater with sitagliptin than oral semaglutide 3 mg at week 26 (p<0.05) for the trial product estimand, but not for the treatment policy estimand (Figure 14)

- Compared with sitagliptin, the estimated proportions of patients achieving body weight loss ≥5% were significantly greater with oral semaglutide 7 and 14 mg at weeks 26 and 78 (p<0.001, for both estimands), and with oral semaglutide 3 mg at week 78 (p<0.05, for both estimands), but not at week 26

# Overview of results from the PIONEER programme

## Figure 14. Estimated proportions of patients achieving the target of $HbA_{1c}$ <7.0% at weeks 26 and 78




*p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs sitagliptin; †p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs oral semaglutide 3 mg.

## 7.3.5 Safety

- The proportions of patients experiencing AEs or SAEs were similar between the oral semaglutide and sitagliptin groups (Table 6)
- There were 12 deaths; no pattern or clustering of causes of death were observed
- The most frequent AEs were nausea for oral semaglutide 7 and 14 mg, which was mostly mild to moderate, and nasopharyngitis for oral semaglutide 3 mg and for sitagliptin
- GI AEs were the most common cause of premature trial product discontinuation in all treatment groups
- Severe or BG-confirmed symptomatic hypoglycaemia episodes mainly occurred in patients who were receiving background SU treatment
- The incidences of external event adjudication committee-confirmed acute kidney injury, acute pancreatitis, CV events, malignant neoplasms and lactic acidosis were low and similar across treatment groups
- AEs related to diabetic retinopathy were reported infrequently, with similar incidence across treatment groups, were mostly mild or moderate in severity and did not require treatment (see appendix section 11.1)

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## Table 6. Overview of on-treatment AEs

| | Oral semaglutide 3 mg n=466 | Oral semaglutide 7 mg n=464 | Oral semaglutide 14 mg n=465 | Sitagliptin 100 mg n=466 |
|---|---|---|---|---|
| **AEs** | 370 (79.4) | 363 (78.2) | 370 (79.6) | 388 (83.3) |
| **SAEs** | 64 (13.7) | 47 (10.1) | 44 (9.5) | 58 (12.4) |
| **AEs leading to premature trial product discontinuation** | 26 (5.6) | 27 (5.8) | 54 (11.6) | 24 (5.2) |
| **AEs by severity** | | | | |
| **Mild** | 323 (69.3) | 318 (68.5) | 321 (69.0) | 340 (73.0) |
| **Moderate** | 186 (39.9) | 171 (36.9) | 199 (42.8) | 197 (42.3) |
| **Severe** | 47 (10.1) | 37 (8.0) | 40 (8.6) | 53 (11.4) |
| **GI disorders** | | | | |
| **Nausea** | 34 (7.3) | 62 (13.4) | 70 (15.1) | 32 (6.9) |
| **Diarrhoea** | 45 (9.7) | 53 (11.4) | 57 (12.3) | 37 (7.9) |
| **Vomiting** | 13 (2.8) | 28 (6.0) | 42 (9.0) | 19 (4.1) |
| **Severe or BG-confirmed symptomatic hypoglycaemia*** | 23 (4.9) | 24 (5.2) | 36 (7.7) | 39 (8.4) |
| **In patients on metformin alone, n/N (%)** | 1/246 (0.4) | 5/247 (2.0) | 6/245 (2.4) | 4/248 (1.6) |
| **In patients on metformin + SU, n/N (%)** | 22/220 (10.0) | 19/217 (8.8) | 30/220 (13.6) | 35/218 (16.1) |
| **Severe hypoglycaemic episodes*** | 0 | 0 | 1 (0.2) | 4 (0.9) |
| **Select external event adjudication committee-confirmed events†** | | | | |
| **Death** | 5 (1.1) | 3 (0.6) | 1 (0.2) | 3 (0.6) |
| **Acute kidney injury** | 3 (0.6) | 2 (0.4) | 5 (1.1) | 3 (0.6) |
| **Acute pancreatitis** | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| **CV events** | 15 (3.2) | 7 (1.5) | 5 (1.1) | 10 (2.1) |
| **Malignant neoplasm‡** | 5 (1.1) | 9 (1.9) | 3 (0.6) | 7 (1.5) |
| **Lactic acidosis** | 0 | 1 (0.2) | 0 | 0 |

All data are n (%) unless otherwise stated.
*Severe (ADA classification) or confirmed by BG <56 mg/dL (3.1 mmol/L), with symptoms consistent with hypoglycaemia; hypoglycaemic episodes were reported on a separate form to AEs; †data are reported for the in-trial period; ‡excluding malignant thyroid neoplasms.

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# Overview of results from the PIONEER programme

## 7.3.6 Summary

- Oral semaglutide 7 and 14 mg were superior to sitagliptin in reducing $HbA_{1c}$ and body weight over 26 weeks
  - Non-inferiority of oral semaglutide 3 mg versus sitagliptin with respect to $HbA_{1c}$ could not be demonstrated
- For both $HbA_{1c}$ and body weight reductions, the significant effect of oral semaglutide 7 and 14 mg over sitagliptin was maintained at week 78 (except for change from baseline in $HbA_{1c}$ with oral semaglutide 7 mg at week 78 for the treatment policy estimand)
- The safety and tolerability profile of oral semaglutide was consistent with that of other GLP-1RAs



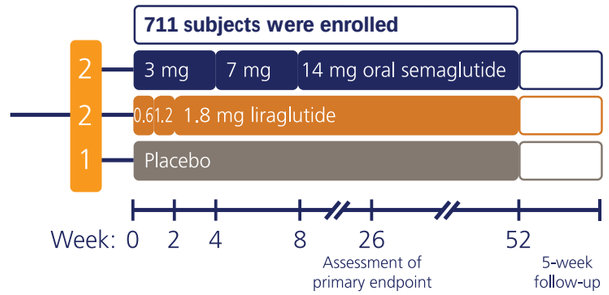
## 7.4 PIONEER 4: oral semaglutide versus liraglutide[4]

- PIONEER 4 (NCT02863419) compared the efficacy, safety and tolerability of oral semaglutide 14 mg once daily with liraglutide 1.8 mg once daily and placebo in patients with T2D on metformin ± SGLT2i (Figure 15)

**Figure 15. Trial design**

### Key inclusion criteria

- Age ≥18 years*
- T2D ≥90 days
- Stable doses of metformin or metformin ± SGLT2i for ≥90 days
- $HbA_{1c}$ 7.0–9.5% (53–80 mmol/mol)




### Trial information

- A 52-week randomised, double-blind, double-dummy, active- and placebo-controlled, parallel-group, multicentre, multinational, phase 3a trial with three arms

*≥20 years in Japan.

### Primary endpoint

- Change from baseline to week 26 in $HbA_{1c}$

### Key secondary endpoints

- Change from baseline to week 26 in body weight
- Change from baseline to week 52 in $HbA_{1c}$ and body weight
- Change in other parameters of efficacy, safety and tolerability

# Overview of results from the PIONEER programme

## 7.4.1 Baseline characteristics

- Baseline demographics and characteristics were similar between groups (Table 7)

**Table 7. Baseline characteristics**

| | Oral semaglutide 14 mg n=285 | Liraglutide 1.8 mg n=284 | Placebo n=142 |
|---|---|---|---|
| **Age, years** | 56 (10) | 56 (10) | 57 (10) |
| **Female, % of patients** | 48 | 48 | 48 |
| **White, % of patients** | 73 | 75 | 70 |
| **$HbA_{1c}$, %** | 8.0 (0.7) | 8.0 (0.7) | 7.9 (0.7) |
| **Diabetes duration, years** | 7.8 (5.7) | 7.3 (5.3) | 7.8 (5.5) |
| **FPG, mmol/L*** | 9.27 (2.23) | 9.30 (2.22) | 9.25 (2.27) |
| **FPG, mg/dL*** | 167.1 (40.2) | 167.6 (40.0) | 166.7 (40.9) |
| **Body weight, kg** | 92.9 (20.6) | 95.5 (21.9) | 93.2 (20.0) |
| **BMI, kg/m²** | 32.5 (5.9) | 33.4 (6.7) | 32.9 (6.1) |

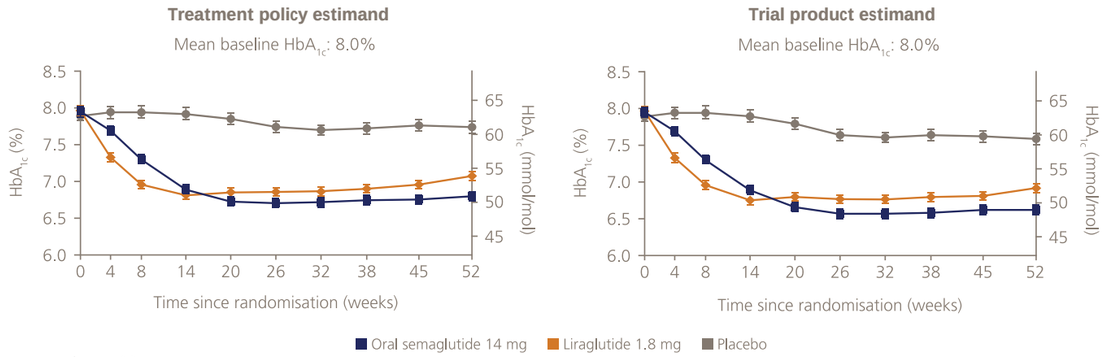
All data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.



## 7.4.2 Efficacy: change in $HbA_{1c}$ (primary endpoint)

- For both estimands, mean $HbA_{1c}$ was rapidly reduced over the first 14–20 weeks in both active treatment groups, with reductions largely sustained thereafter (Figure 16). The initial reduction in $HbA_{1c}$ was more rapid in the liraglutide group than with oral semaglutide, likely due to faster dose escalation of liraglutide

**Figure 16. Observed mean change in HbA1c to week 52**

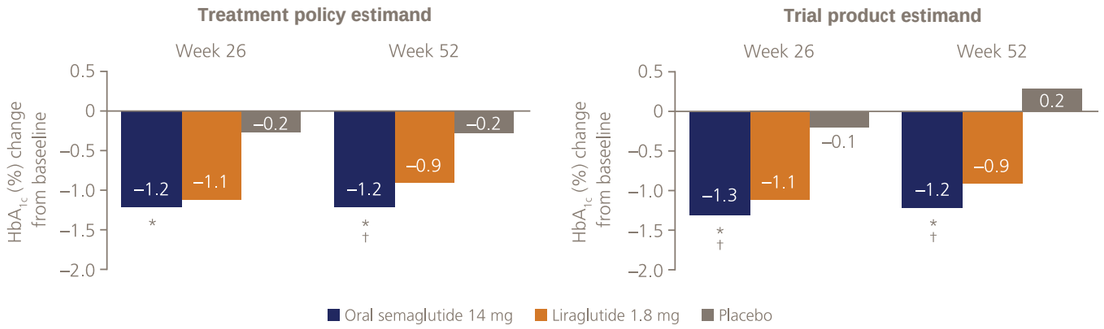



Error bars are SD.

- For the treatment policy estimand, oral semaglutide 14 mg was non-inferior to liraglutide and superior to placebo in reducing HbA1c from baseline at week 26 (Figure 17):
  - ETDs [95% CI] at week 26 were –0.1% [–0.3, 0.0] (p=0.065) versus liraglutide and –1.1% [–1.2, –0.9] (p<0.001) versus placebo
  - At 52 weeks, oral semaglutide provided significantly greater reductions in $HbA_{1c}$ from baseline than liraglutide (ETD: –0.3 [95% CI –0.5, –0.1]) and placebo (–1.0 [–1.2, –0.8]); both p<0.001
- Similar results were found for the trial product estimand, except that the ETD for oral semaglutide versus liraglutide was statistically significant at week 26
  - ETDs [95% CI] were –0.2% [–0.3, –0.1] (p<0.01) versus liraglutide and –1.2% [–1.4, –1.0] (p<0.001) versus placebo
  - The effect of oral semaglutide compared with liraglutide and placebo was conserved at week 52

# Overview of results from the PIONEER programme

**Figure 17. Estimated mean change from baseline in HbA1c at weeks 26 and 52**

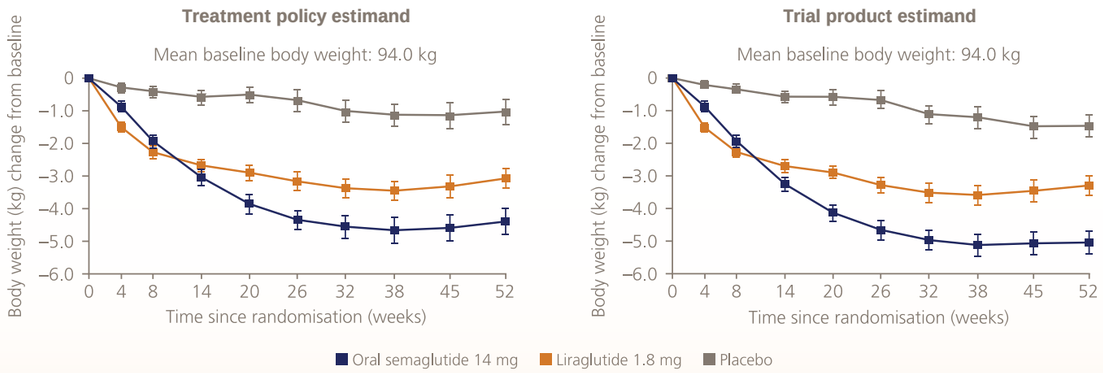



*p<0.05 vs placebo; †p<0.05 vs liraglutide for the ETDs.

## 7.4.3 Efficacy: changes in body weight (confirmatory secondary endpoint)

- For both estimands, mean body weight gradually decreased from baseline in both active treatment groups, with the largest reductions seen at week 38 (Figure 18)

**Figure 18. Observed mean change from baseline in body weight to week 52**

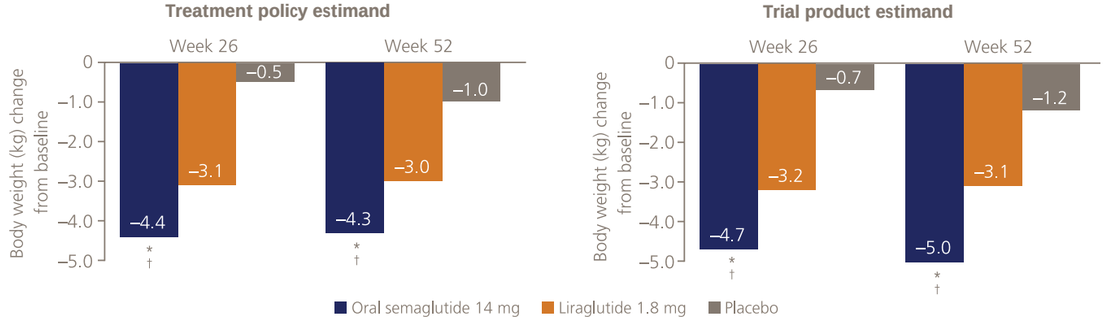



Error bars are SD.



- For the treatment policy estimand, superior and significant reductions in body weight were seen for oral semaglutide versus liraglutide and placebo (Figure 19)
  - ETDs [95% CI] at week 26 were –1.2 kg [–1.9, –0.6] (p<0.001) for oral semaglutide versus liraglutide, and –3.8 kg [–4.7, –3.0] (p<0.001) for oral semaglutide versus placebo
  - The effect of oral semaglutide over liraglutide and placebo was conserved at week 52
- Reductions in body weight were also significant for oral semaglutide versus liraglutide and placebo for the trial product estimand (Figure 19)
  - ETDs [95% CI] at week 26 were –1.5 kg [–2.2, –0.9] (p<0.001) for oral semaglutide versus liraglutide, and –4.0 kg [–4.8, –3.2] (p<0.001) for oral semaglutide versus placebo
  - The effect of oral semaglutide compared with liraglutide and placebo was conserved at week 52

**Figure 19. Estimated mean change from baseline in body weight at weeks 26 and 52**




*p<0.05 vs placebo; †p<0.05 vs liraglutide for the ETDs.

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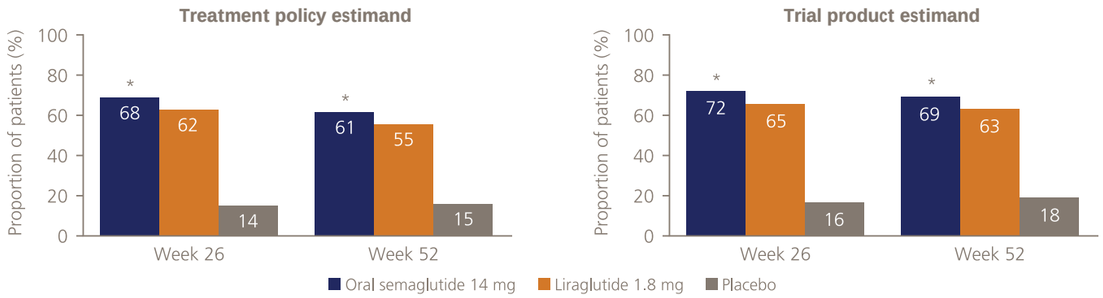
# Overview of results from the PIONEER programme

## 7.4.4 Efficacy: other secondary endpoints

- The odds of achieving HbA1c <7.0% were not significantly different with oral semaglutide than with liraglutide at weeks 26 or 52, but were significantly greater than placebo at both timepoints (p<0.001, both estimands) (Figure 20)
- FPG was significantly reduced with oral semaglutide versus placebo at weeks 26 and 52 (p<0.001) and versus liraglutide at week 52 (p<0.05) for both estimands (Figure 21)
- For the treatment policy estimand, the odds of achieving body weight reduction ≥5% at week 26 were significantly greater with oral semaglutide versus liraglutide (p<0.001) and placebo (p<0.001); treatment differences remained significant at week 52 (both p<0.001). Similar results were found for the trial product estimand

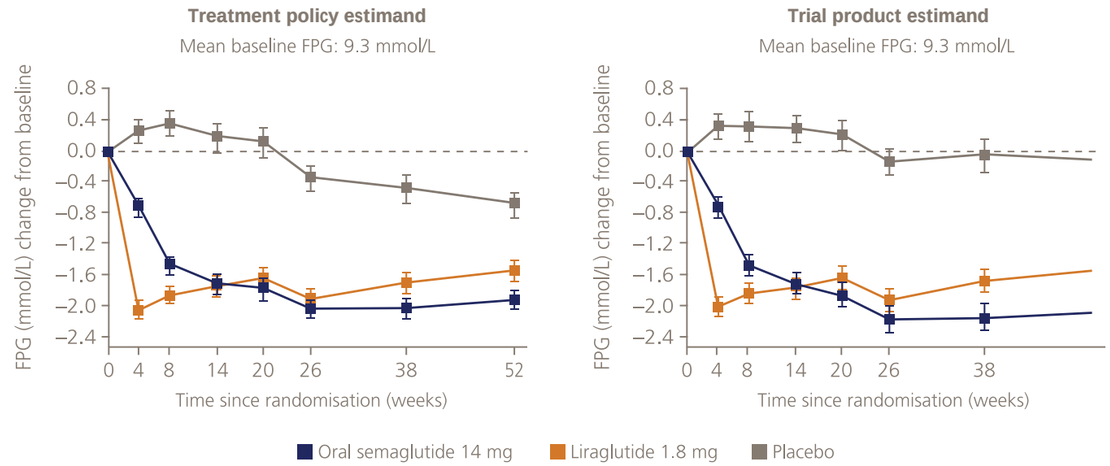
**Figure 20. Observed proportions of patients achieving the target of $HbA_{1c}$ <7.0% at weeks 26 and 52**




*p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs placebo.



**Figure 21. Change from baseline in FPG to week 52**




## 7.4.5 Safety

- The proportion of patients who reported AEs was higher for oral semaglutide than for liraglutide or placebo (Table 8)
- The proportion of SAEs was similar between oral semaglutide and placebo, and slightly lower for liraglutide
- Eight deaths occurred during the trial; none were considered to be treatment-related
- The slightly higher occurrence of AEs with oral semaglutide versus liraglutide was largely attributable to GI events, with the most frequent being transient nausea and diarrhoea (generally mild to moderate in severity)
- The proportion of patients who discontinued was also similar between oral semaglutide and liraglutide, mainly due to GI AEs

# Overview of results from the PIONEER programme

### Table 8. Overview of on-treatment AEs

| | Oral semaglutide 14 mg n=285 | Liraglutide 1.8 mg n=284 | Placebo n=142 |
|---|---|---|---|
| AEs | 229 (80) | 211 (74) | 95 (67) |
| SAEs | 31 (11) | 22 (8) | 15 (11) |
| AEs leading to premature trial product discontinuation | 31 (11) | 26 (9) | 5 (4) |
| AEs by severity | | | |
| Mild | 192 (67) | 180 (63) | 87 (61) |
| Moderate | 120 (42) | 102 (36) | 32 (23) |
| Severe | 23 (8) | 22 (8) | 7 (5) |
| GI disorders* | | | |
| Nausea | 56 (20) | 51 (18) | 5 (4) |
| Diarrhoea | 43 (15) | 31 (11) | 11 (8) |
| Vomiting | 25 (9) | 13 (5) | 3 (2) |
| Severe or BG-confirmed symptomatic hypoglycaemia† | 2 (1) | 7 (2) | 3 (2) |
| Deaths‡ | 3 (1) | 4 (1) | 1 (<1) |

All data are n (%). *≥5% in either group; †severe (ADA classification) or confirmed by BG <56 mg/dL (3.1 mmol/L), with symptoms consistent with hypoglycaemia; hypoglycaemic episodes were reported on a separate form to AEs; ‡data are reported for the in-trial period.

## 7.4.6 Summary

- At week 26, oral semaglutide 14 mg was non-inferior to daily injections of liraglutide 1.8 mg and superior to placebo in reducing $HbA_{1c}$, and was superior to liraglutide and placebo in reducing body weight
- Oral semaglutide provided significantly greater reductions in $HbA_{1c}$ and body weight compared with both liraglutide and placebo at week 52
- The safety and tolerability profile of oral semaglutide was consistent with that of liraglutide





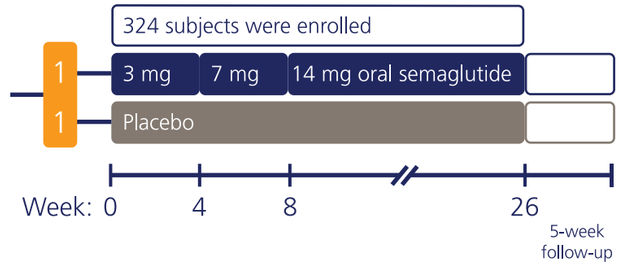
## 7.5 PIONEER 5: oral semaglutide in patients with T2D and moderate renal impairment[5]

- PIONEER 5 (NCT02827708) evaluated the efficacy and safety of oral semaglutide 14 mg once daily versus placebo in patients with T2D and moderate renal impairment (Figure 22)

### Figure 22. Trial design

**Key inclusion criteria**

- Age ≥18 years
- T2D ≥90 days
- eGFR 30–59 mL/min/1.73 $m^2$
- Stable doses of 1–2 OADs (metformin, SU) or insulin ±metformin for ≥90 days
- $HbA_{1c}$ 7.0–9.5% (53–80 mmol/mol)




**Trial information**

- Randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational, phase 3a trial with two arms

**Primary endpoint**

- Change from baseline to week 26 in $HbA_{1c}$

**Key secondary endpoints**

- Change from baseline to week 26 in body weight
- Change in other parameters of efficacy, safety and tolerability

# Overview of results from the PIONEER programme

## 7.5.1 Baseline characteristics

- Baseline characteristics were similar between the two treatment groups (Table 9)

**Table 9. Baseline characteristics**

| | Oral semaglutide 14 mg n=163 | Placebo n=161 |
|---|---|---|
| **Age, years** | 71 (8) | 70 (8) |
| **Female, % of patients** | 49 | 55 |
| **White, % of patients** | 97 | 94 |
| **$HbA_{1c}$, %** | 8.0 (0.7) | 7.9 (0.7) |
| **Diabetes duration, years** | 14.1 (8.6) | 13.9 (7.4) |
| **FPG, mmol/L*** | 9.1 (2.7) | 9.1 (2.8) |
| **FPG, mg/dL*** | 163.6 (47.7) | 163.5 (50.0) |
| **Body weight, kg** | 91.3 (17.8) | 90.4 (17.5) |
| **BMI, kg/m²** | 32.2 (5.4) | 32.6 (5.5) |
| **eGFR, mL/min/1.73 m²** | 47 (10) | 48 (10) |

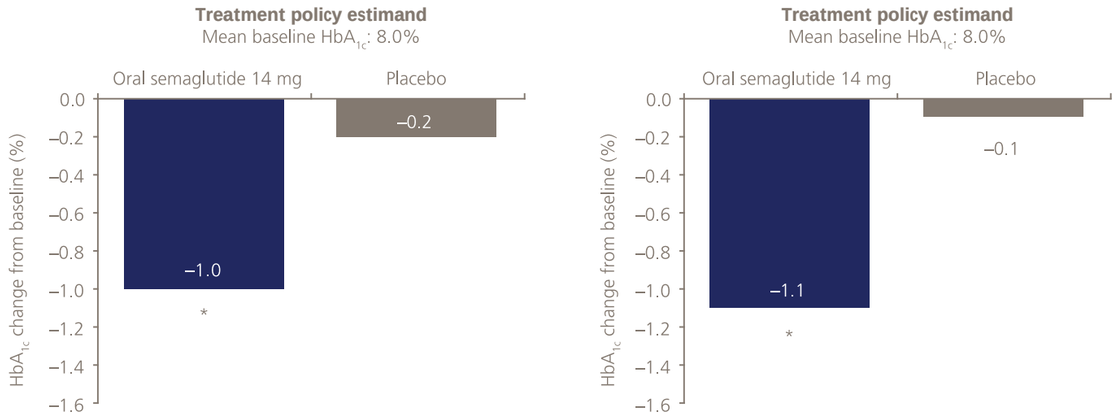
Data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.



## 7.5.2 Efficacy: change in $HbA_{1c}$ (primary endpoint)

- For the treatment policy estimand, superior and significant $HbA_{1c}$ reductions were seen with oral semaglutide versus placebo in patients with moderate renal impairment (Figure 23):
  - The ETD for oral semaglutide versus placebo at week 26 was –0.8% [95% CI –1.0, –0.6] (p<0.001)
- Similarly, greater $HbA_{1c}$ reductions were seen with oral semaglutide versus placebo for the trial product estimand (Figure 23):
  - The ETD for oral semaglutide versus placebo at week 26 was –1.0% [95% CI –1.2, –0.8] (p<0.001)

**Figure 23. Estimated mean change from baseline in $HbA_{1c}$ at week 26**




*p<0.05 vs placebo for the ETDs.

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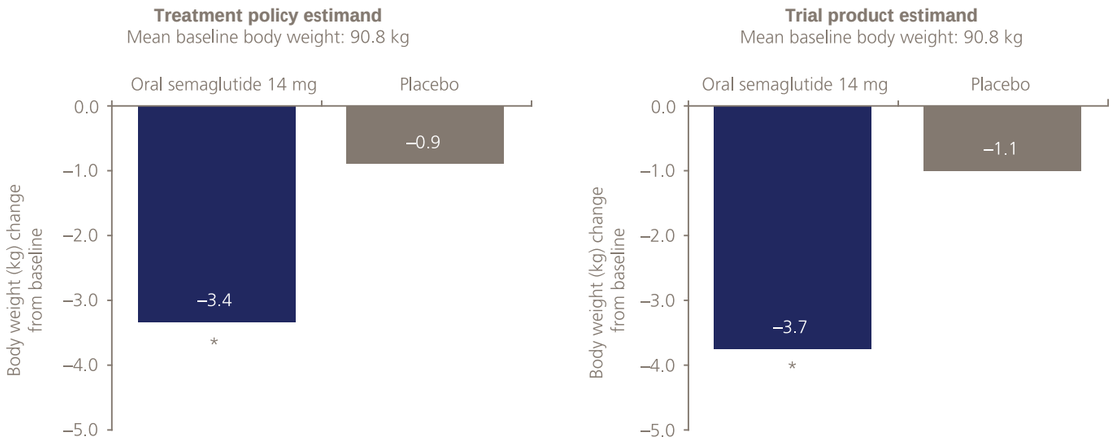
# Overview of results from the PIONEER programme

## 7.5.3 Efficacy: changes in body weight (confirmatory secondary endpoint)

- For the treatment policy estimand, superior and significant body weight reductions were seen with oral semaglutide versus placebo in patients with moderate renal impairment (Figure 24):
  - ETD for oral semaglutide versus placebo at week 26 was –2.5 kg [95% CI –3.2, –1.8] (p<0.001)
- Similarly, greater $HbA_{1c}$ reductions were seen with oral semaglutide versus placebo for the trial product estimand (Figure 24):
  - ETD for oral semaglutide versus placebo at week 26 was –2.7 kg [95% CI –3.5, –1.9] (p<0.001)

**Figure 24. Estimated mean change from baseline in body weight at week 26**



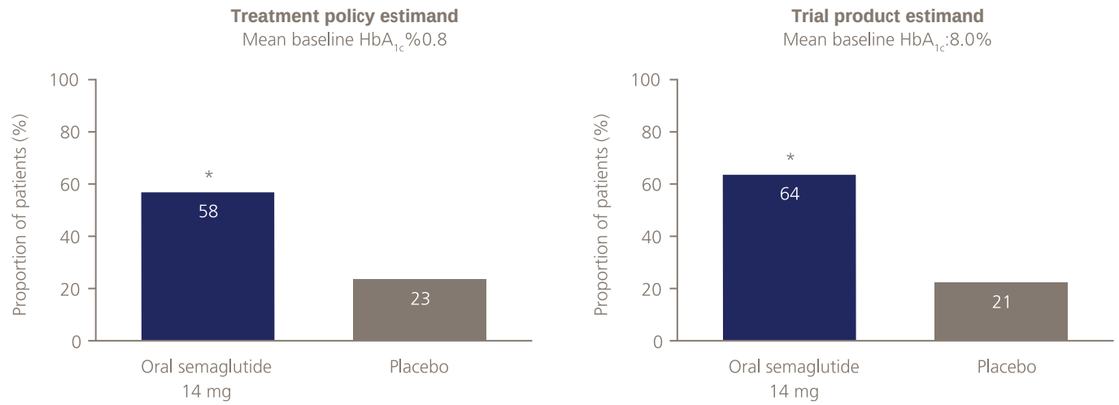

*p<0.05 vs placebo for the ETDs.



## 7.5.4 Efficacy: other secondary endpoints

- The odds of achieving $HbA_{1c}$ <7.0% were significantly greater with oral semaglutide than placebo at week 26 (p<0.001, both estimands) (Figure 25)
- The odds of achieving weight loss ≥5% at week 26 were significantly greater with oral semaglutide compared with placebo (p<0.001 for both estimands)

**Figure 25. Observed proportions of patients achieving the target of $HbA_{1c}$ <7.0% at week 26**




*p<0.05 for odds of achieving HbA1c <7.0% vs placebo.

## 7.5.5 Safety

- AEs were reported by 74% of patients with oral semaglutide and 65% with placebo (Table 10)
- There was a similar proportion of SAEs in the two groups
- The most common AE with oral semaglutide was transient mild or moderate nausea
- The proportion of premature trial product discontinuations due to AEs was 15% with oral semaglutide 14 mg and 5% with placebo, mainly due to GI events
- Overall, renal function was unchanged throughout the trial period in both treatment groups
- Three deaths occurred during the trial, and all were judged to be unlikely related to treatment

# Overview of results from the PIONEER programme

**Table 10. Overview of on-treatment AEs**

| | Oral semaglutide 14 mg n=163 | Placebo n=161 |
|---|---|---|
| AEs | 120 (74) | 105 (65) |
| SAEs | 17 (10) | 17 (11) |
| AEs by severity | | |
| Mild | 106 (65) | 89 (55) |
| Moderate | 61 (37) | 42 (26) |
| Severe | 10 (6) | 15 (9) |
| AEs leading to premature trial product discontinuation | 24 (15) | 8 (5) |
| GI disorders AEs | | |
| Nausea | 31 (19) | 12 (7) |
| Vomiting | 19 (12) | 2 (1) |
| Diarrhoea | 17 (100 | 6 (4) |
| Severe or BG-confirmed symptomatic hypoglycaemia* | 9 (60 | 3 (2) |
| Severe hypoglycaemic events | 0 | 0 |
| Deaths† | 1 (1) | 2 (1) |

Data are n (%) unless otherwise stated.
*Severe (ADA classification) or confirmed by BG <56 mg/dL (3.1 mmol/L), with symptoms consistent with hypoglycaemia; †data are reported for the in-trial period.

## 7.5.6 Summary

- In PIONEER 5, oral semaglutide 14 mg provided superior and significant reductions from baseline in $HbA_{1c}$ and body weight compared with placebo at week 26 in patients with T2D and moderate renal impairment, potentially providing a new treatment option in this patient population
- Safety, including renal safety, was consistent with the GLP-1RA class

## 7.6 PIONEER 7: flexible dose adjustment of oral semaglutide based on clinical evaluation versus sitagliptin[6]

- PIONEER 7 (NCT02849080) compared the efficacy and safety of flexible dose adjustments with oral semaglutide 3, 7 or 14 mg once daily versus fixed dose sitagliptin 100 mg once daily in patients with T2D inadequately controlled on 1-2 oral glucose-lowering agents (Figure 26)
  - Oral semaglutide dose adjustment was performed at week 8 and every 8 weeks thereafter based on pre-specified $HbA_{1c}$ and tolerability criteria
  - Amongst those who remained on-treatment with flexible dosing of oral semaglutide at week 52, 9.0%, 30.2% and 59.4% were receiving oral semaglutide 3, 7 and 14 mg, respectively
- Data shown in this version of the scientific synopsis are for the main phase only; data have not yet been reported for the extension study

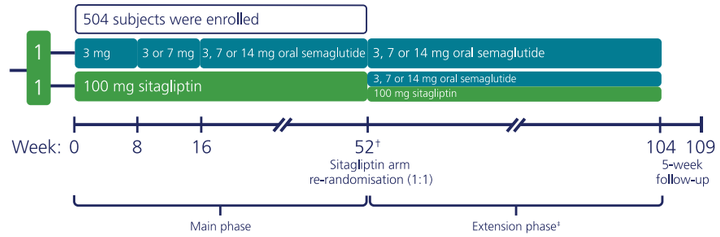




**Figure 26. Trial design**

### Key inclusion criteria

- Age ≥1 8 years*
- T2D ≥90 days
- Stable doses of 1–2 OADs (metformin, SU, TZD, SGLT2i) for ≥90 days
- $HbA_{1c}$ 7.5–9.5% (58–80 mmol/mol)
- Treatment target of $HbA_{1c}$ <7% (53 mmol/ mol), as judged by the investigator




### Trial information

- Randomised, open-label, active-controlled, parallel-group, multicentre, multinational, phase 3a, two-armed trial
- Flexible dose adjustment (3, 7 or 14 mg) based on clinical evaluation (glycaemic target and tolerability) every 8 weeks

### Primary endpoint

- Proportion of patients who achieved $HbA_{1c}$ <7.0% (<53 mmol/mol) at week 52

### Key secondary endpoints

- Change from baseline to week 52 in body weight
- Change from baseline to week 52 in $HbA_{1c}$
- Change in other parameters of efficacy, safety and tolerability

*≥19 years in South Korea; †5-week follow-up at week 57 for patients who did not continue into the extension phase; ‡the extension phase will be included in a future update. Patients randomised to the oral semaglutide flexible dose group initially received oral semaglutide 3 mg. At week 8 and every 8 weeks thereafter, the oral semaglutide dose was adjusted based on $HbA_{1c}$ and GI tolerability, with three dose levels of oral semaglutide available (3, 7 and 14 mg). Oral semaglutide dose was maintained if $HbA_{1c}$ was <7.0% and escalated to the next dose level if $HbA_{1c}$ was above this threshold, unless patients had experienced moderate-to-severe nausea or vomiting for 3 or more days in the prior week. Patients reporting moderate-to-severe nausea or vomiting received maintained or reduced oral semaglutide doses (minimum of 3 mg) at the investigator's discretion and regardless of $HbA_{1c}$ level.

# Overview of results from the PIONEER programme

## 7.6.1 Baseline characteristics (main phase)

- Demographics and baseline characteristics were similar between the treatment groups (Table 11)

**Table 11. Baseline characteristics (main phase)**

| | Oral semaglutide flex n=253 | Sitagliptin 100 mg n=251 |
|---|---|---|
| Age, years | 56.9 (9.7) | 57.9 (10.1) |
| Female, % of patients | 43 | 44 |
| White, % of patients | 77 | 74 |
| $HbA_{1c}$, % | 8.3 (0.6) | 8.3 (0.6) |
| Diabetes duration, years | 8.6 (6.3) | 9.0 (6.2) |
| FPG, mmol/L* | 9.8 (2.4) | 9.8 (2.6) |
| FPG, mg/dL* | 177.3 (42.4) | 176.0 (46.1) |
| Body weight, kg | 88.9 (19.6) | 88.4 (20.1) |
| BMI, $kg/m^2$ | 31.5 (6.5) | 31.5 (6.1) |

Data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

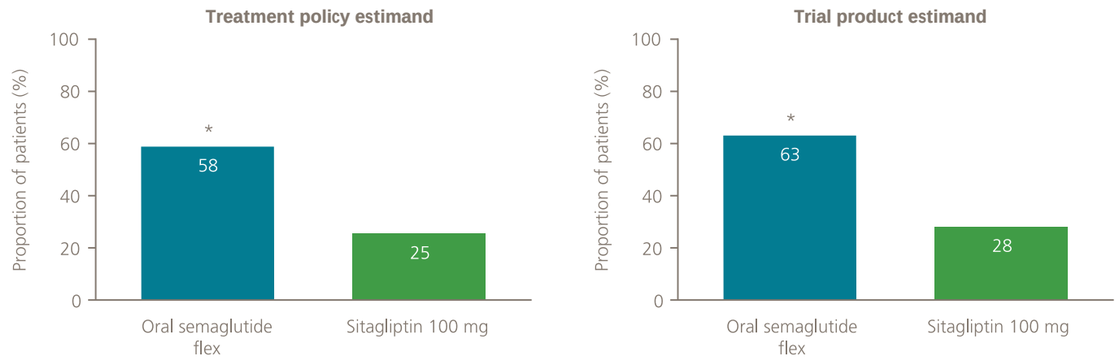




## 7.6.2 Efficacy: achievement of $HbA_{1c}$ <7% (main phase: primary endpoint)

- For the treatment policy estimand, oral semaglutide was superior to sitagliptin for the odds of patients achieving $HbA_{1c}$ <7% at week 52 (Figure 27):
  - Odds ratio 4.40 [95% CI 2.89, 6.70]; p<0.001
- Results were similar for the trial product estimand (Figure 27):
  - Odds ratio 5.54 [95% CI 3.54, 8.68]; p<0.001

**Figure 27. Observed proportions of patients achieving the target $HbA_{1c}$ <7.0% at week 52**



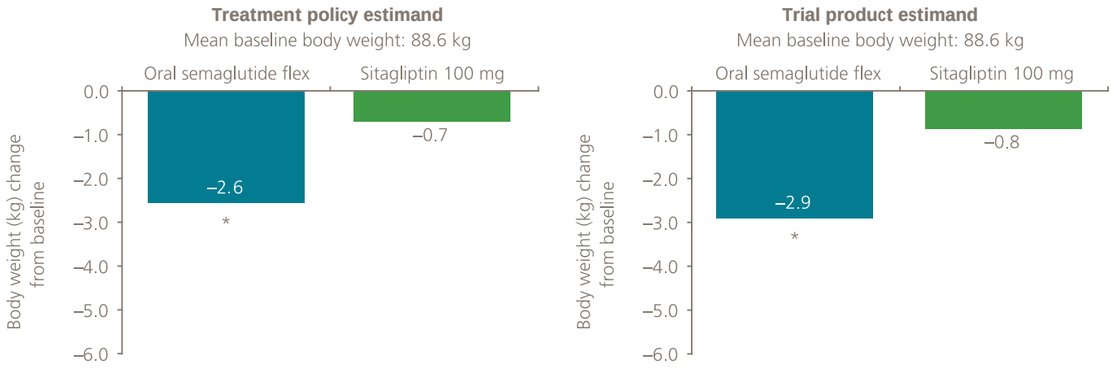

*p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs sitagliptin.

# Overview of results from the PIONEER programme

## 7.6.3 Efficacy: changes in body weight (main phase: confirmatory secondary endpoint)

- For the treatment policy estimand, superior and significant body weight reductions were seen with oral semaglutide flexible dosing versus sitagliptin (Figure 28):
  - ETD for oral semaglutide flexible dosing versus sitagliptin at week 52 was –1.9 kg [95% CI –2.6, –1.2] (p<0.001)
- Similarly, greater body weight reductions were seen with oral semaglutide flexible dosing versus sitagliptin for the trial product estimand (Figure 28):
  - ETD for oral semaglutide flexible dosing versus sitagliptin at week 52 was –2.2 kg [95% CI –2.9, –1.5] (p<0.001)

**Figure 28. Estimated mean change from baseline in body weight at week 52**




*p<0.05 vs sitagliptin for the ETDs.

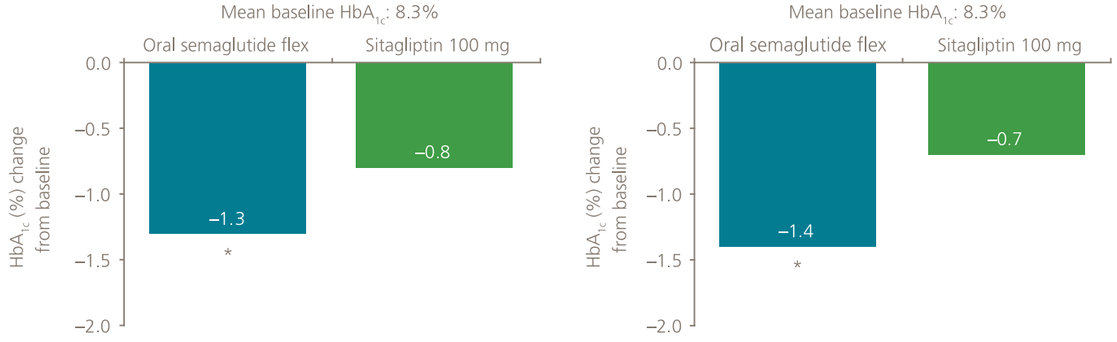




## 7.6.4 Efficacy: other secondary endpoints (main phase)

- For the treatment policy estimand, significant $HbA_{1c}$ reductions were seen with oral semaglutide flexible dosing versus sitagliptin (Figure 29):
  - ETD for oral semaglutide flexible dosing versus sitagliptin at week 52 was –0.5% [95% CI –0.7, –0.4] (p<0.001)
- Similarly, greater $HbA_{1c}$ reductions were seen with oral semaglutide flexible dosing versus sitagliptin for the trial product estimand (Figure 29):
  - ETD for oral semaglutide flexible dosing versus sitagliptin at week 52 was –0.7% [95% CI –0.9, –0.5] (p<0.001)

**Figure 29. Estimated mean change from baseline in $HbA_{1c}$ at week 52**




*p<0.05 vs sitagliptin for the ETDs.

- The odds of achieving body weight loss ≥5% at week 52 were significantly greater with oral semaglutide flexible dosing versus sitagliptin (p<0.001 for both estimands)

# Overview of results from the PIONEER programme

## 7.6.5 Safety (main phase)

- AEs were reported by 78% of patients with oral semaglutide and 69% with sitagliptin (Table 12)
- The proportion of patients reporting SAEs was similar in both treatment groups
- There were no deaths in the oral semaglutide group. There were two CV deaths in the sitagliptin group (one was on-treatment, and one was in-trial but not on-treatment)
- The most common AE with oral semaglutide was transient mild or moderate nausea
- The proportion of premature trial product discontinuations due to AEs was 9% with oral semaglutide and 3% with sitagliptin, mainly due to GI events
- The proportion of patients with BG-confirmed, symptomatic hypoglycaemic episodes was low and similar between treatment groups, with most episodes occurring in those receiving background SU treatment





### Table 12. Overview of on-treatment AEs (main phase)

| | Oral semaglutide flex n=253 | Sitagliptin 100 mg n=250 |
|---|---|---|
| AEs | 197 (78) | 172 (69) |
| SAEs | 24 (9) | 24 (10) |
| AEs leading to premature discontinuation of trial product | 22 (9) | 8 (3) |
| AEs by severity | | |
| Mild | 167 (66) | 144 (58) |
| Moderate | 104 (41) | 75 (30) |
| Severe | 16 (6) | 18 (7) |
| GI disorders AEs*† | | |
| Nausea | 53 (21) | 6 (2) |
| Diarrhoea | 22 (9) | 8 (3) |
| Vomiting | 14 (6) | 2 (1) |
| Severe or BG-confirmed symptomatic hypoglycaemic events‡ | 14 (6) | 14 (6) |
| In patients on SU, n/N (%) | 13/124 (10)§ | 13/125 (10)§ |
| In patients not on SU, n/N (%) | 1/129 (1)§ | 1/125 (1)§ |
| Severe hypoglycaemic events | 0 | 0 |
| Deaths | 0 | 1 (<1) |

Data are n (%) unless otherwise stated. The n number indicates the number of patients with at least one event.
*MedDRA version 20.1; †≥5% in either group; ‡severe (ADA classification) or confirmed by BG <56 mg/dL (3.1 mmol/L), with symptoms consistent with hypoglycaemia; §percentages relative to the total number of patients (N) within the respective SU treatment status group

## 7.6.5 Summary

- In the main phase of PIONEER 7, flexible dose adjustment of oral semaglutide based on efficacy and safety provided superior glycaemic control and weight loss compared with sitagliptin. The safety profile of oral semaglutide was consistent with the GLP-1RA class.

# Overview of results from the PIONEER programme

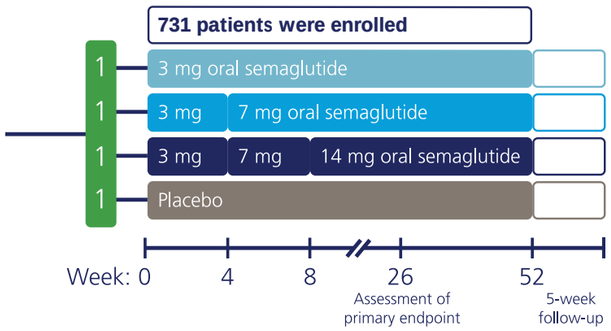
## 7.7 PIONEER 8: oral semaglutide added to insulin therapy[7,8]

- PIONEER 8 (NCT03021187) evaluated the efficacy and safety of three doses of oral semaglutide once daily versus placebo (Figure 30) added to insulin treatment in patients with T2D

**Figure 30. Trial design**

### Key inclusion criteria

- T2D ≥90 days
- HbA1c 7.0–9.5% (53–80 mmol/mol)
- On stable insulin treatment (± metformin)
  - Basal
  - Basal–bolus
  - Premixed
- Age ≥18 years*




### Trial information

- Randomised, double-blinded, placebo-controlled, parallel-group, multicentre trial with four arms

*°20 years in Japan.

### Primary endpoint

- Change from baseline to week 26 in $HbA_{1c}$

### Key secondary endpoints

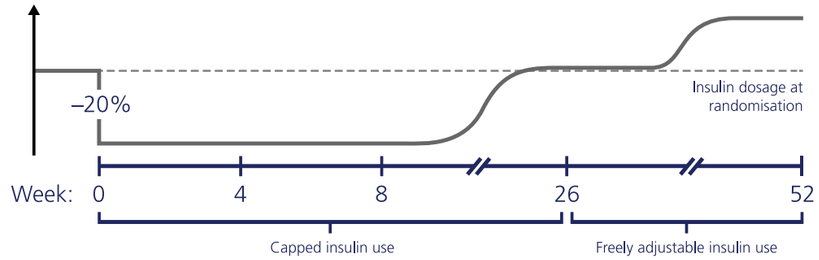
- Change from baseline to week 26 in body weight
- Change from baseline to week 52 in HbA1c and body weight
- Change in other parameters of efficacy, safety and tolerability



- A 20% reduction in total daily insulin dosage was recommended at randomisation and maintained to week 8. The treatment period was then split into two insulin dosing stages (Figure 31). A capped insulin period covered weeks 8–26, during which total daily insulin dosage was not to exceed the dosage at randomisation. For weeks 26–52, total daily insulin dosage was freely adjustable at the discretion of the investigator.

**Figure 31. Insulin dosing periods in PIONEER 8**

**Aim of insulin titration:** FPG 71–99 mg/dL; $HbA_{1c}$ <7.0% (53 mmol/mol)




Adjustments to total daily insulin dosage were made based on the lowest of three self-measured BG values measured on three consecutive days before each visit. A >20% increase relative to baseline in total daily insulin dosage was considered rescue medication.

## 7.7.1 Baseline characteristics

- Baseline characteristics are described in Table 13
  - The mean total daily insulin dosage at baseline was 58 U, and was slightly greater in the oral semaglutide 3- and 7-mg arms compared with the 14-mg and placebo arms

**Table 13. Baseline characteristics**

| | Oral semaglutide 3 mg n=184 | Oral semaglutide 7 mg n=182 | Oral semaglutide 14 mg n=181 | Placebo n=184 |
|---|---|---|---|---|
| Age, years | 61 (9) | 60 (10) | 60 (10) | 60 (10) |
| Female, % of patients | 44.6 | 43.4 | 53.0 | 42.9 |
| White, % of patients | 48.4 | 52.2 | 51.9 | 53.3 |
| $HbA_{1c}$, % | 8.2 (0.7) | 8.2 (0.7) | 8.2 (0.7) | 8.2 (0.7) |
| Diabetes duration, years | 15.1 (7.9) | 16.2 (8.6) | 14.1 (8.0) | 14.8 (7.9) |
| FPG, mmol/L* | 8.8 (3.2) | 8.5 (2.7) | 8.3 (2.6) | 8.3 (2.6) |
| FPG, mg/dL* | 158.4 (57.8) | 153.3 (49.2) | 150.1 (46.8) | 149.5 (47.4) |
| Body weight, kg | 85.9 (21.5) | 87.1 (23.6) | 84.6 (21.0) | 86.0 (21.4) |
| BMI, $kg/m^2$ | 31.0 (6.8) | 31.1 (7.0) | 30.8 (6.3) | 31.0 (6.5) |
| Total daily insulin dose, U | 61 (54) | 63 (77) | 53 (43) | 55 (48) |

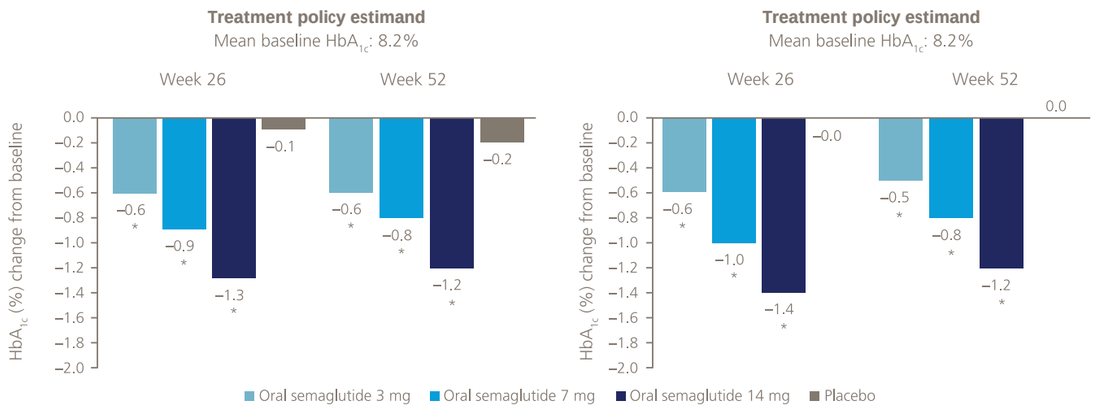
Data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

# Overview of results from the PIONEER programme

## 7.7.2 Efficacy: change in $HbA_{1c}$ (primary endpoint)

- For the treatment policy estimand, superior and significant $HbA_{1c}$ reductions were seen with all doses of oral semaglutide versus placebo:
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.5% [–0.7, –0.3]; 7 mg, –0.9% [–1.1, –0.7]; 14 mg, –1.2% [–1.4, –1.0]; p<0.001 for all
- Similarly, greater HbA1c reductions were seen for the trial product estimand at week 26 (Figure 32):
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.6% [–0.7, –0.4]; 7 mg, –1.0% [–1.2, –0.8]; 14 mg, –1.4% [–1.6, –1.2]; p<0.001 for all
- Significantly greater reductions in $HbA_{1c}$ with oral semaglutide versus placebo were maintained to week 52 in both estimands (Figure 32)

**Figure 32. Estimated mean change from baseline in $HbA_{1c}$ at weeks 26 and 52**




*p<0.05 vs placebo for the ETDs.

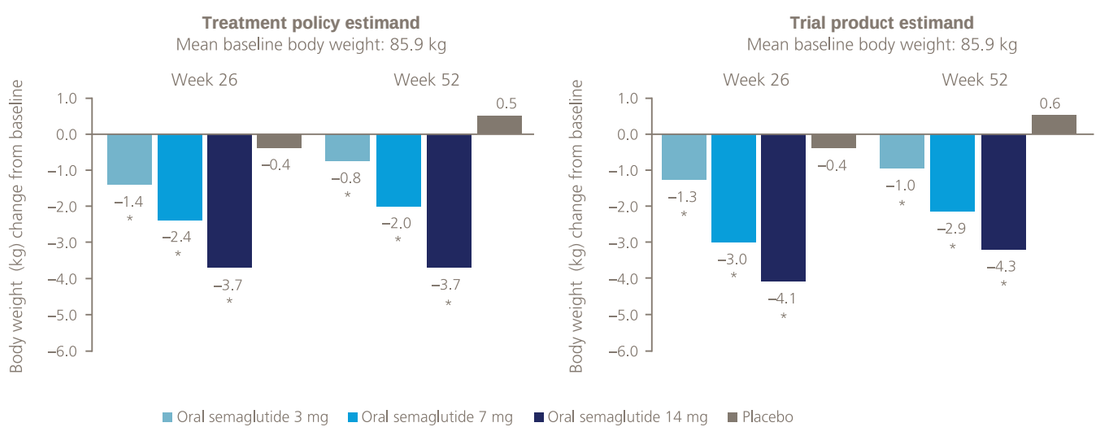




## 7.7.3 Efficacy: changes in body weight (confirmatory secondary endpoint)

- For the treatment policy estimand, superior and significant reductions in body weight were seen with oral semaglutide versus placebo (Figure 33):
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.9 kg [–1.8, –0.0], p<0.05; 7 mg, –2.0 kg [–3.0, –1.0], p<0.001; 14 mg, –3.3 kg [–4.2, –2.3], p<0.001
- Similarly, greater body weight reductions were seen for the trial product estimand at week 26 (Figure 33):
  - ETDs [95% CI] for oral semaglutide versus placebo at week 26 were: 3 mg, –0.9 kg [–1.6, –0.2], p<0.05; 7 mg, –2.5 kg [–3.2, –1.8], p<0.001; 14 mg; –3.7 kg [–4.4, –3.0], p<0.001
- The effect of oral semaglutide over placebo was conserved at week 52 in both estimands

**Figure 33. Estimated mean change from baseline in body weight at weeks 26 and 52**



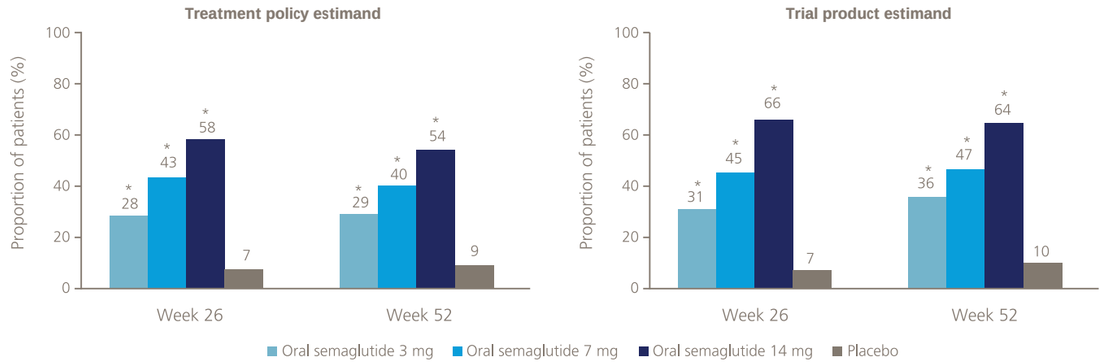

*p<0.05 vs placebo for the ETDs.

# Overview of results from the PIONEER programme

## 7.7.4 Efficacy: other secondary endpoints

- The odds of achieving $HbA_{1c}$ <7.0% were significantly greater with all three doses of oral semaglutide than with placebo at week 26 and 52 (p<0.001 for all comparisons; both estimands) (Figure 34)

**Figure 34. Observed proportions of patients achieving the target of $HbA_{1c}$ <7.0% at weeks 26 and 52**




*p<0.05 for odds of achieving HbA1c <7.0% vs placebo.

- For both estimands, the odds of achieving °5% body weight loss were significantly greater at week 26 and 52 with oral semaglutide 3 mg (p<0.01), 7 mg (p<0.001) and 14 mg (p<0.001) compared with placebo

## 7.7.5 Safety

- Comparable proportions of patients experienced at least one AE while on treatment (Table 14)
- The most common AE with oral semaglutide was transient mild or moderate nausea
- GI disorders were the most frequently reported AEs leading to discontinuation with oral semaglutide
- The proportion of patients with a severe or BG-confirmed symptomatic hypoglycaemic episode was similar between patients receiving oral semaglutide and placebo
- Three deaths occurred on-treatment with oral semaglutide 14 mg
  - The events adjudication committee confirmed cause of death as infection for one patient, and cause of death undetermined for the remaining two patients because there were no medical records available





**Table 14. Overview of on-treatment AEs**

| | Oral semaglutide 3 mg n=184 | Oral semaglutide 7 mg n=181 | Oral semaglutide 14 mg n=181 | Placebo n=184 |
|---|---|---|---|---|
| **AEs** | 137 (74.5) | 142 (78.5) | 151 (83.4) | 139 (75.5) |
| **SAEs** | 25 (13.6) | 19 (10.5) | 12 (6.6) | 17 (9.2) |
| **AEs leading to premature discontinuation of trial product** | 13 (7.1) | 16 (8.8) | 24 (13.3) | 5 (2.7) |
| **AEs by severity** | | | | |
| **Mild** | 123 (66.8) | 126 (69.6) | 134 (74.0) | 119 (64.7) |
| **Moderate** | 62 (33.7) | 65 (35.9) | 62 (34.3) | 59 (32.1) |
| **Severe** | 17 (9.2) | 17 (9.4) | 13 (7.2) | 9 (4.9) |
| **GI disorder AEs** | | | | |
| **Nausea** | 21 (11.4) | 30 (16.6) | 42 (23.2) | 13 (7.1) |
| **Diarrhoea** | 16 (8.7) | 22 (12.2) | 27 (14.9) | 11 (6.0) |
| **Vomiting** | 11 (6.0) | 14 (7.7) | 18 (9.9) | 7 (3.8) |
| **Severe or BG-confirmed symptomatic hypoglycaemic events*** | 52 (28.3) | 47 (26.0) | 48 (26.5) | 54 (29.3) |
| **In patients on background basal insulin, n/N (%)** | 8/77 (10.4)† | 12/76 (15.8)† | 10/76 (13.2)† | 16/80 (20.0)† |
| **In patients on background basal-bolus insulin, n/N (%)** | 36/71 (50.7)† | 29/73 (39.7)† | 31/70 (44.3)† | 27/72 (37.5)† |
| **In patients on background premixed insulin, n/N (%)** | 8/36 (22.2)† | 6/32 (18.8)† | 7/35 (20.0)† | 11/32 (34.4)† |
| **Deaths§** | 0 | 0 | 3 (1.7) | 0 |

All data are n (%), unless otherwise stated. The n number indicates the number of patients with at least one event.
*Severe (according to ADA classification) or BG-confirmed (<56 mg/dL [3.1 mmol/L]) symptomatic episodes (hypoglycaemic episodes were reported on a separate form to adverse events); †percentages relative to the total number of patients (N) within the respective background insulin regimen group; §in-trial events.

## 7.7.6 Summary

- When added to insulin in the setting of inadequately controlled T2D, oral semaglutide was superior to placebo at improving glycaemic control and at reducing body weight over 26 weeks, with significant differences also seen at 52 weeks, and with no increase in the risk of hypoglycaemia

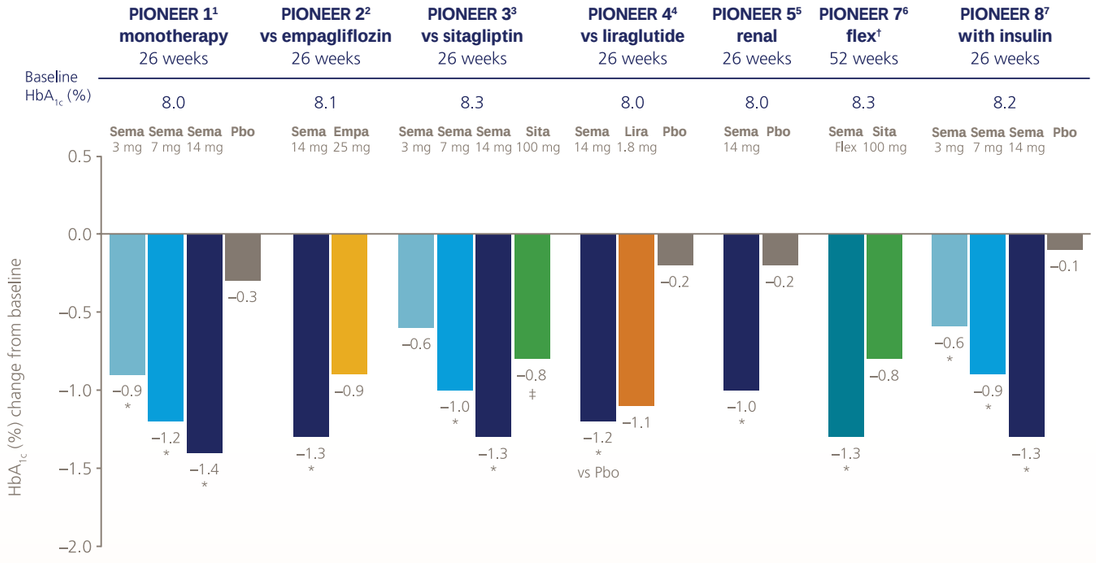
# Overview of results from the PIONEER programme

## 7.8 Overview of results from PIONEER 1–5, 7 and 8[1–8]

### 7.8.1 Key efficacy endpoints

- In each case, the trials achieved their primary endpoint according to the treatment policy estimand for the 7- and 14-mg doses of oral semaglutide
- Results using the trial product estimand were generally consistent with the treatment policy estimand
- HbA1c improvements from baseline to 26 weeks (52 weeks in PIONEER 7) according to the treatment policy estimand are shown in (Figure 35)
  - In the head-to-head trials versus active comparators (empagliflozin 25 mg, sitagliptin 100 mg or liraglutide 1.8 mg), oral semaglutide 14 mg provided significantly greater reductions in HbA1c from baseline, at end of trial with the treatment policy estimand (Figure 36)

**Figure 35. Change in $HbA_{1c}$ from baseline by treatment policy estimand**



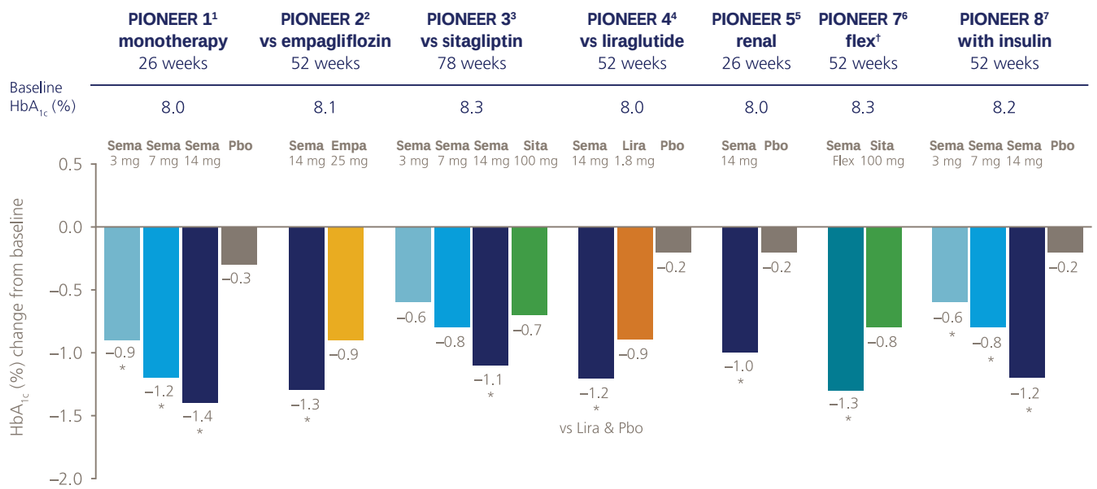

*p<0.05 vs placebo or active comparator for the ETDs; †primary endpoint in PIONEER 7, patients achieving HbA1c <7%; ‡p<0.05 vs oral semaglutide 3 mg for the ETD.

RYBELSUS® semaglutide tablets



- Dose-dependent HbA1c reductions were maintained by the end of treatment (Figure 36)

**Figure 36. Change in $HbA_{1c}$ from baseline by treatment policy estimand at the end of treatment**

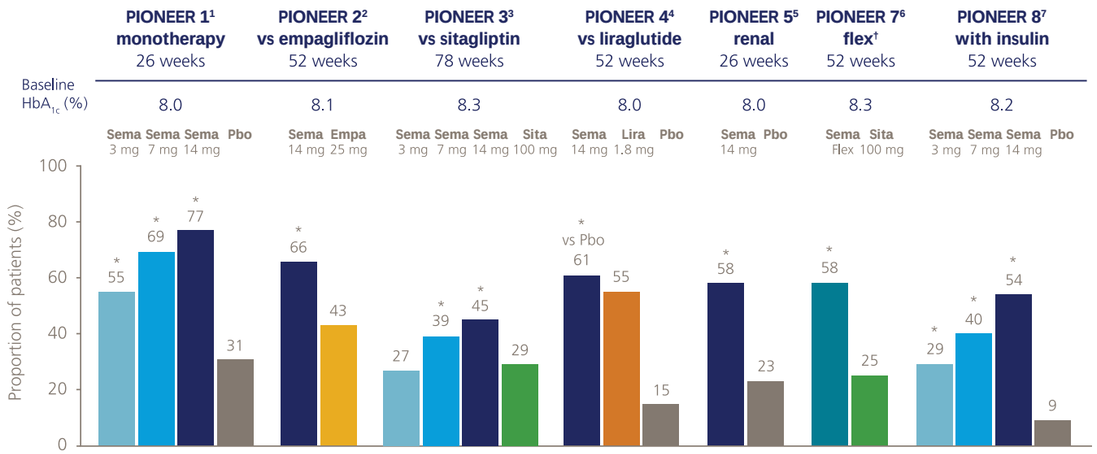



*p<0.05 vs placebo or active comparator for the ETDs; †primary endpoint in PIONEER 7, patients achieving $HbA_{1c}$ <7%.

- In all placebo-controlled trials, the odds of achieving $HbA_{1c}$ <7.0% was significantly greater with oral semaglutide versus placebo at the end of treatment according to the treatment policy estimand (Figure 37)
- In active-controlled trials, the odds of achieving $HbA_{1c}$ <7.0% was significantly greater with oral semaglutide 14 mg versus empagliflozin 25 mg or sitagliptin 100 mg at the end of treatment according to the treatment policy estimand, but there was no significant difference between oral semaglutide 14 mg and liraglutide 1.8 mg (Figure 37)

# Overview of results from the PIONEER programme

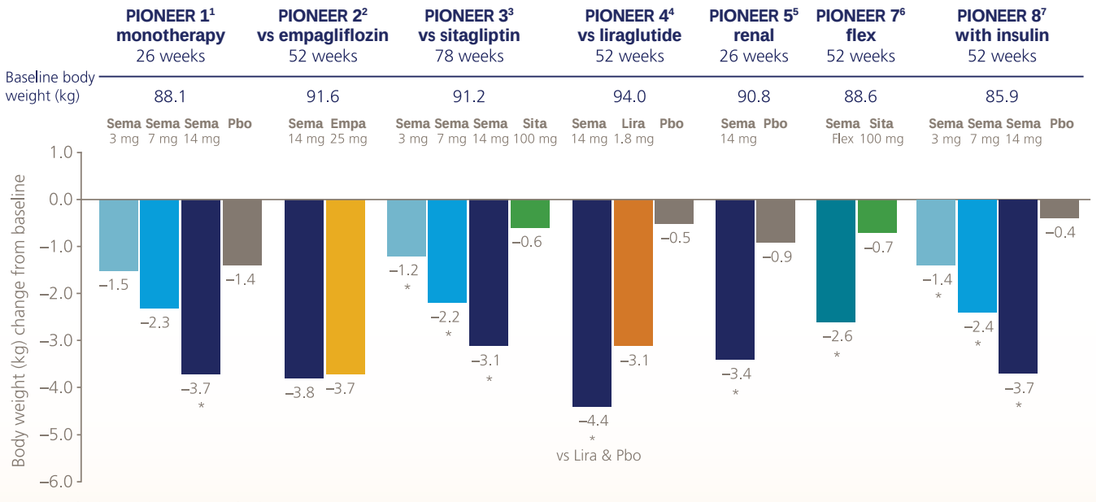
**Figure 37. Observed proportion of patients achieving $HbA_{1c}$ <7.0% by treatment policy estimand at the end of treatment**




*p<0.05 for odds of achieving HbA1c <7.0% vs placebo or active comparator; †primary endpoint in PIONEER 7, patients achieving $HbA_{1c}$ <7%.

- Body weight reductions from baseline to 26 weeks (52 weeks in PIONEER 7) according to the treatment policy estimand are shown in Figure 38. Significantly greater reductions in body weight were achieved with the 7- and 14-mg doses of oral semaglutide versus placebo (except oral semaglutide 7 mg in PIONEER 1) or active comparators (except versus empagliflozin in PIONEER 2)

**Figure 38. Change in body weight from baseline by treatment policy estimand**



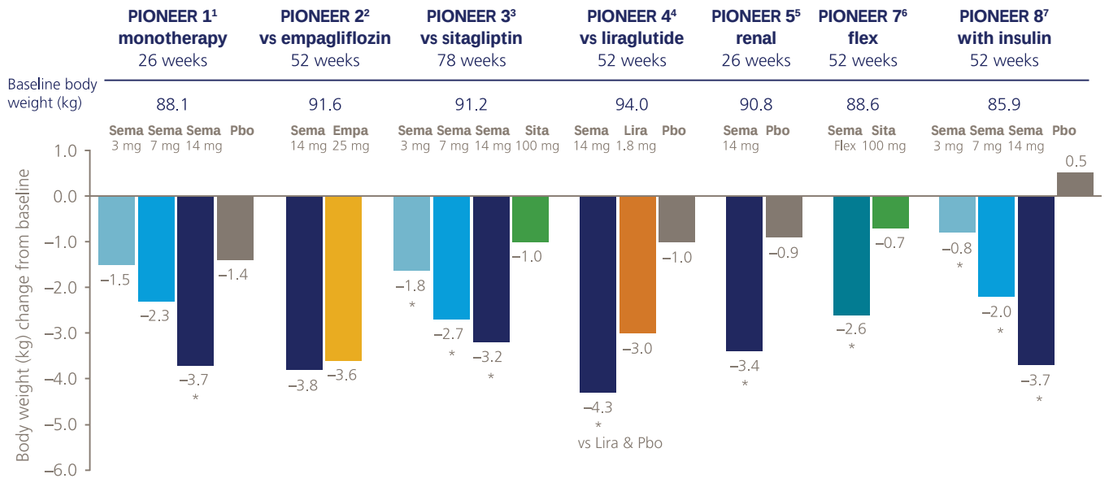

*p<0.05 vs placebo or active comparator for the ETDs.





- In studies that continued beyond 26 weeks, dose-dependent body weight reductions were maintained at the end of treatment (Figure 39)

**Figure 39. Change in body weight from baseline by treatment policy estimand at the end of treatment**




*p<0.05 vs placebo or active comparator for the ETDs.

## 7.8.2 Composite endpoints

- Two composite endpoints were assessed in the PIONEER studies:
  - i. Achievement of HbA1c <7.0% without severe or BG-confirmed symptomatic hypoglycaemic episodes, and without weight gain
  - ii. Achievement of $HbA_{1c}$ reduction 1% with body weight loss 3%
- In all placebo-controlled trials, the odds of achieving these composite endpoints was significantly greater with oral semaglutide versus placebo at the end of treatment according to the treatment policy estimand (Table 15)
- In active-controlled trials, the odds of achieving these composite endpoints was significantly greater with oral semaglutide 14 mg versus empagliflozin 25 mg and sitagliptin 100 mg at the end of treatment according to the treatment policy estimand (Table 15)

# Overview of results from the PIONEER programme

**Table 15. Observed proportion of patients achieving composite endpoints by treatment policy estimand at the end of treatment**

| | PIONEER 1[1] monotherapy 26 weeks | | | | PIONEER 2[2] vs empagliflozin 52 weeks | | PIONEER 3[9] vs sitagliptin 78 weeks | | | | PIONEER 4[4] vs liraglutide 52 weeks | | | PIONEER 5[5] renal 26 weeks | | PIONEER 7[6] flex 52 weeks | | PIONEER 8[7] with insulin 52 weeks | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sema 3 mg | Sema 7 mg | Sema 14 mg | Pbo | Sema 14 mg | Empa 25 mg | Sema 3 mg | Sema 7 mg | Sema 14 mg | Sita 100 mg | Sema 14 mg | Lira 1.8 mg | Pbo | Sema 14 mg | Pbo | Sema Flex | Sita 100 mg | Sema 3 mg | Sema 7 mg | Sema 14 mg | Pbo |
| **$HbA_{1c}$ <7.0% without hypoglycaemia* and without weight gain** | | | | | | | | | | | | | | | | | | | | | |
| **Proportion of patients, %** | 37 | 57 | 69 | 23 | 56 | 39 | 20 | 32 | 36 | 19 | 56 | 48 | 11 | 51 | 17 | 45 | 15 | 16 | 25 | 36 | 5 |
| **p value for odds ratio†** | <0.05 | <0.05 | <0.05 | – | <0.05 | – | NS | <0.05 | <0.05 | – | – | NS | <0.05‡ | <0.05 | – | <0.05 | – | <0.05 | <0.05 | <0.05 | – |
| **$HbA_{1c}$ reduction ≥1% and body weight loss ≥3%** | | | | | | | | | | | | | | | | | | | | | |
| **Proportion of patients, %** | 18 | 37 | 51 | 11 | 43 | 26 | 18 | 27 | 35 | 14 | 44 | 29 | 7 | 39 | 8 | 35 | 11 | 12 | 22 | 38 | 3 |
| **p value for odds ratio†** | NS | <0.05 | <0.05 | – | <0.05 | – | NS | <0.05 | <0.05 | – | – | <0.05‡ | <0.05‡ | <0.05 | – | <0.05 | – | <0.05 | <0.05 | <0.05 | – |

*Severe (according to ADA classification) or BG-confirmed (plasma glucose <3.1 mmol/L [56 mg/dL]) symptomatic hypoglycaemic episode;
†for oral semaglutide vs placebo or active treatment arm, unless indicated otherwise; ‡p value for comparison with oral semaglutide.

## 7.8.3 Safety and tolerability

- In all individual PIONEER trials, oral semaglutide was well tolerated, with a safety profile consistent with other GLP-1RAs
- The most common AE for oral semaglutide was mild-to-moderate nausea, which was transient in nature and which diminished over time
- Across the PIONEER trials, 15–23% of patients experienced nausea with oral semaglutide 14 mg
- Across the PIONEER trials, 7–15% of patients discontinued oral semaglutide 14 mg due to AEs





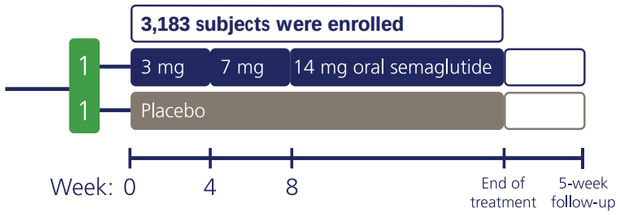
## 7.9 CV safety: PIONEER 6[10]

- PIONEER 6 (NCT02692716) was designed to confirm that treatment with oral semaglutide does not result in an unacceptable increase in CV risk compared with placebo (to rule out 80% excess risk, i.e. upper limit of the 95% CI below 1.8) in patients with T2D at high risk of CV events (Figure 40)
- PIONEER 6 completed after the accumulated occurrence of 137 primary MACEs (CV death, non-fatal MI and non-fatal stroke) and a median follow-up time of 16 months

**Figure 40. Trial design**

### Key inclusion criteria

- Age ≥50 years and established CV disease or CKD OR age ≥60 years with CV risk factors only
- Diagnosed with T2D
- Antidiabetic drug-naïve or current treatment with one or more oral or injectable antidiabetes agent(s) (excluding DPP-4i, GLP-1RA or pramlintide)




### Trial information

- Randomised, double-blind, placebo-controlled, parallel group, multicentre, multinational, phase 3a trial to assess the CV safety of oral semaglutide versus placebo when added to SoC in patients with T2D at high risk of CV events
- Event-driven trial that reached completion when at least 122 first MACEs confirmed by adjudication

### Primary endpoint

- Time to first MACE (CV death, non-fatal stroke, or non-fatal MI)

### Key secondary endpoints

- Time to all-cause death
- Time to expanded MACE endpoint*

*Expanded MACE endpoint consisted of the primary outcome plus unstable angina requiring hospitalisation, or HF requiring hospitalisation

# Overview of results from the PIONEER programme

## 7.9.1 Baseline characteristics

- Baseline characteristics were similar between groups and are described in Table 16

**Table 16. Baseline characteristics**

| | Oral semaglutide 14 mg n=1,591 | Placebo n=1,592 |
|---|---|---|
| Age, years | 66 (7) | 66 (7) |
| Female, % of patients | 31.9 | 31.4 |
| White, % of patients | 72.2 | 72.4 |
| $HbA_{1c}$, % | 8.2 (1.6) | 8.2 (1.6) |
| Diabetes duration, years | 14.7 (8.5) | 15.1 (8.5) |
| Body weight, kg | 91.0 (21.4) | 90.8 (21.0) |
| BMI, kg/m² | 32.3 (6.6) | 32.3 (6.4) |
| CV risk stratum, % of patients | | |
| Age ≥50 years and established CVD/CKD | 84.9 | 84.5 |
| Age ≥60 years and risk factors only | 15.1 | 15.5 |
| CV risk factors | | |
| Systolic BP, mmHg | 135 (18) | 135 (18) |
| Diastolic BP, mmHg | 76 (10) | 76 (10) |
| LDL cholesterol, mg/dL, geometric mean (coefficient of variation, %) | 77 (45) | 79 (41) |
| Current smoker, % of patients | 11.6 | 10.4 |
| eGFR, mL/min/1.73 m² | 74 (21) | 74 (21) |
| ≥90 mL/min/1.73 m², % of patients | 29.2 | 28.6 |
| 60–<90 mL/min/1.73 m², % of patients | 43.1 | 44.2 |
| 30–<60 mL/min/1.73 m², % of patients | 26.3 | 25.7 |
| <30 mL/min/1.73 m², % of patients | 1.0 | 0.8 |

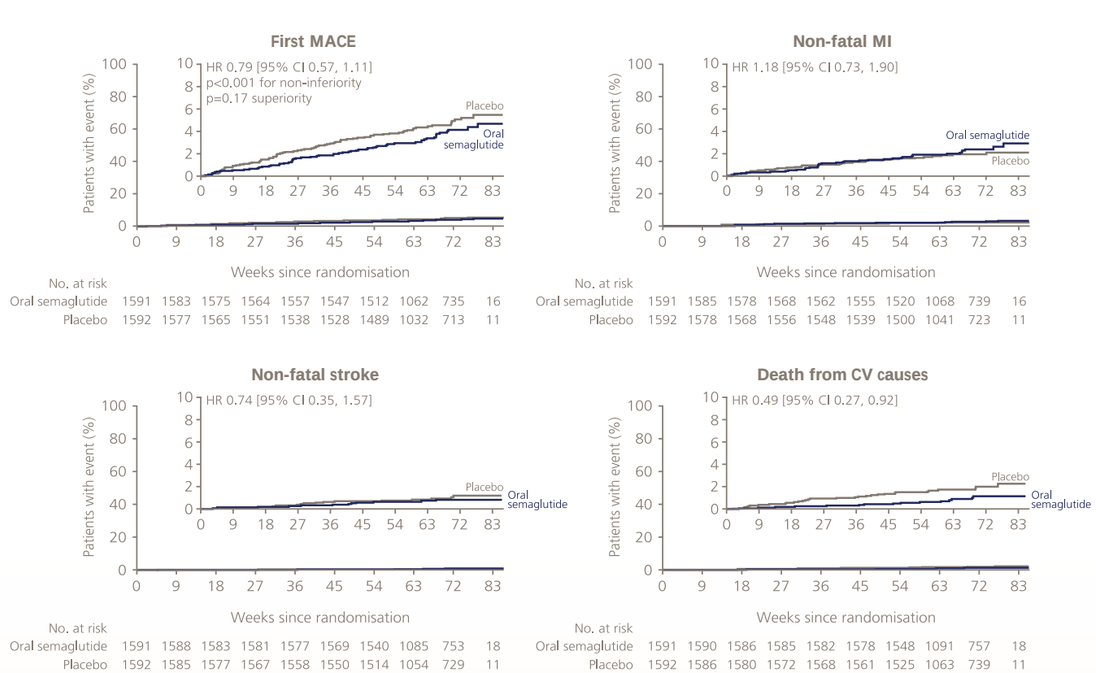
Data are mean (SD) unless otherwise stated.



## 7.9.2 CV outcomes

- In 3,183 patients with T2D at high risk of CV events, PIONEER 6 achieved its primary endpoint by demonstrating non-inferiority (p<0.001) for time to first MACE (composite of CV death, non-fatal MI and non-fatal stroke) for oral semaglutide compared with placebo, both in addition to SoC (Figure 41)
  - For the primary endpoint, an HR of 0.79 in favour of oral semaglutide compared with placebo was observed, but this 21% reduction in MACE did not reach statistical significance (p=0.17 for superiority)
- Among the individual components of the primary endpoint, there was a reduction in CV death of 51% (HR 0.49 [95% CI 0.27, 0.92]) in the oral semaglutide group. The HR for non-fatal MI was 1.18 [95% CI 0.73, 1.90] and for non-fatal stroke was 0.74 [95% CI 0.35, 1.57]
- In addition, a reduction in all-cause mortality of 49% (HR 0.51 [95% CI 0.31, 0.84] in favour of oral semaglutide was observed
- The HR for the expanded MACE outcome was similar to that of the primary outcome (HR 0.82 [95% CI 0.61, 1.10])

**Figure 41. Cumulative incidence plots for CV outcomes**



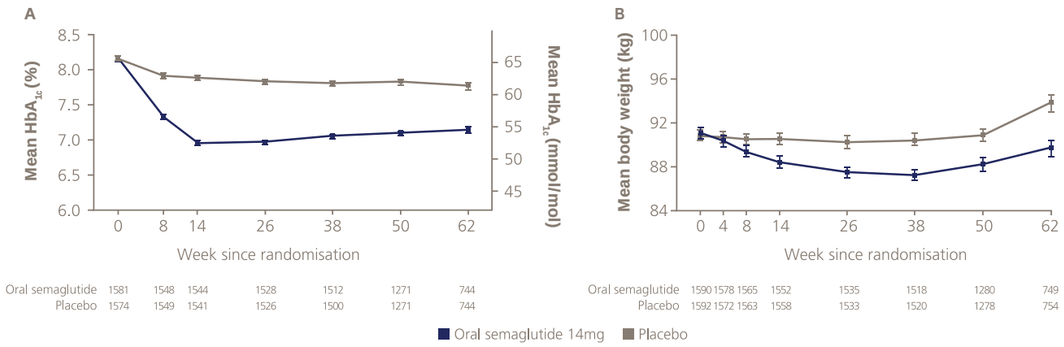

Cumulative incidence estimates are based on time from randomisation to first Event Adjudication Committee-confirmed event, with non-CV deaths or all-cause deaths modelled as competing risks. Subjects were censored at the end of the in-trial observation period (from randomisation to final follow-up visit). CV death includes deaths for which the cause is undetermined.The confirmatory analysis was controlled for multiplicity; p values and CIs for other analyses have not been adjusted for multiplicity.

# Overview of results from the PIONEER programme

## 7.9.3 Efficacy outcomes

- The improvements in secondary endpoints including $HbA_{1c}$ and body weight were similar to results reported throughout the PIONEER programme for oral semaglutide (Figure 42)
  - From baseline to end of study, oral semaglutide was associated with a reduction compared with placebo in both $HbA_{1c}$ (–1.0% vs –0.3%, respectively) and body weight (–4.2 kg vs –0.8 kg, respectively)

**Figure 42. Observed mean changes from baseline in (A) $HbA_{1c}$ and (B) body weight**




Observed data for the in-trial observation period. Error bars are ± standard error of the mean. The in-trial period was the period from randomisation to the final follow-up visit.

## 7.9.4 Safety and tolerability

- The safety profile of oral semaglutide in PIONEER 6 was consistent with the safety profile observed in other PIONEER trials (Table 17)
  - Diabetic retinopathy-related AEs were infrequent and similar across the two groups (see appendix section 11.1)
- There were no imbalances in other AEs of special interest, including acute kidney injury, acute pancreatitis, severe hypoglycaemia or malignant neoplasms





**Table 17. Overview of on-treatment AEs**

| | Oral semaglutide 14 mg n=1591 | Placebo n=1592 |
|---|---|---|
| SAEs | 301 (18.9) | 358 (22.5) |
| AEs leading to discontinuation | 184 (11.6) | 104 (6.5) |
| GI disorder AEs | 108 (6.8) | 26 (1.6) |
| AEs of special interest | | |
| Acute kidney injury* | 32 (2.0) | 37 (2.3) |
| Acute pancreatitis* | 1 (0.1) | 3 (0.2) |
| Retinopathy or related complications†‡ | 113 (7.1) | 101 (6.3) |
| Severe hypoglycaemia† | 23 (1.4) | 13 (0.8) |
| Malignant neoplasms*‡§ | 41 (2.6) | 48 (3.0) |
| Deaths | 23 (1.4) | 45 (2.8) |
| CV cause | 10 (0.6) | 23 (1.4) |
| Non-CV cause | 8 (0.5) | 15 (0.9) |
| Undetermined cause | 5 (0.3) | 7 (0.4) |

Data are n (%). *Event Adjudication Committee-confirmed events; †identified using a search of MedDRA terms, version 20.1; ‡in-trial observation period; §excluding malignant thyroid neoplasms (two malignant thyroid neoplasms occurred in the oral semaglutide group: one patient with medullary thyroid cancer and one with recurrence of previous thyroid cancer).AEs were summarised descriptively for both the on-treatment observation period (from first date of trial product administration to the date of last dose plus 38 days or final follow-up visit [whichever was first]) and in-trial observation period (from randomisation to final follow-up visit).

## 7.9.5 Summary

- PIONEER 6 demonstrated CV safety with non-inferiority of oral semaglutide compared with placebo, ruling out an 80% excess CV risk in patients with T2D
- A 21% reduction in the risk of MACE was observed for oral semaglutide compared with placebo, but this difference did not reach statistical significance

# Overview of results from the PIONEER programme

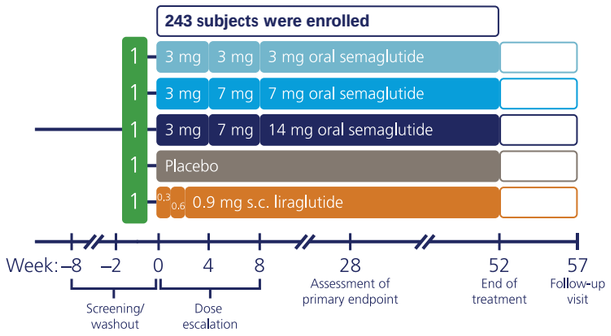
## 7.10 PIONEER 9: oral semaglutide as monotherapy in Japanese patients[11]

- PIONEER 9 (NCT03018028) assessed the dose–response relationship of oral semaglutide in the Japanese population, and compared efficacy and safety with placebo and liraglutide 0.9 mg (Figure 43)

**Figure 43. Trial design**

### Key inclusion criteria

- Age ≥20 years
- T2D ≥30 days
- Diet and exercise therapy alone or stable daily dose of one OAD (metformin, SU, glinide, α-GI, DPP-4i or SGLT2i)
- $HbA_{1c}$ 7.0–10.0% (53–86 mmol/mol) on diet/exercise or $HbA_{1c}$ 6.5–9.5% (48–80 mmol/mol) if on one OAD




### Trial information

- A randomised, double-blind placebo-controlled, and open-label active-controlled, parallel-group, multicentre, phase 2/3a trial

### Primary endpoint

- Change from baseline to week 26 in $HbA_{1c}$

### Key secondary endpoints

- Change from baseline to week 52 in $HbA_{1c}$
- Change from baseline to week 26 and 52 in body weight
- Change in other parameters of efficacy, safety and tolerability





## 7.10.1 Baseline characteristics

- Baseline demographics and disease characteristics were similar between treatment groups (Table 18)

**Table 18. Baseline characteristics**

| | Oral semaglutide 3 mg n=49 | Oral semaglutide 7 mg n=49 | Oral semaglutide 14 mg n=48 | Placebo n=49 | Liraglutide 0.9 mg n=48 |
|---|---|---|---|---|---|
| **Age, years** | 58 (9) | 60 (10) | 61 (9) | 59 (9) | 59 (10) |
| **Female, %** | 13 (27) | 13 (27) | 8 (17) | 9 (18) | 9 (19) |
| **$HbA_{1c}$, %** | 8.1 (0.8) | 8.3 (1.0) | 8.0 (0.9) | 8.3 (1.1) | 8.3 (0.8) |
| **Diabetes duration, years** | 7.4 (5.5) | 7.4 (5.6) | 7.9 (5.9) | 8.4 (6.0) | 6.7 (5.2) |
| **FPG, mmol/L*** | 9.0 (1.9) | 8.9 (1.7) | 8.9 (2.0) | 9.0 (1.9) | 9.7 (1.9) |
| **FPG, mg/dL*** | 163.0 (34.3) | 161.0 (30.6) | 160.0 (35.4) | 162.1 (34.7) | 174.5 (34.9) |
| **Body weight, kg** | 71.4 (14.3) | 71.3 (10.8) | 68.0 (13.0) | 70.3 (12.4) | 74.7 (15.4) |
| **BMI, kg/m²** | 26.5 (4.6) | 26.3 (3.5) | 24.7 (4.1) | 25.1 (3.9) | 26.9 (4.8) |

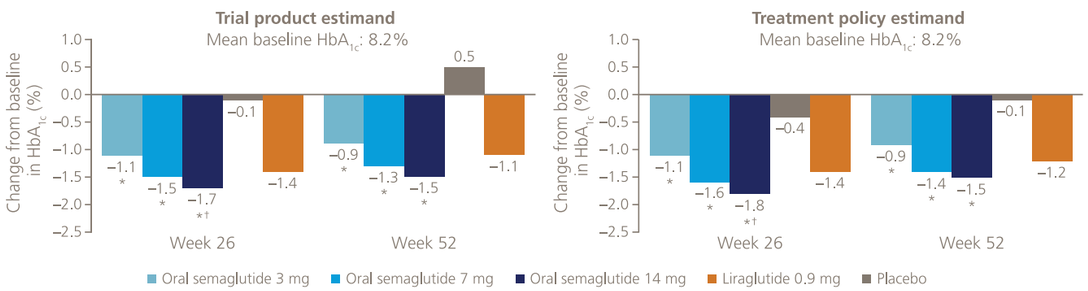
Data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

## 7.10.2 Efficacy: change in $HbA_{1c}$ (primary endpoint)

- For the trial product estimand (primary estimand in PIONEER 9), estimated changes from baseline in $HbA_{1c}$ were significantly greater with oral semaglutide 3, 7 and 14 mg compared with placebo at week 26, and were significantly greater with oral semaglutide 14 mg compared with liraglutide 0.9 mg (Figure 44)
  - ETDs [95% CI] were –1.1% [–1.4, –0.8], –1.5% [–1.7, –1.2] and –1.7% [–2.0, –1.4] for oral semaglutide 3, 7 and 14 mg versus placebo (all $p<0.001$) and –0.3% [–0.6, –0.0] for oral semaglutide 14 mg versus liraglutide ($p<0.05$)
- At the end of treatment (week 52), the effect of oral semaglutide over placebo was maintained for the trial product estimand. $HbA_{1c}$ reductions from baseline were not significantly different between oral semaglutide 14 mg and liraglutide 0.9 mg at this timepoint
- Similar results were seen for the treatment policy estimand (Figure 44)
- The response to oral semaglutide was dose dependent; the maximum estimated change from baseline in HbA1c was –1.96% (versus –0.07% for placebo) and the estimated dose leading to half maximal response was 2.49 mg

# Overview of results from the PIONEER programme

**Figure 44. Estimated mean change from baseline in $HbA_{1c}$ at weeks 26 and 52**




*p<0.05 vs placebo for the ETD; †p<0.05 vs liraglutide 0.9 mg for the ETD

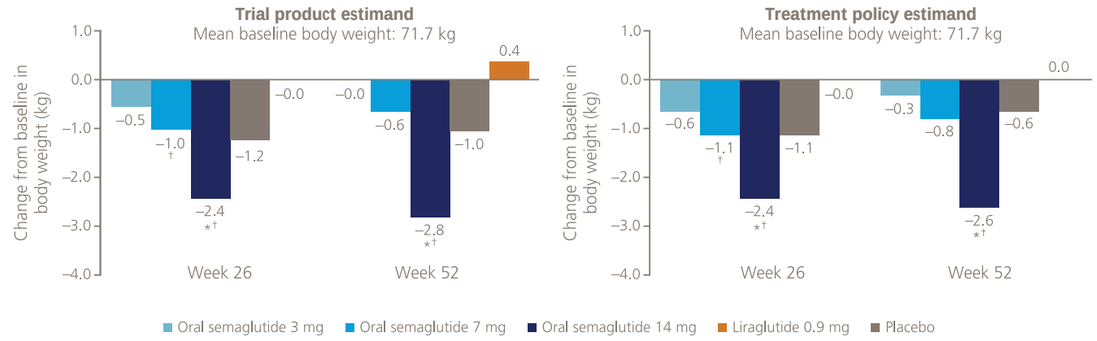
## 7.10.3 Efficacy: changes in body weight (confirmatory secondary endpoint)

- At week 26, significant reductions in body weight were seen for oral semaglutide 14 mg versus placebo, and for oral semaglutide 7 and 14 mg compared with liraglutide (trial product estimand) (Figure 45)
  - ETDs were –1.2 kg [–2.0, –0.3] (p<0.05) for oral semaglutide 14 mg versus placebo, and –0.9 kg [–1.8, –0.1] (p<0.05) and –2.3 kg [–3.2, –1.5] (p<0.001) for oral semaglutide 7 mg and 14 mg, respectively, versus liraglutide
- At week 52, reductions in body weight remained significantly greater with oral semaglutide 14 mg compared with placebo and liraglutide (trial product estimand) (Figure 45)
- Similar results were seen for the treatment policy estimand (Figure 45)





**Figure 45. Estimated mean change from baseline in body weight at weeks 26 and 52**

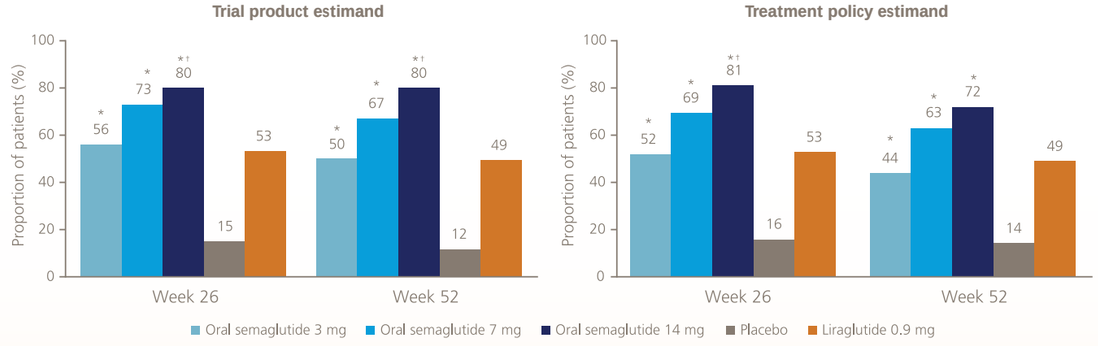



*p<0.05 vs placebo for the ETD; †p<0.05 vs liraglutide 0.9 mg for the ETD.

## 7.10.4 Efficacy: other secondary endpoints

- The odds of achieving $HbA_{1c}$ <7.0% were significantly greater with all oral semaglutide doses than with placebo (p<0.05, both estimands at weeks 26 and 52; Figure 46)
- The odds of achieving $HbA_{1c}$ <7.0% were significantly greater with oral semaglutide 14 mg than with liraglutide for the trial product estimand at weeks 26 and 52 (p<0.05), and for the treatment policy estimand at week 26 (p<0.05) (Figure 46)
- The odds of achieving body weight loss ≥5% were significantly greater with oral semaglutide 14 mg than with placebo and liraglutide (p<0.05 for both) for both estimands

**Figure 46. Observed proportions of patients achieving the target of $HbA_{1c}$ <7.0% at week 26 and 52**




*p<0.05 for odds of achieving HbA1c <7.0% vs placebo; †p<0.05 for odds of achieving HbA1c <7.0% vs liraglutide.

# Overview of results from the PIONEER programme

## 7.10.5 Safety

- The proportion of patients with adverse events during the on-treatment period was similar across the oral semaglutide groups (71–76%), slightly greater in the placebo group (80%) compared with the oral semaglutide groups, and slightly lower in the liraglutide group (67%) (Table 19)
- The incidence of serious adverse events was generally low. No deaths were reported
- The majority of AEs were mild to moderate in severity
- Across all treatment groups, the most frequently reported adverse event during the on-treatment period was nasopharyngitis
  - GI disorders were the second most frequently reported class of adverse events
- AEs leading to premature trial product discontinuation occurred in four patients, one each in the oral semaglutide 3 mg and 7 mg groups, and two in the 14 mg group

### Table 19. Overview of AEs

| | Oral semaglutide 3 mg n=49 | Oral semaglutide 7 mg n=49 | Oral semaglutide 14 mg n=48 | Placebo n=49 | Liraglutide 0.9 mg n=48 |
|---|---|---|---|---|---|
| **AEs** | 37 (76) | 37 (76) | 34 (71) | 39 (80) | 32 (67) |
| **SAEs** | 2 (4) | 3 (6) | 0 | 3 (6) | 0 |
| **AEs leading to premature trial product discontinuation** | 1 (2) | 1 (2) | 2 (4) | 0 | 0 |
| **AEs by severity** | | | | | |
| **Mild** | 35 (71) | 35 (71) | 33 (69) | 37 (76) | 31 (65) |
| **Moderate** | 3 (6) | 5 (10) | 4 (8) | 8 (16) | 2 (4) |
| **Severe** | 1 (2) | 2 (4) | 0 | 0 | 0 |
| **GI disorder AEs** | | | | | |
| **Constipation** | 5 (10) | 6 (12) | 6 (13) | 3 (6) | 9 (19) |
| **Nausea** | 2 (4) | 5 (10) | 4 (8) | 1 (2) | 0 |
| **Diarrhoea** | 4 (8) | 1 (2) | 3 (6) | 1 (2) | 2 (4) |
| **Severe or BG-confirmed symptomatic hypoglycaemic events*** | 0 | 0 | 0 | 0 | 2 (4) |
| **Severe hypoglycaemic events*** | 0 | 0 | 0 | 0 | 0 |
| **Deaths** | 0 | 0 | 0 | 0 | 0 |

Data are n (%). The n number indicates the number of patients with at least one event.
*Severe (according to ADA classification) or BG-confirmed (<56 mg/dL [3.1 mmol/L]) symptomatic episodes.





## 7.10.6 Summary

- In this study conducted in Japanese patients with T2D, oral semaglutide monotherapy reduced $HbA_{1c}$ in a dose-dependent manner

  Significantly greater reductions from baseline in $HbA_{1c}$ were seen at week 26 with all oral semaglutide doses studied compared with placebo, and with oral semaglutide 14 mg compared with liraglutide 0.9 mg

- Furthermore, reductions from baseline in body weight at week 26 were significantly greater with oral semaglutide 14 mg compared with placebo, and for oral semaglutide 7 and 14 mg compared with liraglutide

  Changes in $HbA_{1c}$ and body weight with oral semaglutide were maintained to week 52

  Oral semaglutide was well tolerated and demonstrated a safety and tolerability profile consistent with liraglutide and that of other GLP-1RAs

# Overview of results from the PIONEER programme

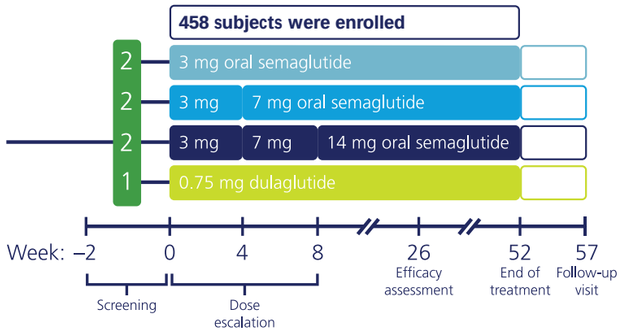
## 7.11 PIONEER 10: oral semaglutide versus dulaglutide in Japanese patients[12]

- PIONEER 10 (NCT03015220) compared the safety and efficacy of three doses of oral semaglutide versus dulaglutide 0.75 mg in combination with one OAD in Japanese patients with T2D (Figure 47)

**Figure 47. Trial design**

### Key inclusion criteria

- Age ≥20 years
- T2D ≥60 days
- Stable doses of one OAD (SU, glinide, TZD, a-GI or SGLT2i) for ≥60 days
- $HbA_{1c}$ 7.0–10.5% (53–91 mmol/mol)




### Trial information

- A multicentre, randomised, open-label, active-controlled, parallel-group, phase 3a trial with four arms

### Primary endpoint

- Number of treatment-emergent AEs at week 57

### Key secondary endpoints

- Change from baseline to week 52 in $HbA_{1c}$ and body weight
- Change in other parameters of efficacy, safety and tolerability





## 7.11.1 Baseline characteristics

- Baseline demographics and disease characteristics were similar between treatment groups (Table 20)

**Table 20. Baseline characteristics**

| | Oral semaglutide 3 mg n=131 | Oral semaglutide 7 mg n=132 | Oral semaglutide 14 mg n=130 | Dulaglutide 0.75 mg n=65 |
|---|---|---|---|---|
| **Age, years** | 59 (10) | 58 (11) | 57 (10) | 61 (9) |
| **Female, %** | 31 (24) | 42 (32) | 30 (23) | 14 (22) |
| **$HbA_{1c}$, %** | 8.2 (0.9) | 8.3 (0.9) | 8.4 (1.0) | 8.4 (0.9) |
| **Diabetes duration, years** | 9.4 (6.3) | 9.3 (6.3) | 9.1 (6.4) | 9.9 (6.3) |
| **FPG, mmol/L*** | 9.0 (1.9) | 9.2 (2.0) | 9.4 (2.1) | 9.5 (2.1) |
| **FPG, mg/dL*** | 161.9 (34.0) | 165.3 (36.7) | 168.5 (37.6) | 171.1 (37.3) |
| **Body weight, kg** | 71.5 (16.0) | 72.7 (16.4) | 72.6 (15.2) | 71.2 (14.3) |
| **BMI, kg/m²** | 25.8 (4.5) | 26.8 (5.0) | 26.3 (5.2) | 26.0 (4.0) |

Data are mean (SD) unless otherwise stated.
*FPG conversion factor: 1 mg/dL = 0.0555 mmol/L.

## 7.11.2 Safety and tolerability

- IThe primary endpoint was the number of AEs during exposure to trial product, assessed up to approximately 57 weeks
- A similar proportion of patients in each group experienced AEs (Table 21)
  - In addition, the rate of AEs was similar across treatment groups: 238, 254 and 243 events per 100 patient years of exposure in the oral semaglutide 3-, 7- and 14-mg groups, respectively, and 262 per 100 patient years of exposure in the dulaglutide group
- SAEs were reported by nine (7%) of 131 patients with oral semaglutide 3 mg, four (3%) of 132 patients with oral semaglutide 7 mg, seven (5%) of 130 patients with oral semaglutide 14 mg, and one (2%) of 65 patients with dulaglutide
  - SAEs were distributed across multiple system organ classes, without any clustering or dose response in the oral semaglutide groups, and only one event led to premature study drug discontinuation (rectal adenocarcinoma in the oral semaglutide 3 mg group)

# Overview of results from the PIONEER programme

- The majority of AEs were mild or moderate in severity, with few severe AEs
- Overall, infections and infestations were the most common form of AEs by system organ class, followed by GI AEs
- GI AEs were reported in a greater proportion of patients in the oral semaglutide 14-mg group than in the oral semaglutide 3- and 7-mg and dulaglutide groups
- The most commonly reported GI AEs were constipation and nausea
- Proportions of patients with AEs leading to premature trial product discontinuation were 3% for oral semaglutide 3 mg, 6% for oral semaglutide 7 and 14 mg and 3% for dulaglutide 0.75 mg
- There were no deaths during either the on-treatment or in-trial observation periods
- There were no cases of severe hypoglycaemia during the on-treatment period. BG-confirmed symptomatic hypoglycaemia was reported in 2–3% of patients in the oral semaglutide groups and no events occurred in dulaglutide-treated patients
  - All except one of the BG-confirmed symptomatic hypoglycaemic events occurred in patients treated with SU

### Table 21. Overview of AEs

| | Oral semaglutide 3 mg n=131 | Oral semaglutide 7 mg n=132 | Oral semaglutide 14 mg n=130 | Dulaglutide 0.75 mg n=65 |
|---|---|---|---|---|
| **AEs** | 101 (77) | 106 (80) | 111 (85) | 53 (82) |
| **SAEs** | 9 (7) | 4 (3) | 7 (5) | 1 (2) |
| **AEs leading to premature trial product discontinuation** | 4 (3) | 8 (6) | 8 (6) | 2 (3) |
| **AEs by severity** | | | | |
| **Mild** | 98 (75) | 105 (80) | 109 (84) | 53 (82) |
| **Moderate** | 15 (11) | 9 (7) | 12 (9) | 1 (2) |
| **Severe** | 3 (2) | 1 (1) | 1 (1) | 0 |
| **GI disorder AEs** | 40 (31) | 51 (39) | 70 (54) | 26 (40) |
| **Constipation** | 12 (9) | 16 (12) | 20 (15) | 6 (9) |
| **Nausea** | 7 (5) | 11 (8) | 12 (9) | 6 (9) |
| **Diarrhoea** | 2 (2) | 2 (2) | 10 (8) | 4 (6) |
| **Vomiting** | 3 (2) | 1 (1) | 9 (7) | 1 (2) |
| **Severe or BG-confirmed symptomatic hypoglycaemic events*** | 3 (2) | 3 (2) | 4 (3) | 0 |
| **Severe hypoglycaemic events*** | 0 | 0 | 0 | 0 |
| **Deaths** | 0 | 0 | 0 | 0 |

Data are n (%). The n number indicates the number of patients with at least one event.
*Severe (according to ADA classification) or BG-confirmed (<56 mg/dL [3.1 mmol/L]) symptomatic episodes.

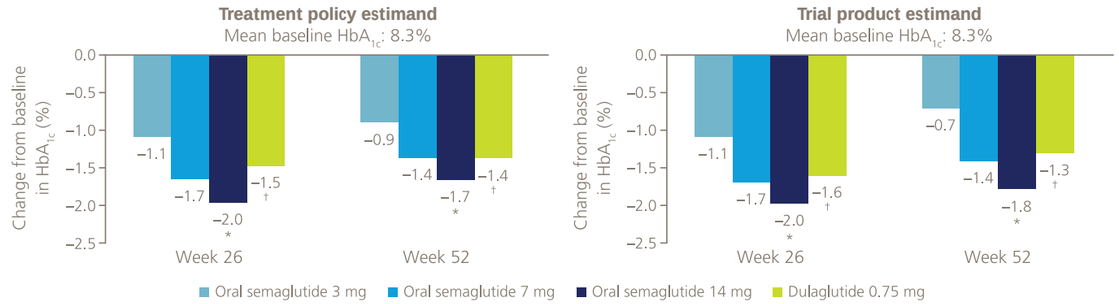




## 7.11.3 Efficacy: change in $HbA_{1c}$

- $HbA_{1c}$ decreased from baseline through week 20 in all treatment groups
- For the treatment policy estimand, the estimated reduction in $HbA_{1c}$ from baseline was significantly greater with oral semaglutide 14 mg compared with dulaglutide at weeks 26 and 52, not significantly different between oral semaglutide 7 mg and dulaglutide at either timepoint, and significantly less with oral semaglutide 3 mg compared with dulaglutide at both timepoints (Figure 48)
  - ETDs at week 26 were 0.4% [0.1, 0.7] (p<0.05 favouring dulaglutide), –0.1% [–0.4, 0.1] (p=0.27) and –0.4% [–0.7, –0.2] (p<0.001 favouring oral semaglutide) for oral semaglutide 3, 7 and 14 mg, respectively, versus dulaglutide
- Similar results were seen for the trial product estimand at both timepoints (Figure 48)

### Figure 48. Estimated mean change from baseline in $HbA_{1c}$ at weeks 26 and 52



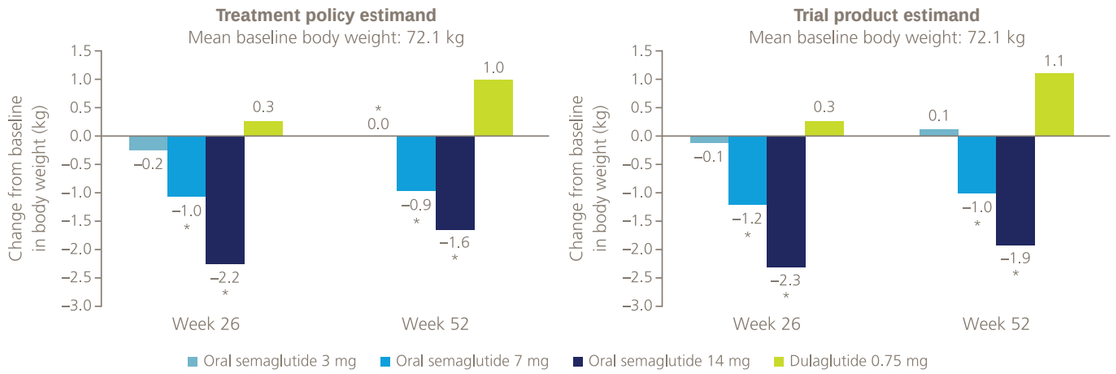

*p<0.05 vs dulaglutide 0.75 mg for the ETD; †p<0.05 vs oral semaglutide 3 mg for the ETD.

# Overview of results from the PIONEER programme

## 7.11.4 Efficacy: change in body weight

- Oral semaglutide 7 and 14 mg were associated with significantly greater reductions in body weight from baseline compared with dulaglutide in the treatment policy estimand at week 26 and week 52 (Figure 49)
  - At week 26, ETDs were –1.3 kg [–2.2, –0.5] and –2.5 kg [–3.3, –1.7] for oral semaglutide 7 mg and 14 mg, respectively, versus dulaglutide (p<0.05 for both)
- At the end of treatment (week 52), estimated changes from baseline in body weight were significantly greater with all oral semaglutide doses compared with dulaglutide in the treatment policy estimand (Figure 49)
- Similar results were seen for the trial product estimand, but the difference between oral semaglutide 3 mg and dulaglutide did not reach statistical significance at week 52 (Figure 49)

**Figure 49. Estimated mean change from baseline in body weight at weeks 26 and 52**



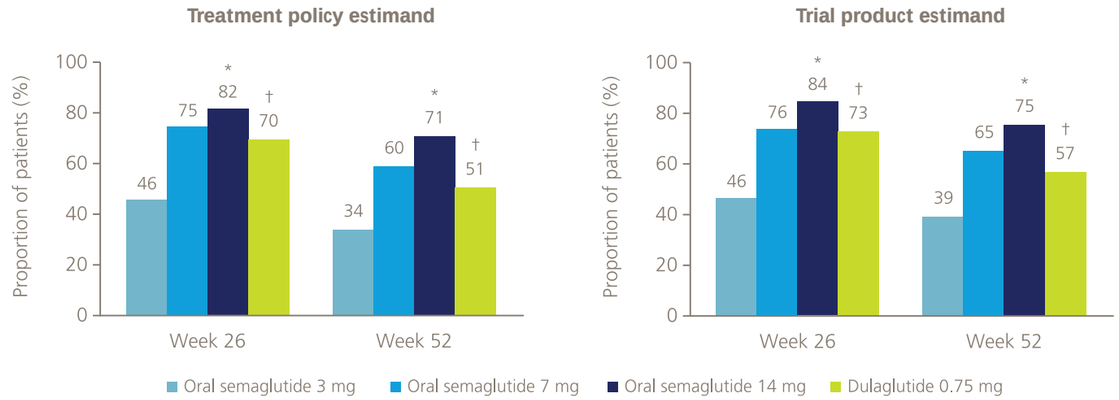

*p<0.05 vs dulaglutide for the ETDs.



## 7.11.5 Efficacy: other secondary endpoints

- When compared with dulaglutide, the odds of achieving $HbA_{1c}$ target of <7.0% at weeks 26 and 52 were significantly greater with oral semaglutide 14 mg and significantly lower with oral semaglutide 3 mg, with no significant difference versus oral semaglutide 7 mg, for both estimands (Figure 50)
- For the treatment policy estimand, the odds of achieving body weight reduction ≥5% at week 26 were significantly greater with oral semaglutide 7 mg (p<0.05) and 14 mg (p<0.001) versus dulaglutide 0.75 mg; the odds remained significantly greater at week 52 for oral semaglutide 14 mg (p<0.05). Similar results were found for the trial product estimand at both timepoints for oral semaglutide 7 mg and 14 mg (Figure 50)

**Figure 50. Observed proportions of patients achieving the target of $HbA_{1c}$ <7.0% at weeks 26 and 52**




*p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs dulaglutide; †p<0.05 for odds of achieving $HbA_{1c}$ <7.0% vs oral semaglutide 3 mg.

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# Overview of results from the PIONEER programme

## 7.11.6 Summary

- Among Japanese patients with T2D receiving one background OAD, treatment with oral semaglutide 3, 7 and 14 mg for 52 weeks had a similar tolerability profile to dulaglutide 0.75 mg, with similar overall rates of AEs and dose-dependent occurrence of GI AEs
- Significantly greater reductions in both HbA1c and body weight were seen with oral semaglutide 14 mg compared with dulaglutide 0.75 mg
  - Oral semaglutide 7 mg provided similar glycaemic control and significantly greater reductions in body weight compared with dulaglutide 0.75 mg
- Patients treated with oral semaglutide 14 mg were significantly more likely to achieve the HbA1c target <7.0% than with dulaglutide 0.75 mg

## 7.12 Summary of the PIONEER trial programme

- Global PIONEER trials achieved their primary objective of demonstrating HbA1c reductions with oral semaglutide 14 mg that were either superior (placebo, empagliflozin and sitagliptin) or non-inferior (liraglutide) to comparators at week 26
- In the global trials, superior and significant reductions in body weight were observed when oral semaglutide 14 mg was compared with placebo, sitagliptin and liraglutide; similar body weight reductions were seen versus empagliflozin at week 26
- Results were consistent when flexible dose adjustment of oral semaglutide, reflecting a real-world dose setting, was investigated versus sitagliptin in the PIONEER 7 trial
- In all trials, oral semaglutide was well tolerated, with a profile consistent with other GLP-1RAs
- There were no unexpected safety concerns across the trial populations, including patients with moderate renal impairment
- Oral semaglutide demonstrated a favourable CV safety profile and reduction in CV death and all-cause mortality versus placebo, both in addition to standard care, in the PIONEER 6 trial
- In the Japanese PIONEER trials, oral semaglutide 14 mg demonstrated greater reductions in HbA1c and body weight versus liraglutide (0.9 mg) or dulaglutide (0.75 mg). Oral semaglutide was well tolerated in Japanese patients with comparable numbers of AEs observed with oral semaglutide versus dulaglutide and a safety profile consistent with injectable GLP-1RAs

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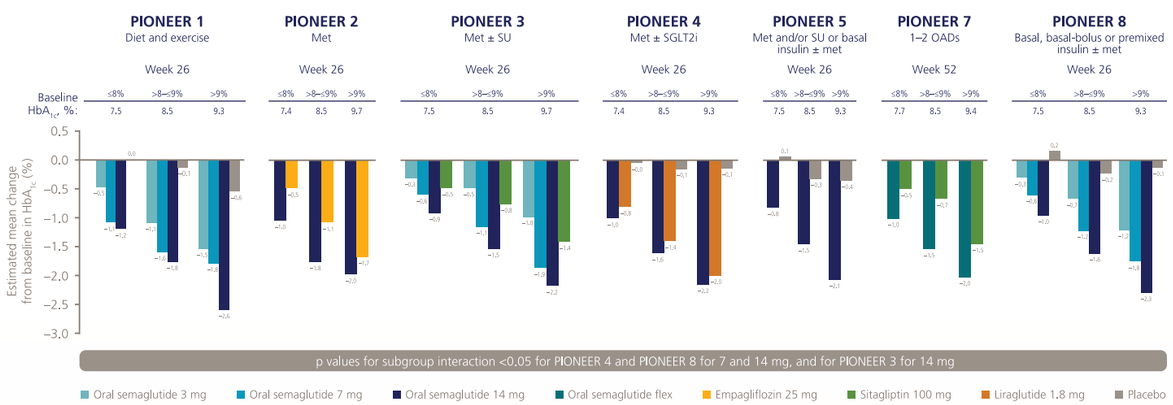
# PIONEER TRIAL PROGRAMME *POST-HOC* ANALYSES

## 8.1 Efficacy of oral semaglutide by baseline $HbA_{1c}$ [1]

- An exploratory subgroup analysis of the PIONEERprogramme evaluated the effect of baseline $HbA_{1c}$ on the overall $HbA_{1c}$ and body weight reductions in patients with T2D
  - Methods: data were included from all patients who participated in PIONEER 1–5, 7 and 8 (n=5,657). In each trial, patients were categorised into three groups based on baseline HbA1c (≤8.0%, >8.0–≤9.0% and >9.0%). Endpoints were change from baseline in HbA1c and body weight at week 26 (week 52 in PIONEER 7), using the trial product estimand
- Overall, the post-hoc analysis on baseline $HbA_{1c}$ showed that oral semaglutide improved glycaemic control with greater HbA1c reductions with oral semaglutide 7 and 14 mg versus comparators across subgroups (Figure 1). $HbA_{1c}$ reductions were greater with higher baseline $HbA_{1c}$, which was supported by a pooled analysis of the placebo-controlled trials

### Figure 1. Change from baseline in $HbA_{1c}$ by baseline HbA1c subgroup in PIONEER 1–5, 7 and 8

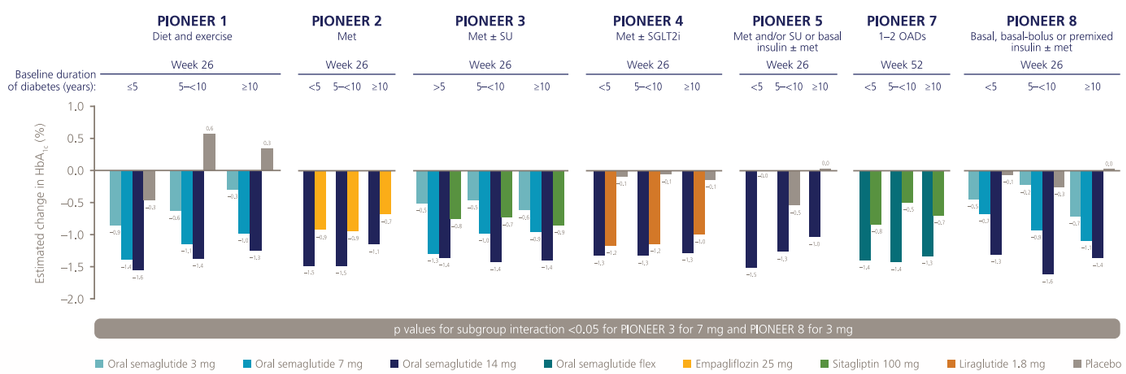



Analysis based on the trial product estimand, using mixed model for repeated measurements.

## 8.2 Efficacy of oral semaglutide by baseline duration of T2D [2]

- An exploratory subgroup analysis of the PIONEER programme evaluated the effect of baseline diabetes duration on the overall $HbA_{1c}$ and body weight reductions in patients with T2D
  - Methods: data were included from all patients who participated in PIONEER 1–5, 7 and 8 (n=5,657). In each trial, patients were categorised into three groups based on baseline diabetes duration (<5, 5–<10 and ≥10 years). Endpoints were change from baseline in $HbA_{1c}$ and body weight at week 26 (week 52 in PIONEER 7), using the trial product estimand
- Overall, this post-hoc analysis showed that the efficacy of oral semaglutide in reducing $HbA_{1c}$ and body weight was unaffected by baseline diabetes duration, with only a few exceptions that did not show a clear pattern (Figure 2). These findings support that oral semaglutide can be used in a broad patient population

### Figure 2. Change from baseline in $HbA_{1c}$ by diabetes duration in PIONEER 1–5, 7 and 8




Analysis based on the trial product estimand, using mixed model for repeated measurements.

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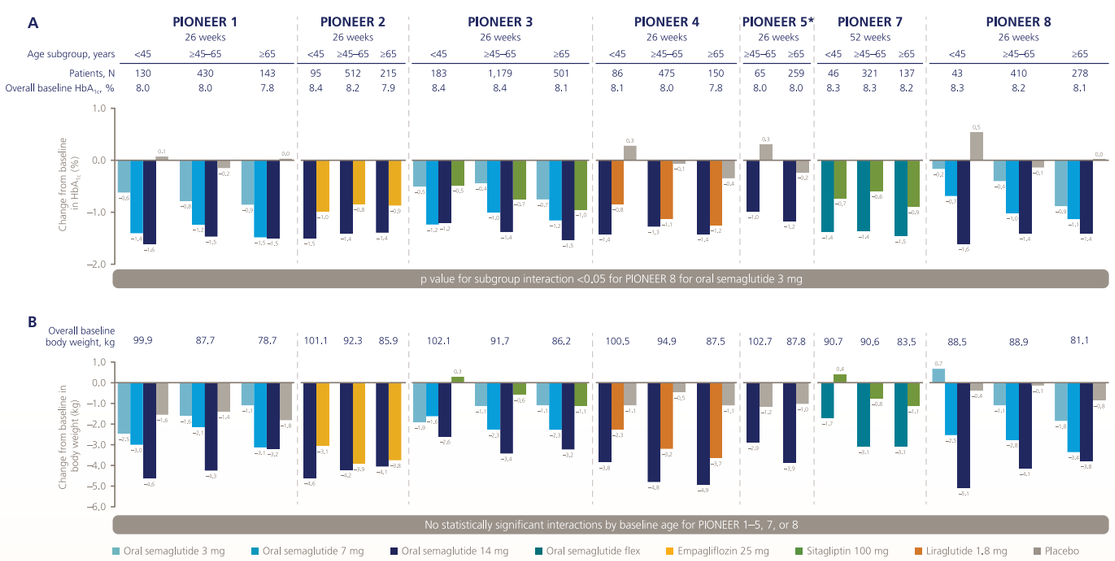
# PIONEER TRIAL PROGRAMME *POST-HOC* ANALYSES

## 8.3 Efficacy and safety of oral semaglutide by baseline age[3]

- An exploratory analysis of the PIONEER trial programme evaluated the effect of age at baseline on efficacy and safety in patients with T2D
  - Methods: data were included from all patients who participated in PIONEER 1–5, 7 and 8 (n=5,657). In each trial, patients were categorised into three groups based on age at baseline (<45, ≥45–<65, and ≥65 years). HbA1c and body weight were assessed at the time of the primary endpoint analysis (week 26 for PIONEER 1–5 and 8, and week 52 for PIONEER 7) using the trial product estimand. Safety was assessed for the on-treatment period
- Treatment with oral semaglutide reduced $HbA_{1c}$ and body weight in a dose-dependent manner, regardless of age at baseline (Figure 3A and B). Reductions in $HbA_{1c}$ and body weight within each trial were generally greater with oral semaglutide vs comparators (Figure 3A and B). Proportions of patients with AEs were similar irrespective of age. There was a generally higher discontinuation rate in older patients

### Figure 3. Change from baseline in (A) HbA1c and (B) body weight by age at baseline in PIONEER 1–5, 7 and 8

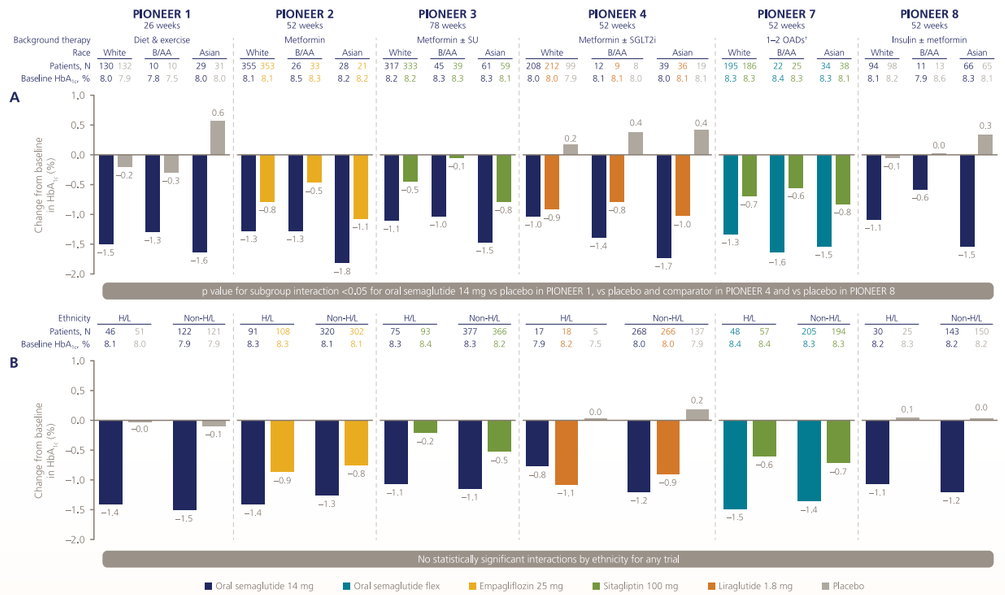



*There were no patients in the <45 years subgroup in PIONEER 5.
Analysis based on the trial product estimand, using mixed model for repeated measurements. The p value is for the unadjusted two-sided test of treatment by subgroup interaction.

## 8.4 Efficacy and safety of oral semaglutide by race and ethnicity[4]

- An exploratory analysis of the PIONEER trial programme evaluated the effect of race and ethnicity on efficacy and safety in patients with T2D
  - Methods: data were included from all patients who participated in PIONEER 1–4, 7 and 8. Patients were grouped by race and ethnicity. $HbA_{1c}$ and body weight were assessed at the end of treatment (week 26, 52 or 78) for the trial product estimand. Safety was assessed for the on-treatment period and pooled across all trials
- Oral semaglutide 14 mg/flex provided clinically relevant reductions in HbA1c and body weight in patients with T2D regardless of race or ethnicity (Figure 4A and B). These reductions were greater with oral semaglutide 14 mg/flex than with comparators, and there was a significant treatment interaction favouring a greater response with oral semaglutide treatment in Asian patients in the placebo-controlled trials (Figure 4A and B). Tolerability was generally comparable for oral semaglutide across race and ethnicity subgroups

### Figure 4. Change from baseline in $HbA_{1c}$ by (A) race subgroup and (B) ethnicity subgroup




p value is for the unadjusted two-sided test of treatment by subgroup interaction. †OADs could include met, SU, SGLT2i or TZD
B/AA, Black/African American; H/L, Hispanic/Latino.

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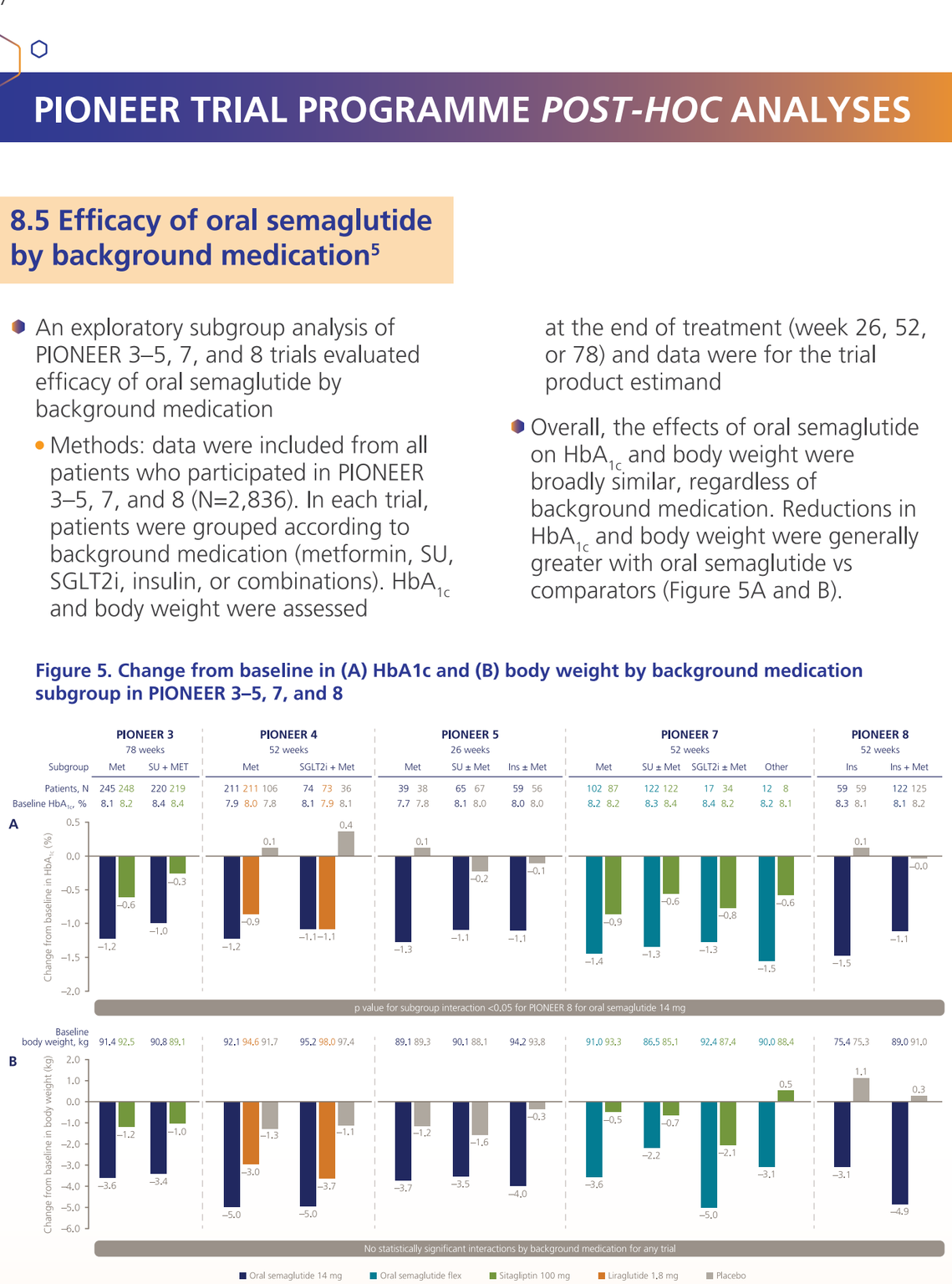
# PIONEER TRIAL PROGRAMME *POST-HOC* ANALYSES

## 8.5 Efficacy of oral semaglutide by background medication[5]

- An exploratory subgroup analysis of PIONEER 3–5, 7, and 8 trials evaluated efficacy of oral semaglutide by background medication
  - Methods: data were included from all patients who participated in PIONEER 3–5, 7, and 8 (N=2,836). In each trial, patients were grouped according to background medication (metformin, SU, SGLT2i, insulin, or combinations). $HbA_{1c}$ and body weight were assessed at the end of treatment (week 26, 52, or 78) and data were for the trial product estimand
- Overall, the effects of oral semaglutide on $HbA_{1c}$ and body weight were broadly similar, regardless of background medication. Reductions in $HbA_{1c}$ and body weight were generally greater with oral semaglutide vs comparators (Figure 5A and B).

**Figure 5. Change from baseline in (A) HbA1c and (B) body weight by background medication subgroup in PIONEER 3–5, 7, and 8**

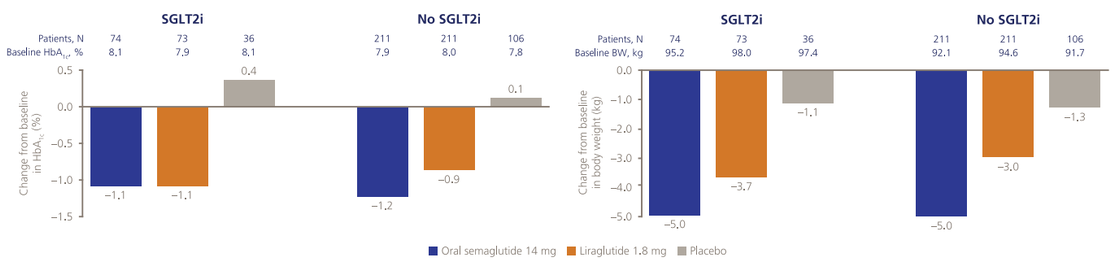



Analysis based on the trial product estimand, using a mixed model for repeated measurements. The p value is for the unadjusted two-sided test of treatment by subgroup interaction.

## 8.6 Effect of oral semaglutide with or without background SGLT2i in PIONEER 4[6]

- A post-hoc subgroup analysis of the 52-week, randomised, double-blind, double-dummy PIONEER 4 assessed the efficacy and tolerability of oral semaglutide in patients with or without background SGLT2i use
  - Methods: patients with T2D uncontrolled on metformin with or without SGLT2i were randomised 2:2:1 to once-daily oral semaglutide 14 mg (n=285), subcutaneous liraglutide 1.8 mg (n=284), or placebo (n=142). $HbA_{1c}$ and body weight changes from baseline at week 52 were analysed by background SGLT2i use for the trial product estimand. Safety was assessed for the on-treatment period
- Improvements in $HbA_{1c}$ and body weight, were similar at week 52 in patients with T2D treated with GLP-1RA, with or without background SGLT2i. The safety profile for patients treated with GLP-1RA was similar regardless of background SGLT2i use (Figure 6A and B)

**Figure 6. Change from baseline in (A) $HbA_{1c}$ and (B) body weight at week 52 by background SGLT2i use**




Data are estimated means for the trial product estimand and analysed using a mixed model for repeated measurements model.
N, total number of patients in each subgroup (full analysis population); BW, body weight.

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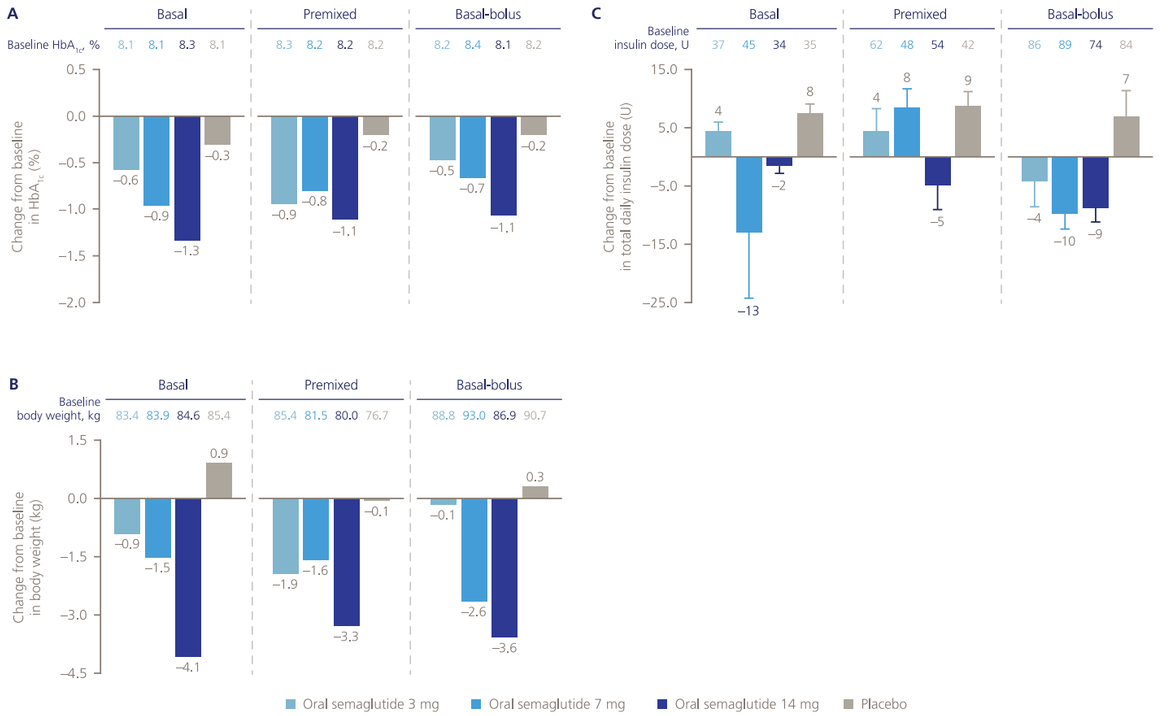
## 8.7 Efficacy and safety of oral semaglutide by background insulin regimen[7]

- An exploratory analysis of the 52-week, randomised, double-blind, placebo-controlled PIONEER 8 trial evaluated the effect of background insulin regimen on the efficacy and safety of oral semaglutide in patients with T2D
  - Methods: data were included from all patients who participated in PIONEER 8 and were receiving insulin therapy ± metformin. Patients were categorised into three groups based on background insulin regimen (basal [n=310], premixed [n=135], and basal-bolus [n=286]). Change from baseline in HbA1c and body weight were assessed at week 52 using the treatment policy estimand. Safety was assessed for the on-treatment period
- Overall, oral semaglutide reduced $HbA_{1c}$ and body weight in a dose-dependent manner, and reduced insulin requirement compared with placebo, regardless of background insulin regimen (Figure 7A, B and C). The safety profile of oral semaglutide was consistent with that of the GLP-1RA class





**Figure 7. Change from baseline in (A) $HbA_{1c}$, (B) body weight and (C) total daily insulin dose at week 52 by basal, premixed, or basal-bolus insulin regimen**

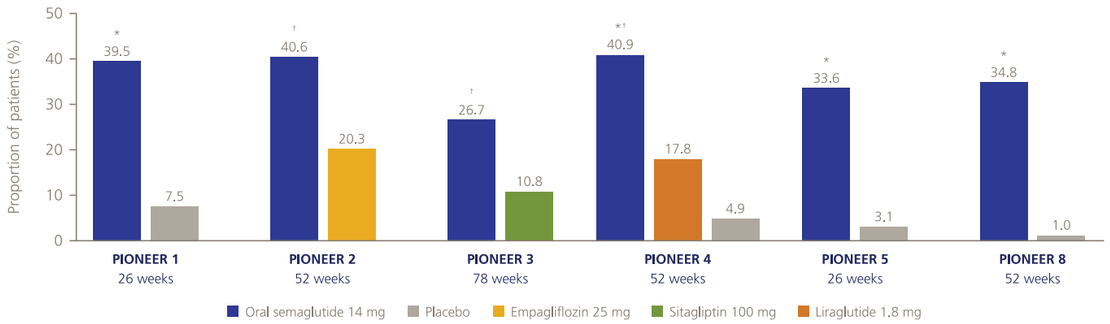



Analysis based on the treatment policy estimand, using an analysis of covariance model.

## 8.8 Glycaemic and body weight responses to oral semaglutide in the PIONEER trial programme[8]

- A post-hoc analysis evaluated the clinical response to oral semaglutide and comparators across several PIONEER trials
  - Methods: data were included from all participants of the PIONEER 1–5, and 8 trials on once-daily oral semaglutide 14 mg or a comparator (placebo, empagliflozin 25 mg, sitagliptin 100 mg, or liraglutide 1.8 mg) (N=3,506)
- The proportions of patients with any reduction in both HbA1c and body weight were greater with oral semaglutide 14 mg compared with placebo or sitagliptin. Patients were more likely to achieve both an HbA1c reduction of ≥1% and a body weight loss of ≥5% with oral semaglutide 14 mg than with any comparators (Figure 8)

**Figure 8. Patients achieving an HbA1c reduction of ≥1% and body weight loss of ≥5%**




Data are observed proportions for the trial product estimand.
*p<0.05 for the EOR in favour of oral semaglutide 14 mg vs placebo. †p<0.05 for the EOR in favour of oral semaglutide 14 mg vs the active comparator.
EOR, estimated odds ratio.





## References

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2. Haluzik M, et al. Efficacy and safety of oral semaglutide according to diabetes duration: an exploratory subgroup analysis of the PIONEER trial programme. European Association for the Study of Diabetes, 55th Annual Meeting 2019. Abstract 49.

3. Aroda VR, et al. Efficacy and safety of oral semaglutide by baseline age in the PIONEER clinical trial program. American Diabetes Association, 80th Scientific Sessions Virtual Meeting, 2020. Abstract 932-P.

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7. Mosenzon O, et al. Efficacy and safety of oral semaglutide when added to basal, premixed, or basal-bolus insulin. American Diabetes Association, 80th Scientific Sessions Virtual Meeting, 2020. Abstract 956-P.

8. Dungan KM, et al. Glycemic and body weight responses to oral semaglutide in the PIONEER trial program. American Diabetes Association 80th Scientific Sessions Virtual Meeting, 2020. Abstract 964-P.

# PIONEER 6 AND SUSTAIN 6 POOLED ANALYSES

## 9.1 CV safety: pooled analysis of SUSTAIN 6 + PIONEER 6[1]

- PIONEER 62 has been described in detail in Section 7.9. SUSTAIN 63 (NCT01720446) had a similar design to PIONEER 6, and was conducted to confirm that treatment with s.c. semaglutide does not result in an unacceptable increase in CV risk compared with placebo, as described in Section 3.2
  - Both trials were conducted in patients with T2D at high risk of CV events: aged ≥50 years with established CV and/or chronic kidney disease or aged ≥60 years with ≥1 CV risk factors.2,3 In SUSTAIN 6, patients could also have CHF[3]
- SUSTAIN 6 completed in March 2016 after the accumulated occurrence of 254 primary MACEs (CV death, non-fatal MI and non-fatal stroke) and a median follow-up time of 2.1 years[3]
- There were two key differences between PIONEER 6 and SUSTAIN 6: i) PIONEER 6 was solely event-driven (≥122 primary outcome events),2 whereas SUSTAIN 6 was time- and event-driven (≥104 weeks' exposure and ≥122 primary outcome events);3 and ii) PIONEER 6 was a 2-armed trial (oral semaglutide target dose 14 mg and placebo),2 while SUSTAIN 6 was a 4-armed trial (s.c. semaglutide 0.5 and 1.0 mg, and volumematched placebo), with primary analysis performed on pooled semaglutide and placebo groups[3]

## 9.1.1 Baseline characteristics

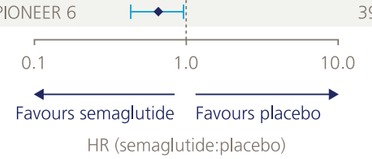
- Baseline characteristics of the pooled PIONEER 6 and SUSTAIN 6 population (Total: N=6,480; semaglutide group [s.c. or oral]: N=3,239; placebo group: N=3,241) and CV risk subgroups, individually and as a combined population, were well-balanced between groups[1]

## 9.1.2 CV outcomes: PIONEER 6 and SUSTAIN 6 pooled analysis

- In the pooled PIONEER 6 and SUSTAIN 6 population, the incidence rates of MACE were 3.1 and 4.2 events per 100 patient years with semaglutide and placebo, respectively (HR 0.76 [95% CI 0.62, 0.92]) (Figure 1)[1]
  - The HRs for each of the individual components of MACE were all <1.0, although the upper limit of the 95% CI was <1.0 for non-fatal stroke only[1]

**Figure 1. Forest plot for CV outcomes[1]**

| | | Time to first event | No. of events/analysed patients (incidence rate per 100 patient-years) Semaglutide | Placebo | HR | [95% CI] |
|---|---|---|---|---|---|---|
| MACE | SUSTAIN 6 | | 108/1,648 (3.2) | 146/1,649 (4.4) | 0.74 | [0.58, 0.95] |
| | PIONEER 6 | | 61/1,591 (2.9) | 76/1,592 (3.7) | 0.79 | [0.57, 1.11] |
| | SUSTAIN 6 + PIONEER 6 | | 169/3,239 (3.1) | 222/3,241 (4.2) | 0.76 | [0.62, 0.92] |
| CV death | SUSTAIN 6 | | 44/1,648 (1.3) | 46/1,649 (1.4) | 0.98 | [0.65, 1.48] |
| | PIONEER 6 | | 15/1,591 (0.7) | 30/1,592 (1.4) | 0.49 | [0.27, 0.92] |
| | SUSTAIN 6 + PIONEER 6 | | 59/3,239 (1.1) | 76/3,241 (1.4) | 0.78 | [0.56, 1.10] |
| Non-fatal MI | SUSTAIN 6 | | 47/1,648 (1.4) | 64/1,649 (1.9) | 0.74 | [0.51, 1.08] |
| | PIONEER 6 | | 37/1,591 (1.8) | 31/1,592 (1.5) | 1.18 | [0.73, 1.90] |
| | SUSTAIN 6 + PIONEER 6 | | 84/3,239 (1.5) | 95/3,241 (1.8) | 0.88 | [0.66, 1.18] |
| Non-fatal stroke | SUSTAIN 6 | | 27/1,648 (0.8) | 44/1,649 (1.3) | 0.61 | [0.38, 0.99] |
| | PIONEER 6 | | 12/1,591 (0.6) | 16/1,592 (0.8) | 0.74 | [0.35, 1.57] |
| | SUSTAIN 6 + PIONEER 6 | | 39/3,239 (0.7) | 60/3,241 (1.1) | 0.65 | [0.43, 0.97] |




Subcutaneous Semaglutide once weekly injection is not approved/marketed in India

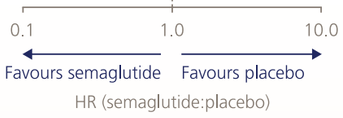
# PIONEER 6 AND SUSTAIN 6 POOLED ANALYSES

## 9.1.3 CV outcomes: stratification by CV risk subgroup[1]

- Incidence rates and HRs [95% CIs] for the effects of semaglutide versus placebo on MACE in each CV risk subgroup in PIONEER 6 and SUSTAIN 6 combined are shown in Figure 2
  - In the combined population, HRs for MACE were <1.0 in each CV risk subgroup, except for patients with prior HF (HR 1.06 [95% CI 0.72, 1.57])
  - The 95% CIs spanned 1.0 for the following subgroups: CV risk factors only, prior MI or stroke, and prior HF
  - The p values for interaction of the presence of CVD and/or CKD at baseline, and prior MI or stroke on MACE were not significant, suggesting no heterogeneity in treatment effects across these subgroups
  - The p value for interaction of prior HF was nominally significant (p=0.046), but this was not controlled for multiple comparisons 204

**Figure 2. Forest plot for CV outcomes overall and by CV risk subgroup[1]**

| SUSTAIN 6 + PIONEER 6 | | Time to first event | No. of events/analysed patients (incidence rate per 100 patient-years) Semaglutide | Placebo | HR | [95% CI] | Interaction p value |
|---|---|---|---|---|---|---|---|
| Total population | | | 169/3,239 (3.1) | 222/3,241 (4.2) | 0.76 | [0.62, 0.92] | |
| Evidence of CVD | Established CVD and/or CKD | | 155/2,703 (3.5) | 205/2,727 (4.6) | 0.75 | [0.61, 0.93] | 0.944 |
| | CV risk factors only | | 14/536 (1.5) | 17/514 (2.0) | 0.77 | [0.38, 1.57] | |
| By prior MI or stroke | Yes | | 107/1,366 (4.8) | 132/1,429 (5.8) | 0.83 | [0.64, 1.07] | 0.292 |
| | No | | 62/1,859 (2.0) | 90/1,800 (3.0) | 0.67 | [0.48, 0.92] | |
| Prior HF (NYHA Class II or III) | Yes | | 51/473 (6.4) | 49/488 (6.0) | 1.06 | [0.72, 1.57] | 0.046 |
| | No | | 116/2,747 (2.5) | 172/2,739 (3.8) | 0.67 | [0.53, 0.84] | |

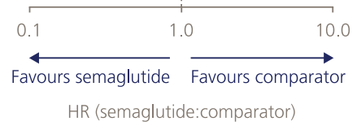



## 9.1.4 CV outcomes: pooled analysis of the PIONEER and SUSTAIN programmes

- To support the PIONEER 6 and SUSTAIN 6 pooled analysis, incidence rates for MACE were also analysed across the combined phase 3a glycaemic efficacy trials (SUSTAIN 1–5, two SUSTAIN JAPAN trials, and PIONEER 1–5 and 7–10), which compared semaglutide with placebo and active comparators in patients with T2D at a relatively low risk of CV events[4-19]
  - Incidence rates for MACE were 0.7 and 0.9 events per 100 patient years with semaglutide and comparator, respectively (HR 0.85 [95% CI 0.55, 1.33]) (Figure 3)[1]

**Figure 3. Forest plot for CV outcomes**

| | Time to first event | No. of events/analysed patients (incidence rate per 100 patient-years) Semaglutide | Comparator | HR | [95% CI] |
|---|---|---|---|---|---|
| SUSTAIN glycaemic efficacy trials | | 13/3,150 (0.4) | 8/1,657 (0.5) | 0.85 | [0.35, 2.06] |
| PIONEER glycaemic efficacy trials | | 42/4,119 (0.9) | 26/2,239 (1.1) | 0.84 | [0.50, 1.40] |
| SUSTAIN and PIONEER glycaemic efficacy trials | | 55/7,269 (0.7) | 34/3,896 (0.9) | 0.85 | [0.55, 1.33] |




## 9.1.5 Summary

- In this post-hoc pooled analysis of PIONEER 6 and SUSTAIN 6, semaglutide reduced the risk of MACE versus placebo in patients with T2D by 24%
- This effect was consistent across several clinically relevant subgroups of varying CV risk
- These findings are further supported by combined data from the PIONEER and SUSTAIN glycaemic efficacy trials
- Collectively, these analyses suggest CV benefits of semaglutide not only in those with a history of CVD, but also in lower CV risk subgroups, and irrespective of route of semaglutide administration

# PIONEER 6 AND SUSTAIN 6 POOLED ANALYSES

## 9.2 CV safety: effects of semaglutide across a continuum of baseline CV risk[20]

- Semaglutide has previously been found to reduce MACE (defined as CV death, non-fatal stroke or non-fatal MI) in patients with T2D and a high risk of CV events.[1] A post-hoc analysis of data from SUSTAIN and PIONEER phase 3 trials sought to better understand the effect of semaglutide on MACE in a broad range of patients with T2D from across the continuum of baseline CV risk, including low-to-medium risk[20]
  - Data from the SUSTAIN 1-6[3–8] and two Japanese trials[9,10] (s.c. semaglutide) and PIONEER 1-10[2,11–19] (oral semaglutide; see Chapter 7) were combined according to randomised treatment (semaglutide or comparators) and analysed to assess time to first MACE or to its individual components. A CV risk model was developed with independent data from the LEADER trial[21] (liraglutide vs placebo), considering baseline variables common to all datasets. Semaglutide data were analysed to assess effects of treatment as a function of CV risk predicted using the CV risk prediction model[20]

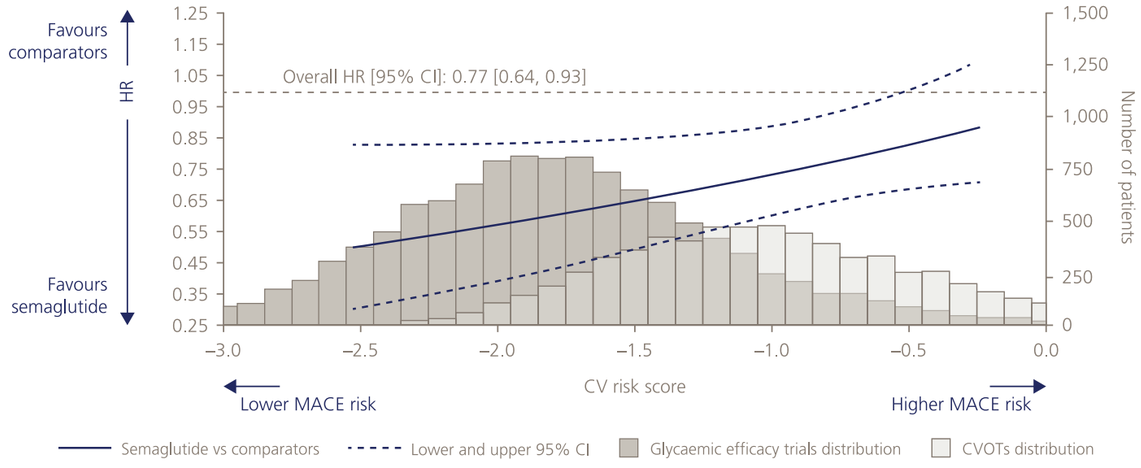
## 9.2.1 Baseline characteristics[20]

- The average CV risk score was lower in the pooled glycaemic efficacy trials (all trials other than the CVOTs) than in the pooled CVOTs but there was substantial overlap in the distributions (Figure 4). Age and the proportions of subjects with HF, prior ischaemic heart disease, prior MI, prior stroke or who used insulin, were higher in the CVOTs than in the pooled glycaemic efficacy trials. LDL-cholesterol, eGFR and the proportion of current smokers were higher in the glycaemic efficacy trials than in the CVOTs. HbA1c, systolic blood pressure and pulse rate were broadly similar between trials[20]

## 9.2.2 Relative MACE risk estimates for semaglutide vs comparators[20]

- The LEADER-derived CV risk prediction model indicated a fair predictive performance[20]
- The percentages of patients experiencing first MACE with semaglutide and comparators in CVOTs were 5.2% and 6.7%, respectively, and were 0.8% and 0.9% in glycaemic efficacy trials[20]
- There was a reduced relative risk of MACE with semaglutide vs comparators across the baseline CV risk continuum (Figure 4), with a non-significant interaction p value between CV risk score and treatment (p=0.06), and a trend towards the largest relative CV benefits (i.e., lower HRs) in those with the lowest CV risk score (i.e., lowest baseline CV risk)[20]

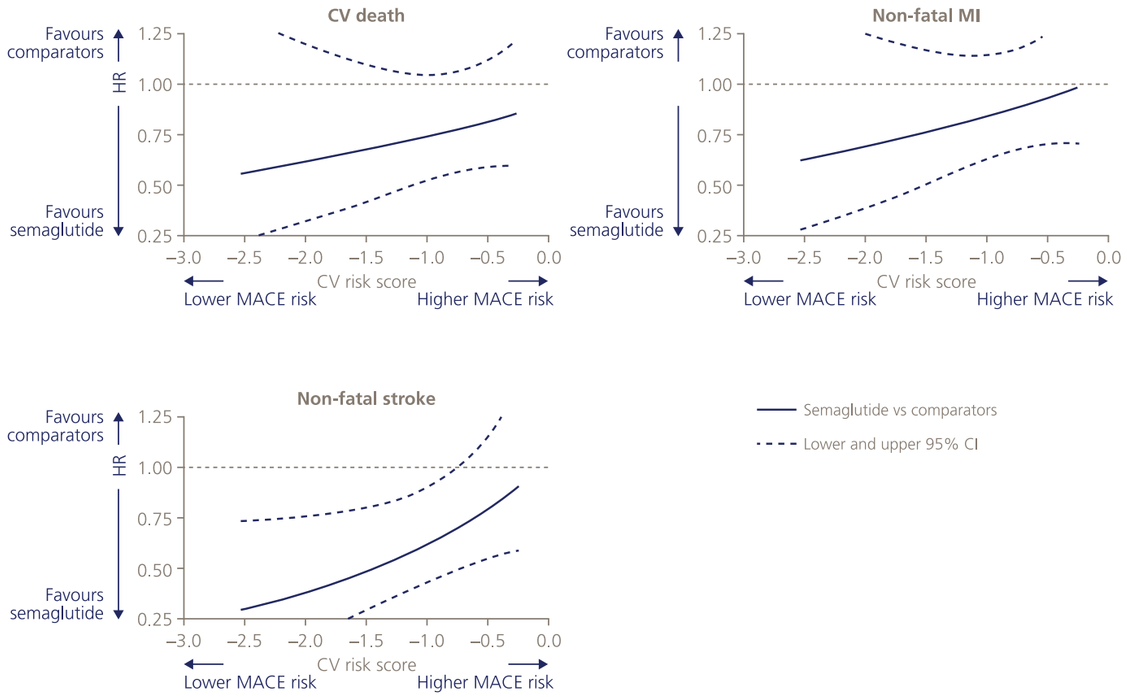
**Figure 4. Relative risk of MACE as a function of baseline CV risk and distribution of subjects[20]**




HR for treatment effect (semaglutide vs comparator) and 95% CI estimated using a stratified Cox proportional hazards model including effects of treatment, CV risk score and interaction between both. The x-axis shows the CV risk score derived from patients' baseline characteristics in the semaglutide trials. Data on graph cut off at the 5th and 95th percentile of the whole dataset. HR value of 1.00 is indicated by a horizontal dashed line. Underlying histograms: distribution of subjects in the glycaemic efficacy trials or CVOTs across baseline CV risk scores (histogram data for 439 subjects not shown, as these subjects had a CV risk score of <–3.0 or >0.0).

- The results for the individual MACE components are shown in Figure 5. The shapes of the individual MACE component HR curves were similar to that of the 3-point composite MACE endpoint, which indicates consistent findings across the components[20]

**Figure 5. Relative risk of each individual MACE component as a function of CV risk[20]**




HRs for treatment effect (semaglutide vs comparators) across all SUSTAIN and PIONEER trials analysed. HRs (semaglutide vs comparators) and 95% CIs estimated using a stratified Cox proportional hazards model including effects of treatment, CV risk score and interaction between both. The x-axis shows the CV risk score derived from patients' baseline characteristics in the semaglutide trials. Data on graph cut off at the 5th and 95th percentile of the whole dataset. HR value of 1.00 is indicated by a horizontal dashed line.

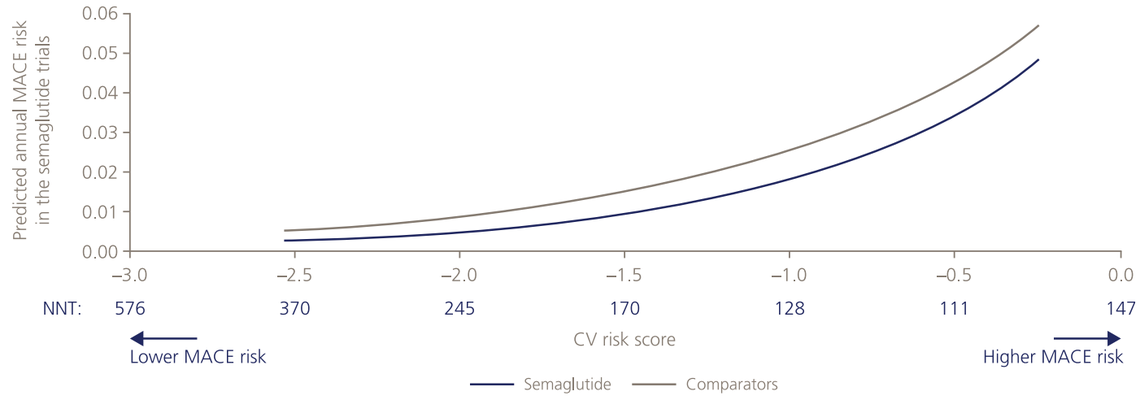
## 9.2.3 Absolute MACE risk estimates for semaglutide vs comparators[20]

- The absolute risk estimates for MACE with semaglutide vs comparators varied across the CV risk spectrum, with a trend for the largest absolute risk reduction in subjects at medium-to-high CV risk, as evidenced by the lowest number needed to treat to avoid one MACE in one year (111) being observed at a medium-to-high CV risk score of –0.483 (Figure 6)[20]





**Figure 6. Estimated yearly risk of MACE as a function of CV risk[20]**




Absolute yearly MACE probabilities for semaglutide and comparators, respectively, estimated using a non-stratified Cox proportional hazards model including effects of treatment, CV risk score and interaction between both. The x-axis shows the CV risk score derived from patients' baseline characteristics in the semaglutide trials. Data on graph cut off at the 5th and 95th percentile of the whole dataset. NNT, number needed to treat to avoid one MACE during 1 year.

## 9.2.4 Summary

- This analysis suggests that semaglutide reduces the relative and absolute risk of MACE vs comparators across a continuum of baseline CV risk characterising a broad T2D population[20]
- Overall, the results are consistent with a post-hoc analysis of pooled SUSTAIN and PIONEER data, which also showed that the effect of semaglutide vs comparators on MACE was largely consistent across different CV subgroups[1]
- These findings may help enable physicians to understand the CV benefits of oral semaglutide in patients with T2D across a broad continuum of CV risk

## 9.3 CV safety: applying REWIND CVD criteria to SUSTAIN 6 AND PIONEER 6[22]

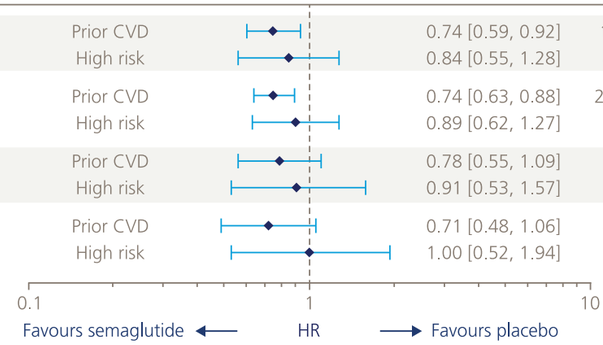
- The REWIND CVOT with dulaglutide[23] used different criteria to define prior CVD or high CV risk compared to the SUSTAIN 6[3] and PIONEER 6[2] trials
  - REWIND included a high proportion of patients without prior cardiovascular disease, and those with a lower mean baseline HbA1c (7.3%),[23] whereas SUSTAIN 6[3] and PIONEER 6[2] focused on high-risk patients either after an acute coronary syndrome event or with a very high prevalence of prior cardiovascular disease, and with higher levels of HbA1c (8.7% and 8.2%, respectively) at baseline
  - An analysis was therefore conducted to understand the impact of using the REWIND criteria for the semaglutide CVOTs[23]
- A post-hoc exploratory analysis of the PIONEER 6[2] and SUSTAIN 6[3] CVOTs assessed CV outcomes with semaglutide vs placebo using criteria for prior CVD and high CV risk from the REWIND trial[23]
  - CV outcomes were assessed with semaglutide vs placebo in a pooled population (N=6,480) of PIONEER 6[2] and SUSTAIN 6[3], re-categorised as having prior CVD (n=4,310; 66.5%) or high CV risk at baseline (n=2,170; 33.5%) using REWIND criteria.[22,23] In the REWIND trial, 3,114 (31.5%) patients had prior CVD, and 6,787 (68.5%) patients had high CV risk[23]
  - The primary endpoint was a composite of MACE. Secondary endpoints included expanded MACE, all-cause death and CV death[22]
- The results from this post-hoc exploratory analysis of a pooled population from PIONEER 6[2] and SUSTAIN 6[3] were consistent with those from the REWIND trial[23]. Semaglutide appeared to reduce CV risk in subgroups of patients as defined by REWIND criteria, suggesting that the CV effects of semaglutide may extend to both primary and secondary prevention in patients with T2D (Figure 7)[22]





**Figure 7. CV events with semaglutide vs placebo by CV risk group using pooled data from PIONEER 6 and SUSTAIN 6[22]**

| Endpoint | CV risk group | HR semaglutide vs placebo [95% CI] | Semaglutide N=3,239 n (%) | Semaglutide N=3,239 IR | Placebo N=3,241 n (%) | Placebo N=3,241 IR | Interaction p value |
|---|---|---|---|---|---|---|---|
| MACE* | Prior CVD | 0.74 [0.59, 0.92] | 129 (6.1) | 3.6 | 117 (8.1) | 4.8 | 0.60 |
| | High risk | 0.84 [0.55, 1.28] | 40 (3.6) | 2.1 | 45 (4.3) | 2.5 | |
| Expanded MACE† | Prior CVD | 0.74 [0.63, 0.88] | 224 (10.5) | 6.2 | 302 (13.8) | 8.2 | 0.39 |
| | High risk | 0.89 [0.62, 1.27] | 58 (5.2) | 3.0 | 62 (5.9) | 3.4 | |
| All-cause death | Prior CVD | 0.78 [0.55, 1.09] | 60 (2.8) | 1.7 | 79 (3.6) | 1.6 | 0.63 |
| | High risk | 0.91 [0.53, 1.57] | 25 (2.2) | 2.6 | 26 (2.5) | 1.4 | |
| CV death | Prior CVD | 0.71 [0.48, 1.06] | 41 (1.9) | 1.1 | 59 (2.7) | 1.6 | 0.38 |
| | High risk | 1.00 [0.52, 1.94] | 18 (1.6) | 0.9 | 17 (1.6) | 0.9 | |




*MACE=death from CV causes, non-fatal MI, or non-fatal stroke. †Expanded MACE=MACE plus coronary or peripheral revascularisation or hospitalisation for unstable angina (UA) or HF. Prior CVD=MI, ischaemic stroke, UA, coronary heart disease or asymptomatic cardiac ischaemia, arterial revascularisation, >50% stenosis of coronary, carotid or lower extremity arteries. High CV risk=microalbuminuria/proteinuria, hypertension and left ventricular hypertrophy, left ventricular dysfunction, ankle-brachial index <0.9, CKD, HF or transient ischaemic attack/haemorrhagic stroke. IR, incidence rate (events/100 patient-years of observation); n, No. of patients with event.

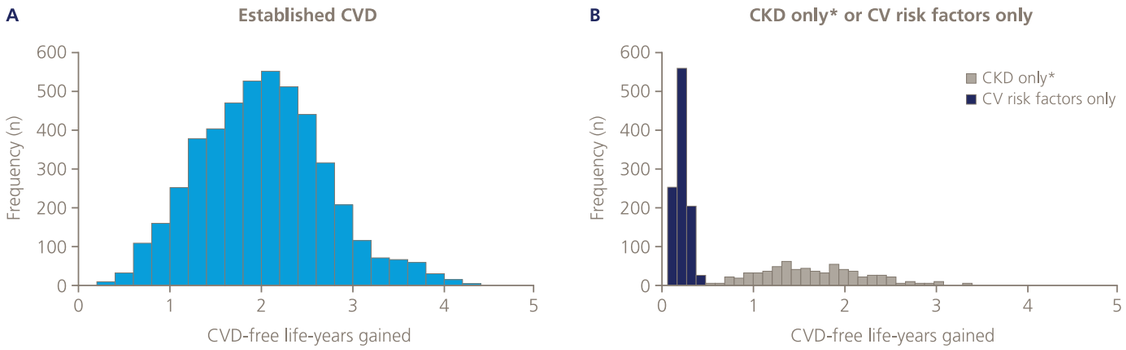
## 9.4 CV safety: CVD-free life years with semaglutide[24,25]

- A post-hoc analysis of pooled data from the PIONEER 6[2] and SUSTAIN 6[3] CVOTs estimated the effect of adding semaglutide to SoC on CVD-free life-years and 10-year CVD risk in patients with T2D. Individual patient-level risk of CVD events in the pooled population were assessed using the Diabetes Lifetimeperspective prediction (DIAL) CVD risk model[24]
  - The DIAL model was validated using data from people with T2D in the Swedish National Diabetes Registry and validated across geographical regions. The 3-point MACE HR from the pooled PIONEER 6 and SUSTAIN 6 population (N=6,480; HR 0.76 [95% CI: 0.62, 0.92]) was applied to the patient level lifetime risk of CVD events derived from the DIAL model. Age-specific risks of CVD events and non-vascular mortality were used to calculate CVD-free life-years and 10-year CVD risk, using standard actuarial methods. CVD events (new and current) were considered. The predicted and observed number of CVD events after 1 year were compared to validate the DIAL model[24]
- Adding semaglutide to SoC was associated with a mean reduction of 20% [95% CI: 6.4, 32.6] in 10-year CVD risk[24]

# PIONEER 6 AND SUSTAIN 6 POOLED ANALYSES

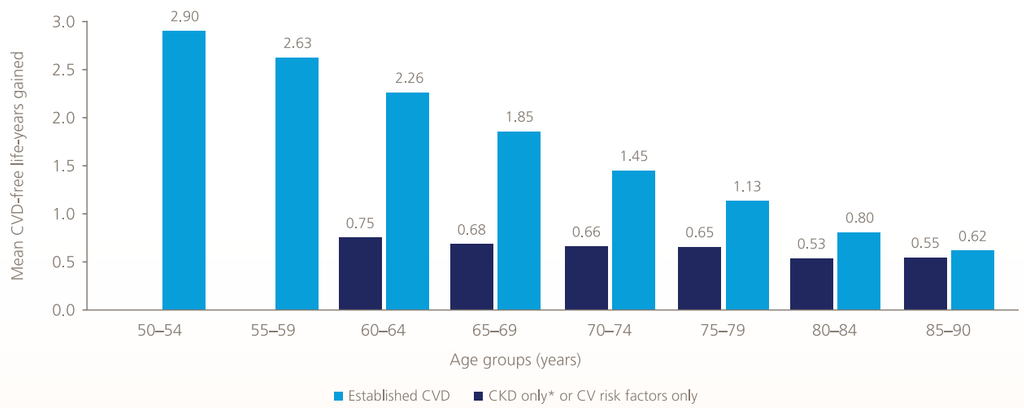
- With semaglutide treatment, patients with established CVD had larger gains in CVD-free life-years (Figure 8a) than patients with CV risk factors only (Figure 8b), although the distribution was wide in both groups[25]
  - A similar gain in CVD-free life-years with semaglutide treatment was observed for patients with CKD only and for patients with established CVD (Figure 8b)[25]
- The gain in CVD-free life-years with semaglutide added to SoC was greater with decreasing age and in patients with established CVD (Figure 9)[24,25]

**Figure 8. Distribution of CVD-free life-years gained with semaglutide in patients with (a) established CVD and (b) CKD only* or CV risk factors only[25]**




*eGFR <60 mL/min/1.73m2 and no established CVD.

**Figure 9. CVD-free life-years gained by adding semaglutide to SoC by age group[25]**




*eGFR <60 mL/min/1.73m2 and no established CVD.



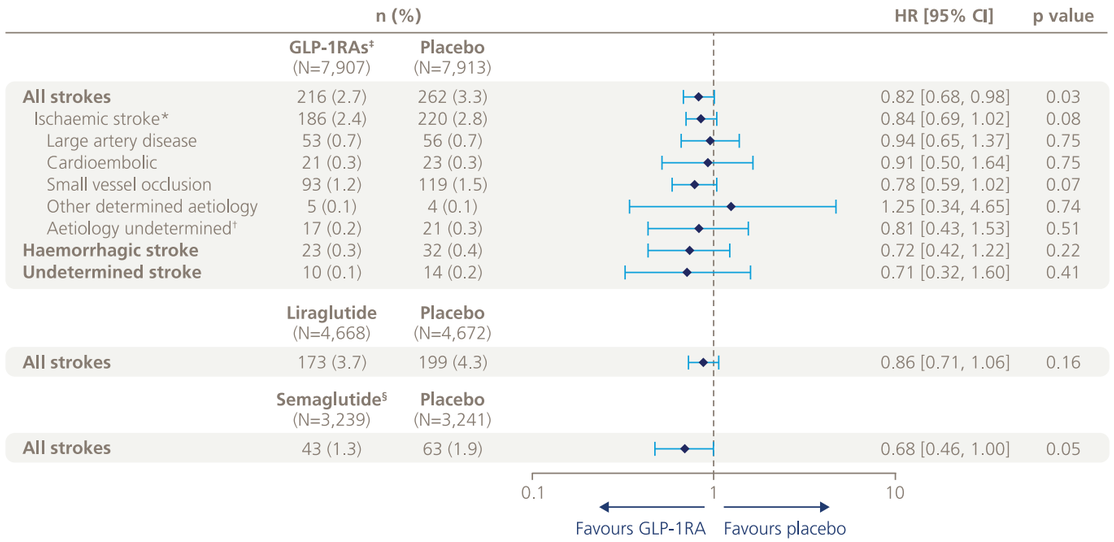


## 9.5 CV safety: effect of liraglutide and semaglutide on stroke and stroke subtypes[26]

- A post-hoc analysis examined the effect of liraglutide and semaglutide on stroke and its subtypes based on pooled data from the LEADER[21], PIONEER 6[2] and SUSTAIN 6[3] trials
  - Pooled data from the LEADER, PIONEER 6 and SUSTAIN 6 trials were used to evaluate the effect of the GLP-1RAs liraglutide and semaglutide on time to first occurrence of all strokes and subtypes of stroke. Ischaemic stroke was subcategorised according to the TOAST classification, based on aetiology by an external blinded reviewer. A Cox proportional hazards model stratified by trial with pooled treatment as a factor was used to examine treatment effects[26]
- This post-hoc analysis demonstrated a significantly reduced risk of all strokes with GLP-1RA treatment vs placebo, with treatment effects being consistent across stroke subtypes (Figure 10)[26]
  - GLP-1RA treatment had the greatest benefit vs placebo in small vessel occlusion strokes compared with large artery disease or cardioembolic strokes but no statistically significant effects were found in any TOAST subcategory (Figure 10)[26]
  - When semaglutide was analysed separately, there were fewer events of all strokes vs placebo (HR 0.68, 95% CI 0.46, 1.00; p=0.05). A similar reduction was observed with liraglutide but was non-significant (Figure 10)[27]

# PIONEER 6 AND SUSTAIN 6 POOLED ANALYSES

**Figure 10. Effect of GLP-1RA treatments (liraglutide and semaglutide) vs placebo in a time-to-first event analysis of stroke, subtypes of stroke and subcategories of ischaemic stroke[27]**

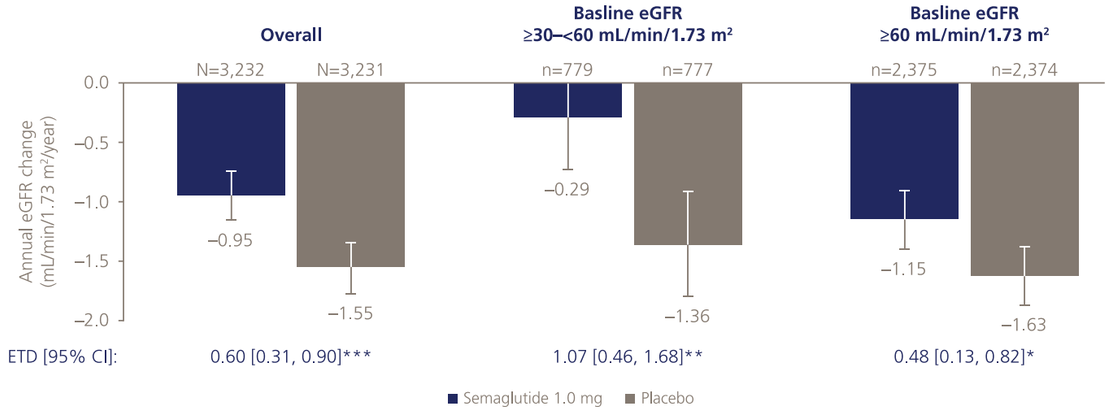



All strokes (including fatal and non-fatal strokes) and the 3 main subtypes were confirmed by the Event Adjudication Committee.
*Ischaemic strokes were subcategorised according to TOAST criteria by an external, blinded reviewer. †Includes patients with ≥2 causes of stroke, undetermined cause despite extensive evaluation or cause of stroke not known due to cursory evaluation. ‡Included liraglutide, once-weekly subcutaneous semaglutide and once-daily oral semaglutide. §Consisted of once-weekly subcutaneous semaglutide and once-daily oral semaglutide.
n, number of patients with specified stroke type; N, number of patients in the treatment group. TOAST classification: 1. large-artery atherosclerosis; 2. cardioembolic; 3. small-vessel occlusion; 4. stroke of other determined aetiology; 5. stroke of undetermined aetiology.

## 9.6 Renal safety: effect of semaglutide on the rate of eGFR decline[28]

- A post-hoc analysis of a pooled cohort from PIONEER 62 and SUSTAIN 63 evaluated the effects of semaglutide vs placebo on kidney function, assessed by annual change in eGFR[28]
  - Data for N=6,480 patients from PIONEER 6[2] and SUSTAIN 6[3] were pooled into semaglutide and placebo treatment groups. Annual change in eGFR was compared between semaglutide and placebo in patients with eGFR data at baseline, both overall and by baseline eGFR subgroup (≥30–<60 or ≥60 mL/min/1.73 m$^2$). The ETD between annual rates of eGFR slope (from baseline to timepoint of interest) was calculated at Year 1 and Year 2 (Year 2 data predominantly from SUSTAIN 6[28]
- Semaglutide was associated with a significantly smaller decline in kidney function compared with placebo (as measured by the ETD of the eGFR change at year 2)
  - There was a numerically larger difference in the ETD for the eGFR ≥30–<60 mL/min/1.73 m$^2$ subgroup vs the eGFR ≥60 mL/min/1.73 m$^2$ subgroup (p value for interaction=0.21) (Figure 11). These findings indicate that those with established CKD may benefit most from treatment with semaglutide[28]

**Figure 11. Annual eGFR change with semaglutide or placebo and ETD between semaglutide and placebo in pooled PIONEER 6 and SUSTAIN 6 trials[28]**



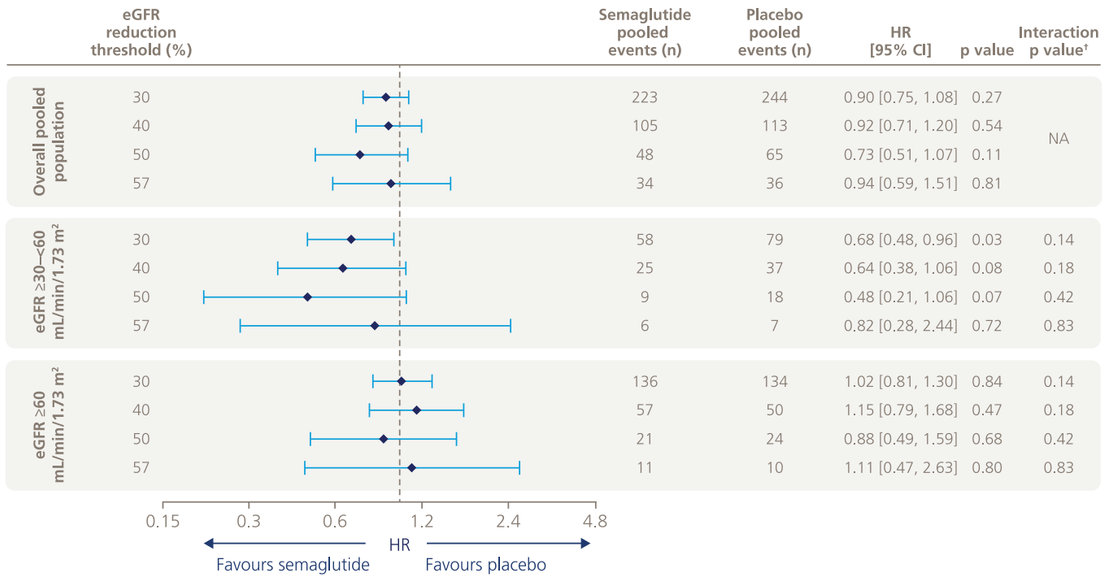

*p<0.01; **p<0.001; ***p<0.0001.
Full analysis set. Data are mean ± 95% CI. Renal function is based on eGFR mL/min/1.73 m2 per Chronic Kidney Disease-Epidemiology Collaboration formula. Statistical significance of ETD tested at Year 2.

# PIONEER 6 AND SUSTAIN 6 POOLED ANALYSES

## 9.7 Renal safety: effect of semaglutide on CKD outcomes[29]

- In this post-hoc study, eGFR data from a pooled cohort of the PIONEER 6[2] and SUSTAIN 6[3] trials were used to evaluate the potential benefit of semaglutide vs placebo on CKD outcomes[29]
  - Data for patients included in PIONEER 6[2] and SUSTAIN 6[3] (N=6,480) were pooled into semaglutide or placebo treatment arms. The time to onset of persistent eGFR reduction from baseline (thresholds of ≥30%, ≥40%, ≥50% and ≥57% [57% corresponds to a doubling of serum creatinine]) were evaluated in the overall pooled population, and by baseline CKD subgroups (eGFR ≥ 30–<60 or ≥60 mL/min/1.73 m$^2$)[29]
- In the overall population, the HRs for time to onset of persistent eGFR reductions according to the different thresholds were <1.0 for semaglutide vs placebo, but did not achieve statistical significance[29]
  - In patients with baseline eGFR ≥30–<60 mL/min/1.73 m$^2$, HRs for time to onset of persistent eGFR reductions with semaglutide vs placebo were consistently lower compared with the overall population. Furthermore, in this subgroup, semaglutide significantly reduced the risk of developing persistent ≥30% eGFR reductions from baseline vs placebo (p=0.03) (Figure 12)[29]
- This analysis of semaglutide CVOTs supports the possibility of a smaller magnitude of eGFR decline with semaglutide vs placebo and suggests a potential kidney disease benefit of semaglutide vs placebo in patients with T2D and established CKD[29]

**Figure 12. Semaglutide treatment effect on time to persistent eGFR reduction* across the overall pooled population and CKD subgroups: a post-hoc pooled analysis from the SUSTAIN 6 and PIONEER 6 trials[29]**




Analyses were performed using a Cox proportional hazards model with treatment group (semaglutide vs placebo) and CKD subgroup as fixed factors and the interaction between both stratified by trial. *Time to 'persistent' reduction in eGFR was defined as the time from randomisation to the first visit in which the value from the subsequent visit was confirmed by fulfilling the same relative reduction from baseline as the value from the previous visit. If no subsequent visit was performed, the confirmation was omitted. †Test for heterogeneity between treatment effects across eGFR subgroups.

# PIONEER 6 AND SUSTAIN 6 POOLED ANALYSES

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# HEALTH PROFESSIONAL INFORMATION

## 10.1 Indications

- RYBELSUS® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:
  - As monotherapy when metformin is considered inappropriate due to intolerance or contraindications;
  - In combination with other medicinal products for the treatment of diabetes (see CLINICAL TRIALS for patient populations and drug combinations tested).

### 10.1.1 Pediatrics

- Pediatrics (< 18 years of age): The safety and efficacy of RYBELSUS® have not been studied in pediatric populations. RYBELSUS® is not indicated for use in pediatric patients.

### 10.1.2 Geriatrics

- Geriatrics (65 years of age): Evidence from a pooled analysis of phase III clinical studies suggests that use in the geriatric population (n=1229) was associated with no significant differences in safety or efficacy, but greater sensitivity of some older individuals cannot be ruled out. Therapeutic experience in patients ˜ ≥75 years of age is limited (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

## 10.2 Contraindications

- RYBELSUS® is contraindicated in patients who are hypersensitive to RYBELSUS® or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging. See WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity.
- RYBELSUS® is contraindicated in patients who have a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). See WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis, Risk of Thyroid C-Cell Tumours.
- RYBELSUS® should not be used during pregnancy or breastfeeding. See WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and Breastfeeding.

## 10.3 Serious Warnings and Precautions

### Risk of Thyroid C-cell Tumours

- Semaglutide causes treatment-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice (see WARNINGS AND PRECAUTIONS and NON-CLINICAL TOXICOLOGY). It is unknown whether semaglutide causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies.
- RYBELSUS® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumours. Patients should be counseled regarding the risk and symptoms of thyroid tumours (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and NON-CLINICAL TOXICOLOGY).

## 10.4 Dosage and Administration

### 10.4.1 Dosing Considerations

- Do not take more than one tablet of RYBELSUS® daily. Do not take two or more tablets of RYBELSUS® to obtain a higher dose.

### 10.4.2 Recommended Dose and Dosage Adjustment

- The starting dose of RYBELSUS® is 3 mg once daily. After 30 days, the dose should be increased to a maintenance dose of 7 mg once daily. If additional glycemic control is needed after at least 30 days on the 7 mg dose, the dose can be increased to a maintenance dose of 14 mg once daily. This regimen is intended to mitigate gastrointestinal symptoms during dose escalation.
- The safety and efficacy of RYBELSUS® in children and adolescents below 18 years have not been studied (see 1.1 Pediatrics).
- No dose adjustment of RYBELSUS® is recommended based on age, sex, race, ethnicity, upper gastrointestinal disease, or hepatic, and renal impairment.

### 10.4.3 Administration

- RYBELSUS® must be taken on an empty stomach at least 30 minutes before the first food, beverage or other oral medications of the day. Waiting less than 30 minutes is likely to decrease the amount of semaglutide absorbed.
- RYBELSUS® should be taken with no more than half a glass of water equivalent to 120 mL. A larger volume of water is likely to decrease the amount of semaglutide absorbed.
- RYBELSUS® should be swallowed whole. Do not split, crush or chew.

## 10.4.4 Missed Dose

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

## 10.5 Overdosage

- For management of a suspected drug overdose, contact your regional poison control centre.
- Clinical trials have studied repeat doses of RYBELSUS® of up to 40 mg. Overdose with semaglutide may be associated with gastrointestinal disorders (e.g., nausea). All patients in clinical studies who reported overdosing with semaglutide recovered without complications. Ensure that patients are instructed that only a single tablet of RYBELSUS® should be administered daily.
- There is no specific antidote for overdose with RYBELSUS®. 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 RYBELSUS® of approximately 1 week.

## 10.6 Dosage Forms, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral | Tablet / 3 mg, 7 mg, 14 mg | Magnesium stearate, microcrystalline cellulose, povidone K 90 and salcaprozate sodium (SNAC) |





## 10.7 Description

- The physical characteristics of the tablets and their packaging are as follows:
- 3 mg tablets are white to light yellow, oval shaped debossed with "3" on one side and "novo" on the other side. The tablets are supplied in green coloured cartons containing alu/alu blisters in pack sizes of 30.
- 7 mg tablets are white to light yellow, oval shaped debossed with "7" on one side and "novo" on the other side. The tablets are supplied in red coloured cartons containing alu/alu blisters in pack sizes of 30.
- 14 mg tablets are white to light yellow, oval shaped debossed with "14" on one side and "novo" on the other side. The tablets are supplied in blue coloured cartons containing alu/alu blisters in pack sizes of 30.

## 10.8 Warnings and Precautions

### General

RYBELSUS® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

### Carcinogenesis and Mutagenesis

#### Risk of Thyroid C-Cell Tumours

In mice and rats, semaglutide caused a treatment-duration-dependent increase in the incidence of thyroid C-cell tumours (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures (see NON-CLINICAL TOXICOLOGY). It is unknown whether semaglutide causes thyroid C-cell tumours, including Medullary Thyroid Carcinoma (MTC), in humans as human relevance could not be determined. Thyroid C-cell tumours in rodents are a known class effect for GLP-1 receptor agonists.

Cases of MTC have been observed in patients treated with GLP-1 receptor agonists in clinical trials and the post-marketing period. The data is insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonists use in humans.

It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calciton in and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with RYBELSUS® if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

# HEALTH PROFESSIONAL INFORMATION

## Driving and Operating Machinery

In rare cases, RYBELSUS® has the potential to cause hypoglycemia, which may impact an individual's ability to drive or use machines. When RYBELSUS® is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycemia while driving and using machines.

## Cardiovascular

### Heart Rate Increase

Semaglutide causes an increase in heart rate (see ACTION AND CLINICAL PHARMACOLOGY). Caution should be observed in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as tachyarrhythmias (see DRUG INTERACTIONS).

### PR Interval Prolongation

Semaglutide causes a prolongation of the PR interval of the electrocardiogram (see ACTION AND CLINICAL PHARMACOLOGY). Caution should be observed in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) or a history of rhythm disturbances (e.g., tachyarrhythmias).

## Endocrine and Metabolism

### Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients treated with semaglutide in combination with an insulin secretagogue (e.g., sulfonylureas) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by reducing the dose of the secretagogue or insulin when initiating treatment with RYBELSUS®.

## Hepatic/Biliary/Pancreatic

### Pancreatic

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. In glycemic control trials, pancreatitis was reported as a serious adverse event in 6 RYBELSUS®-treated patients (0.1 cases per 100 patient years) versus 1 in comparator-treated patients (<0.1 cases per 100 patient years).

Patients should be informed of the characteristic symptoms of acute pancreatitis. After initiation of RYBELSUS®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, RYBELSUS® should be discontinued and appropriate management initiated; if confirmed, RYBELSUS® should not be restarted.

## Immune

### Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, may occur with any GLP-1 receptor agonist, including RYBELSUS®. If a hypersensitivity reaction occurs, the patient should discontinue RYBELSUS® and promptly seek medical advice. Do not use in patients with a previous hypersensitivity to RYBELSUS®. Caution should be exercised with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with RYBELSUS®.

## Monitoring and Laboratory Tests

Regular self-monitoring of blood glucose is not needed in order to adjust the dose of RYBELSUS®. However, when initiating treatment with RYBELSUS® in combination with a sulfonylurea or insulin it may become necessary to reduce the dose of the sulfonylurea or insulin in order to reduce the risk of hypoglycemia.

However, patients should be informed that response to all diabetic therapies should be monitored by periodic measurement of HbA1C levels, with a goal of decreasing these levels towards the normal range. HbA1C is especially useful for evaluating long-term glycemic control.

## Ophthalmologic

### Diabetic Retinopathy

In a pooled analysis of glycemic control trials with RYBELSUS®, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS® and 3.8% with comparator).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines.

Undesirable Effects: In 10 phase 3a trials, 5,707 patients were exposed to Rybelsus® alone or in combination with other glucoselowering medicinal products. The duration of the treatment ranged from 26 weeks to 78 weeks. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration. Other undesirable effects being delayed gastric emptying, dysgeusia and

dizziness

## Renal

### Renal Insufficiency

Patients with renal impairment: No dose adjustment is required for patients with renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended in patients with end stage renal

disease.

In patients treated with GLP-1 receptor agonists, there have been post-marketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease.

## Fertility

The effect of semaglutide on fertility in humans is unknown. In female rats, following administration of subcutaneous semaglutide, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss.

# HEALTH PROFESSIONAL INFORMATION

## 10.8.1 Special Population

### 10.8.1.1 Pregnant Women

- The extent of exposure in pregnancy during clinical trials was very limited and there are no adequate and well-controlled studies of RYBELSUS® in pregnant women. Therefore, RYBELSUS® should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, RYBELSUS® should be discontinued. RYBELSUS® should be discontinued at least 2 months before a planned pregnancy due to the long half-life of semaglutide (see ACTION AND CLINICAL PHARMACOLOGY).

  Use of RYBELSUS® during pregnancy may cause fetal harm based on animal studies. Animal studies with subcutaneous semaglutide have shown reproductive and developmental toxicity at exposures below human exposure levels. Adverse developmental effects included fetal malformations in rats, rabbits, and monkeys and pre- and post-natal losses in monkeys. In addition, SNAC was shown to result in fetotoxicity in rats (increase in the number of dams with stillborn pups) at a maternal dose of 1000 mg/kg/day (see NON-CLINICAL TOXICOLOGY).

  As semaglutide and SNAC have both been demonstrated to cause developmental toxicity in animals, there may be a potential risk for an additive adverse developmental effect from exposure to RYBELSUS® during pregnancy.

### 10. 8.1.2 Breastfeeding

- Breastfeeding is not recommended during treatment with RYBELSUS® as a risk to the nursing infant cannot be excluded. There are no data on the presence of semaglutide and SNAC in human milk, the effects on the breastfed infant, or the effects on human milk production.

  However, semaglutide has been shown to be present in the milk of lactating rats. SNAC and/or its metabolites have also been shown to be concentrated in the milk of lactating rats (see NON-CLINICAL TOXICOLOGY).

### 10. 8.1.3 Pediatrics

- Breastfeeding is not recommended during treatment with RYBELSUS® as a risk to the nursing infant cannot be excluded. There are no data on the presence of semaglutide and SNAC in human milk, the effects on the breastfed infant, or the effects on human milk production.

  However, semaglutide has been shown to be present in the milk of lactating rats. SNAC and/or its metabolites have also been shown to be concentrated in the milk of lactating rats (see NON-CLINICAL TOXICOLOGY).

### 10. 8.1.3 Pediatrics

- Pediatrics (< 18 years): The safety and efficacy of RYBELSUS® have not been studied in pediatric populations. RYBELSUS® is not indicated for use in pediatric patients.

### 10. 8.1.4 Geriatrics

- Geriatrics (˜65 years of age): In the pool of glycemic control trials, 1229 (29.9%) RYBELSUS®-treated patients were 65 years of age or over and 199 RYBELSUS®-treated patients (4.8%) patients were 75 years of age and over. In PIONEER 6, the cardiovascular outcome trial, 891 (56.0%) RYBELSUS®-treated patients were 65 years of age or older and 200 RYBELSUS®-treated patients (12.6%) were 75 years of age and over.

  No overall differences in safety were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### 10. 8.1.5 Renal Impairment

- The safety and efficacy of RYBELSUS® was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m2) and no overall differences in safety were observed.

### 10.8.1.6 Hepatic Impairment

- There is limited clinical experience regarding the safety profile of RYBELSUS® in patients with mild, moderate or severe hepatic insufficiency.

## 10.9 Adverse Reactions

### 10. 9.1 Adverse Reaction Overview

- The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders (including nausea, diarrhea, and vomiting). In general, these reactions were mild or moderate in severity. More patients taking RYBELSUS® versus comparator drugs had severe or serious adverse events and/or discontinued treatment due to gastrointestinal disorders.

The following serious adverse reactions are described below or elsewhere in the Product Monograph (see WARNINGS AND PRECAUTIONS):

- Risk of Thyroid C-cell Tumours
- Pancreatitis
- Diabetic Retinopathy
- Hypoglycemia with Concomitant Use of Insulin or Sulfonylureas
- Renal Insufficiency
- Hypersensitivity

## 10. 9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In 10 phase 3a trials, 5707 patients were exposed to RYBELSUS® alone or in combination with other glucose-lowering medicinal products. The duration of the treatment ranged from 26 weeks to 78 weeks.

The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhea and vomiting. In general, these reactions were mild or moderate in severity and of short duration.

### Pool of Placebo-Controlled Trials

The data in Table 2 are derived from 2 placebo-controlled trials [1 monotherapy trial (PIONEER 1) and 1 trial in combination with insulin (PIONEER 8)] in patients with type 2 diabetes (see CLINICAL TRIALS). These data reflect exposure of 1071 patients to RYBELSUS® and a mean duration of exposure to RYBELSUS® of up to 41.8 weeks. Across the treatment arms, the mean age of patients was 58 years, 3.9% were 75 years or older and 52% were male. In these trials 63% were White, 6% were Black or African American, and 27% were Asian; 19% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 9.4 years and had a mean HbA1c of 8.1%. At baseline, 20.1% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ˜90 mL/min/1.73m$^2$) in 66.2%, mildly impaired (eGFR 60 to 90 mL/min/1.73m$^2$) in 32.4% and moderately impaired (eGFR 30 to 60 mL/min/1.73m$^2$) in 1.4% of patients.

### Pool of Placebo- and Active-Controlled Trials

In a pool of 9 phase 3a trials, 4116 patients were exposed to RYBELSUS® with a mean duration of exposure to RYBELSUS® of 55.5 weeks. The mean age of patients was 58 years, 5.0% were 75 years or older and 55% were male. In these trials 65% were White, 6% were Black or African American, and 24% were Asian; 15% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.8 years and had a mean HbA1c of 8.2%. At baseline, 16.6% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR 90 mL/min/1.73m2) in 65.9%, mildly impaired (eGFR 60 to 90 mL/min/1.73m2) in 28.5% and moderately impaired (eGFR 30 to 60 mL/min/1.73m2) in 5.4% of patients.

### Common Adverse Reactions

Table 2 shows common adverse reactions, excluding hypoglycemia, associated with the use of RYBELSUS® in the pool of placebo-controlled trials (PIONEER 1 and PIONEER 8). These adverse reactions occurred more commonly on RYBELSUS® than on placebo, and occurred in at least 1% of patients treated with RYBELSUS®.





**Table 2 Adverse Reactions in Placebo-Controlled Trials Reported in 1% of RYBELSUS® - Treated Patients with Type 2 Diabetes Mellitusa**

| | RYBELSUS® 7 mg (N=356) % | RYBELSUS® 14 mg (N=356) % | Placebo (N=362) % |
|---|---|---|---|
| Eye Disorders | | | |
| Dry eye | 1.7 | 0 | 0.3 |
| Diabetic Retinopathy | 3.7 | 2.8 | 2.8 |
| Gastrointestinal | | | |
| Nausea | 11.0 | 19.7 | 6.4 |
| Diarrhea | 8.7 | 10.1 | 4.1 |
| Vomiting | 6.2 | 8.4 | 3.0 |
| Constipation | 5.9 | 5.3 | 2.5 |
| Abdominal pain | 10.1 | 10.7 | 4.1 |
| Abdominal Distension | 1.7 | 2.8 | 1.1 |
| Gastrooesophageal reflux disease | 1.7 | 2.2 | 0.3 |
| Eructation | 0.6 | 2.0 | 0 |
| Flatulence | 1.7 | 1.1 | 0 |
| Gastritis | 1.7 | 1.7 | 0.8 |
| Dyspepsia | 3.1 | 0.6 | 0.6 |
| General Disorders and Administration Site Conditions | | | |
| Pyrexia | 0.8 | 1.7 | 1.1 |
| Fatigue | 3.7 | 2.8 | 0 |
| Infections and Infestations | | | |
| Upper Respiratory Tract Infection | 2.2 | 3.9 | 3.6 |
| Urinary Tract Infections | 1.7 | 3.7 | 3.3 |
| Influenza | 3.4 | 3.4 | 2.5 |
| Injury, Poisoning and Procedural Complications | | | |

# HEALTH PROFESSIONAL INFORMATION

**Table 2 Adverse Reactions in Placebo-Controlled Trials Reported in 1% of RYBELSUS® - Treated Patients with Type 2 Diabetes Mellitusa**

| | RYBELSUS® 7 mg (N=356) % | RYBELSUS® 14 mg (N=356) % | Placebo (N=362) % |
|---|---|---|---|
| Contusion | 0.6 | 2.2 | 0.8 |
| Fall | 1.1 | 0.6 | 0.3 |
| Hepatobiliary Disorders | | | |
| Cholelithiasis | 1.1 | 0 | 0 |
| Investigations | | | |
| Weight Decreased | 0.6 | 1.4 | 0.3 |
| Blood Creatinine Phosphokinase Increased | 1.1 | 1.4 | 0 |
| Lipase Increased | 2.8 | 1.1 | 0.3 |
| Metabolism and Nutrition Disorders | | | |
| Decreased Appetite | 5.9 | 9.0 | 0.8 |
| Nervous System Disorders | | | |
| Headache | 4.8 | 4.5 | 3.9 |
| Dizziness | 1.1 | 2.8 | 2.2 |
| Vertigo | 1.4 | 1.4 | 0 |
| Respiratory, Thoracic and Mediastinal Disorders | | | |
| Pharyngitis | 1.7 | 2.0 | 1.7 |
| Sinusitis | 2.5 | 1.4 | 1.9 |
| Respiratory Tract Infection Viral | 0 | 1.1 | 0.8 |
| Upper Respiratory Tract Inflammation | 1.1 | 0.8 | 0.3 |

aThe values are proportions of subjects with at least one event from a pool of two clinical trials, PIONEER 1 (26 weeks) and PIONEER 8 (52 weeks).

In the pool of glycemic controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 2.

- Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving RYBELSUS® than placebo (placebo 21.3%, RYBELSUS® 7 mg 31.8%, RYBELSUS® 14 mg 41.0%). The majority of the reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving RYBELSUS® 7 mg (4.5%) and RYBELSUS® 14 mg (7.9%) prematurely discontinued trial product due to gastrointestinal adverse reactions than patients receiving placebo (0.6%). Rates of gastrointestinal adverse events were increased in both female patients and patients with a lower BMI, correlating with higher RYBELSUS® exposure observed in these patient populations.

## Other Adverse Reactions

- Hypoglycemia

**Table 3 summarizes the frequency of events related to hypoglycemia by various definitions in the placebo-controlled trials.**

| | Placebo | RYBELSUS® 7 mg | RYBELSUS® 14 mg |
|---|---|---|---|
| Monotherapy (26 weeks) | N = 178 | N = 175 | N = 175 |
| Severea (Level 3) | 0% | 0.6% | 0% |
| Clinically significantb (Level 2) | 1.1% | 0% | 0% |
| Moderate renal impairmentc (26 weeks) | N = 161 | - | N = 163 |
| Severea (Level 3) | 0% | - | 0% |
| Clinically significantb (Level 2) | 2.5% | - | 5.5% |
| Add-on to insulin with or without metformin (52 weeks) | N = 184 | N = 181 | N = 181 |
| Severea (Level 3) | 0.5% | 0% | 1.1% |
| Clinically significantb (Level 2) | 27.2% | 25.4% | 26.5% |

[a] "Severe" hypoglycemia adverse reactions are episodes requiring the assistance of another person.

[b] "Clinically significant" hypoglycemia adverse reactions are episodes with a plasma glucose of < 3.0 mmol/L

[c] As an add-on to metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin

Hypoglycemia was more frequent when RYBELSUS® was used in combination with insulin secretagogues (e.g. sulfonylurea) or insulin (see WARNINGS AND PRECAUTIONS and CLINICAL TRIALS).

- Discontinuation due to an adverse event

  In the placebo dose pool, discontinuation of treatment due to adverse events was higher in patients receiving RYBELSUS® than placebo (placebo 2.5%, RYBELSUS® 7 mg 6.5%, RYBELSUS® 14 mg 10.4%). The most frequent adverse events leading to discontinuation were gastrointestinal.

- Heart Rate Increase

  In placebo-controlled trials, RYBELSUS® 7 mg and 14 mg resulted in a mean increase in heart rate of 1 to 3 beats per minute. There was no change in heart rate in placebo-treated patients.

## 10. 9.3 Less Common Clinical Trial Adverse Reactions (<1%)

In addition to Table 2, the following Adverse Reactions have been identified based on an overall causality assessment including data from placebo- and active-controlled glycemic trials.

- Cardiovascular: Increased heart rate
- Immune System: Anaphylactic reaction

- Immunogenicity

  Across the placebo- and active-controlled glycemic control trials with antibody measurements, 14 (0.5%) RYBELSUS®-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in RYBELSUS® (i.e., semaglutide). Of the 14 semaglutide-treated patients that developed semaglutide ADAs, 7 patients (0.2% of the overall population) developed antibodies cross-reacting with native GLP-1. The in vitro neutralizing activity of the antibodies is uncertain at this time.

  The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlyingdisease. For these reasons, the incidence of antibodies to semaglutide in the studies described below cannot be directly compared with the incidence of antibodies in other studies or to other products.





## 10. 9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

- Increases in Amylase and Lipase

  In placebo-controlled trials, patients exposed to RYBELSUS® 7 mg and 14 mg had a mean increase from baseline in amylase of 10% and 13%, respectively, and lipase of 30% and 34%, respectively. These changes were not observed in placebo-treated patients.

# 10.10 Drug Interactions

## 10. 10.1 Overview

- Semaglutide delays gastric emptying which may influence the absorption of other oral medications. Trials were conducted to study the potential effect of semaglutide on the absorption of oral medicinal products taken with semaglutide administered orally at steady- state exposure.

## 10. 10.2 Drug-Drug Interactions

- The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 4 Established or Potential Drug-Drug Interactions**

| | | | |
|---|---|---|---|
| Levothyroxine | CT | The AUC of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single 600 ug dose of levothyroxine concurrently administered with semaglutide. Cmax was unchanged. | Monitoring of thyroid parameters should be considered when treating patients with RYBELSUS® at the same time as levothyroxine. |
| Metformin<br>Furosemide<br>Rosuvastatin | CT | No clinically relevant change in AUC or Cmax | None |
| Warfarin (S- warfarin and R- warfarin)<br>Digoxin<br>Lisinopril<br>Oral Contraceptives (containing ethinylestradiol and levonorestrel) | CT | Semaglutide did not change the AUC or Cmax | None |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical





No clinically relevant drug-drug interaction with semaglutide was observed based on the evaluated medications. Therefore, no dose adjustment is required for drugs taken with RYBELSUS®.

- Effects of other medicinal products on RYBELSUS®

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 $AUC^{0-24h}$ of semaglutide decreased by 34% and $C_{max}$ by 32%. The presence of multiple tablets in the stomach influences the absorption of semaglutide if co-administered at the same time. Patients taking RYBELSUS® should wait at least 30 minutes before taking other oral medications (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

- Drugs that Increase Heart Rate

RYBELSUS® causes an increase in heart rate (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY). The impact on heart rate of co-administration of RYBELSUS® with other drugs that increase heart rate (e.g., sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of RYBELSUS® with these drugs should be undertaken with caution.

- Drugs that Cause PR Interval Prolongation

RYBELSUS® causes an increase in the PR interval (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY). The impact on the PR interval of co- administration of RYBELSUS® with other drugs that prolong the PR interval (including, but not limited to, antiarrhythmics, calcium channel blockers, beta-adrenoceptor blockers, digitalis glycosides, HIV protease inhibitors) has not been evaluated. As a result, co-administration of RYBELSUS® with these drugs should be undertaken with caution.

## 10. 10.3 Drug-Food Interactions

- Concomitant intake of food reduces the exposure of semaglutide.

## 10. 10.4 Drug-Herb Interactions

- Interactions with herbal products have not been studied.

## 10. 10.5 Drug-Laboratory Test Interactions

- Interactions with herbal products have not been studied.

## 10. 10.6 Drug-Lifestyle Interactions

- Interactions with lifestyle products have not been studied.

# HEALTH PROFESSIONAL INFORMATION

## 10.11 Action and Clinical Pharmacology

### 10. 11.1 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 GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, semaglutide has a half-life of approximately one week. This long plasma half-life is based on binding to albumin, which reduces renal clearance, and increased enzymatic stability towards the dipeptidyl peptidase (DPP-IV) enzyme.
- Semaglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Semaglutide stimulates insulin secretion in a glucose-dependent manner. Simultaneously, semaglutide lowers glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, when blood glucose is low semaglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

### 10. 11.2 Pharmacodynamics

- All pharmacodynamic evaluations were performed at steady state after 12 weeks of treatment (including dose escalation) with 1 mg subcutaneous semaglutide.
- Fasting and Postprandial Glucose

  Semaglutide lowered postprandial glucose concentration. In patients with type 2 diabetes, treatment with semaglutide resulted in a reduction compared to placebo for fasting glucose, 2- hour postprandial glucose, mean 24-hour glucose concentration and post prandial glucose excursions over 3 meals.
- First and Second Phase Insulin Secretion

  Both first-and second-phase insulin secretion are increased in patients with type 2 diabetes treated with semaglutide compared with placebo.
- Glucagon Secretion

  Semaglutide lowered fasting glucagon, postprandial glucagon response, and mean 24-hour glucagon concentrations compared to placebo in patients with type 2 diabetes.
- 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 similar to that of healthy subjects.

  During induced hypoglycemia, semaglutide did not alter the counter-regulatory responses of increased glucagon compared to placebo, and did not impair the decrease of C-peptide in patients with type 2 diabetes
- Gastric emptying

  Semaglutide causes a delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.
- Fasting and postprandial lipids

  Semaglutide compared to placebo lowered fasting triglyceride and very-low-density lipoproteins (VLDL) cholesterol concentrations. The postprandial triglyceride and VLDL cholesterol response to a high fat meal was reduced in patients with type 2 diabetes treated with semaglutide compared to placebo.
- Cardiac electrophysiology (QTc)

  The effect of semaglutide on cardiac repolarization was tested in a QTc trial using supratherapeutic doses of subcutaneous semaglutide. At an average exposure level 4-fold higher than that of the maximum recommended dose of RYBELSUS®, semaglutide did not prolong QTc intervals to any clinically relevant extent.
- Heart Rate: Treatment with subcutaneous semaglutide was associated with an increase in heart rate at all dose levels (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).
- PR Interval: Treatment with subcutaneous semaglutide causes PR interval prolongation, with no evidence of dose-dependency over the 0.5 to 1.5 mg dose range studied (see WARNING AND PRECAUTIONS and DRUG INTERACTIONS).
- QTcI Interval: Treatment with subcutaneous semaglutide at doses of 0.5, 1.0, and 1.5 mg was associated with a QTcI-shortening effect over the 0-48 h time frame studied, with no evidence of dose-dependency.

# HEALTH PROFESSIONAL INFORMATION

## 10. 11.3 Pharmacokinetics

**Table 5 Summary of semaglutide Pharmacokinetic Parameters in Patients with Type 2 Diabetes**

| | $C_{max}$ | $AUC_{0-24h}$ [a] | $T_{max}$ | $t_{½}$ | CL | Vd |
|---|---|---|---|---|---|---|
| Steady-State | 7 mg: 7.6 nmol/L<br>14 mg: 16.5 nmol/L | 7 mg: 161 nmol*h/L<br>14 mg: 350 nmol*h/L | 1 hour | ≈ 1 week | Estimated absolute clearance: 0.04 L/h | Estimated absolute volume of distribution: 8 L |

- Absorption:

  Semaglutide has been co-formulated with salcaprozate sodium, which facilitates the absorption of semaglutide after oral administration. The absorption of semaglutide predominantly occurs in the stomach.

  Absorption of semaglutide is decreased if taken with food.

  The pharmacokinetics of semaglutide have been extensively characterised in healthy subjects and patients with type 2 diabetes. Following oral administration, maximum plasma concentration of semaglutide occurred 1 hour post dose. Steady-state exposure was reached after 4-5 weeks of once-daily administration. Systemic exposure of semaglutide increased in an approximately dose-proportional manner. In patients with type 2 diabetes, the average steady-state concentrations were approximately 6.7 nmol/L and 14.6 nmol/L with RYBELSUS® 7 and 14 mg, respectively; with 90% of subjects treated with RYBELSUS® 7 mg having an average concentration between 1.7-22.7 nmol/L and 90% of subjects treated with RYBELSUS® 14 mg having an average concentration between 3.7-41.3 nmol/L.

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

- Distribution:

  The estimated absolute volume of distribution is approximately 8 L in subjects with type 2 diabetes. Semaglutide is extensively bound to plasma proteins (>99%).

- Metabolism:

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

- Elimination:

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

  Clearance of semaglutide in patients with type 2 diabetes is approximately 0.04 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 Populations and Conditions

  Based on a population pharmacokinetic analysis, age (18-92 years), sex, race, ethnicity, upper gastrointestinal disease and renal impairment (mild or moderate) do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. Semaglutide exposure is inversely related to body weight. Lower body weight was associated with higher exposure and a greater incidence of gastrointestinal adverse events (see ADVERSE REACTIONS, Gastrointestinal Adverse Reactions). However, RYBELSUS® doses of 7mg and 14mg provide adequate systemic exposure over the bodyweight range of 40-188kg evaluated in the clinical trials.

- Storage, Stability and Disposal

  Store at room temperature (15°C to 30°C) out of the reach of children.

- Special Handling Instructions

  RYBELSUS® must be stored in the original blister packaging to protect from moisture and light. Take the tablet directly after removing from blister card.

# HEALTH PROFESSIONAL INFORMATION

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# APPENDIX

## 11.1 Retinopathy in the PIONEER programme[1,2]

- Patients with diabetic retinopathy were included in studies in the PIONEER trial programme; however, patients with proliferative retinopathy or maculopathy requiring acute treatment were excluded
- The proportions of patients with diabetic retinopathy at baseline in the two longer-term trials of the PIONEER programme, PIONEER 3 (78 weeks) and PIONEER 6 (CVOT, median follow-up 16 months), are shown in Tables 1 and 2

**Table 1. Diabetic retinopathy in PIONEER 3 at baseline[1]**

| | Oral semaglutide 3 mg n=466 | Oral semaglutide 7 mg n=465* | Oral semaglutide 14 mg n=465 | Sitagliptin 100 mg n=467 |
|---|---|---|---|---|
| Diabetic retinopathy | 73 (15.7) | 73 (15.7) | 74 (15.9) | 81 (17.3) |

Data are n (%). Events identified using MedDRA (version 20.1) terms. *One patient was randomised in error; no assessments were done after screening.

**Table 2. Diabetic retinopathy in PIONEER 6 at baseline[2]**

| | Oral semaglutide 14 mg n=1591 | Placebo n=1592 |
|---|---|---|
| Diabetic retinopathy | 454 (28.5) | 444 (27.9) |

Data are n (%). Events identified using MedDRA (version 20.1) terms.

- Across both of these studies, diabetic retinopathy-related AEs were infrequent and similar across all treatment groups
- In PIONEER 3, diabetic retinopathy-related AEs were mostly mild or moderate in severity, were reported at routine eye examinations, and did not require treatment (Table 3)





**Table 3. In-trial AEs related to diabetic retinopathy in PIONEER 3[1]**

| | Oral semaglutide 3 mg n=466 | Oral semaglutide 7 mg n=464 | Oral semaglutide 14 mg n=465 | Sitagliptin 100 mg n=466 |
|---|---|---|---|---|
| Eye disorders | 31 (6.7) | 28 (6.0) | 26 (5.6) | 36 (7.7) |
| Diabetic retinopathy | 28 (6.0) | 24 (5.2) | 17 (3.7) | 29 (6.2) |
| Retinopathy | 1 (0.2) | 2 (0.4) | 4 (0.9) | 0 |
| Retinal haemorrhage | 1 (0.2) | 0 | 3 (0.6) | 2 (0.4) |
| Macular oedema | 0 | 2 (0.4) | 2 (0.4) | 1 (0.2) |
| Maculopathy | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| Diabetic retinal oedema | 3 (0.6) | 0 | 0 | 1 (0.2) |
| Retinal detachment | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Retinopathy proliferative | 0 | 0 | 0 | 1 (0.2) |
| Vitreous detachment | 1 (0.2) | 0 | 0 | 2 (0.4) |
| Vitreous haemorrhage | 0 | 1 (0.2) | 0 | 1 (0.2) |

Data are n (%). Events identified using search of MedDRA (version 20.1) terms. In-trial is defined as the period from randomisation to the final follow-up visit.

- In PIONEER 6, most diabetic retinopathy-related AEs were non-proliferative, and more than 70% required no treatment (Table 4)

**Table 4. In-trial AEs related to diabetic retinopathy in PIONEER 6[2]**

| | Oral semaglutide 14 mg n=1591 | Placebo n=1592 |
|---|---|---|
| Eye disorders | 113 (7.1) | 101 (6.3) |
| Diabetic retinopathy | 93 (5.8) | 76 (4.8) |
| Retinopathy | 7 (0.4) | 17 (1.1) |
| Maculopathy | 5 (0.3) | 3 (0.2) |
| Diabetic retinal oedema | 4 (0.3) | 1 (0.1) |
| Macular oedema | 4 (0.3) | 8 (0.5) |
| Vitreous detachment | 4 (0.3) | 0 |
| Retinal haemorrhage | 2 (0.1) | 0 |
| Retinal detachment | 1 (0.1) | 0 |
| Vitreous haemorrhage | 1 (0.1) | 1 (0.1) |
| Retinopathy proliferative | 0 | 1 (0.1) |

Data are n (%). Events identified using search of MedDRA (version 20.1) terms. In-trial is defined as the period from randomisation to the final follow-up visit.

# APPENDIX

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