

**EVIDENCE BRIEFING**  
**August 2018**

**Oral Semaglutide for the treatment of type 2  
diabetes mellitus**

<b>NIHRI ID</b>	11550	<b>NICE ID</b>	9551
<b>Developer/Company</b>	Novo Nordisk Ltd	<b>UKPS ID</b>	643361

**Licencing and market  
availability plans**

Oral semaglutide is currently in phase III clinical studies for the treatment of type 2 diabetes mellitus

**SUMMARY**

Semaglutide is in clinical development as an oral treatment for type 2 diabetes mellitus. Diabetes is a condition that causes blood sugar level to become too high. The majority of diabetes cases are type 2 diabetes, where the pancreas does not produce enough insulin or the body cells do not respond properly to insulin ('insulin resistance'). Treatment of type 2 diabetes aim to control blood glucose levels and involves a combination of lifestyle strategies (healthy diet, weight control) and use of oral medications. Medication is usually used for those where lifestyle changes do not control blood glucose. Insulin injections are usually used for those in whom lifestyle changes and medications cannot control blood glucose levels.

Semaglutide works by increasing the amount of insulin released from the pancreas and by delaying how quickly food moves through your digestive system, which aid in controlling blood sugar levels. Semaglutide belongs to a class of antidiabetic medications called glucagon-like peptide 1 (GLP-1) receptor agonist. Most other medications in this class are administered by injection under the skin. If licensed, semaglutide will be the first effective oral GLP-1 analogue for the treatment of type 2 diabetes and may improve acceptance and adherence for some patients compared with the injectable formulation of GLP-1 receptor agonists.

## PROPOSED INDICATION

Type 2 diabetes mellitus in adults<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Semaglutide (NN-9924) is a glucagon-like peptide 1 (GLP-1) receptor agonist. Semaglutide affects glucose control through several different mechanisms including; the increase of insulin secretion, slowing of gastric emptying, and the reduction of postprandial glucagon and food intake. Glucose homeostasis depends on hormones such as insulin and amylin secreted in pancreatic beta cells, glucagon secreted in pancreatic alpha cells and gastrointestinal peptides like GLP-1 and glucose-dependent insulinotropic polypeptide. When glucose is administered orally, GLP-1 stimulates the synthesis of insulin by stimulating pancreatic islets, and will slow the gastric emptying, inhibit post-meal glucagon release and reduce food intake. GLP-1 has a major role in glucose management and semaglutide presents an analog structure which allows it to perform all the activities of natural GLP-1.<sup>2</sup>

Oral semaglutide is in clinical development for the treatment of type 2 diabetes mellitus. In the phase III clinical trial (PIONEER 3; NCT02607865), semaglutide is administered orally at a dose of 3mg, 7mg or 14mg once daily.<sup>1,3</sup>

### INNOVATION AND/OR ADVANTAGES

GLP-1 analogues are peptide based drugs, which presents significant challenges in the development of oral formulations as peptide based drugs usually undergo proteolytic degradation in the gastrointestinal tract. However, oral semaglutide combines semaglutide in a tablet co-formulated with the absorption enhancer sodium N-[8 (2-hydroxybenzoyl) amino] caprylate (SNAC). Semaglutide tablets are absorbed in the stomach, where SNAC causes a localized increase in pH, leading to higher solubility and protection against proteolytic degradation. Semaglutide is then believed to be absorbed via the transcellular route.<sup>4</sup>

Oral semaglutide would be the first oral GLP-1 analogue licenced for the treatment of type 2 diabetes and may improve acceptance and adherence for some patients compared with the injectable formulation of GLP-1 receptor agonists.<sup>4</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Oral semaglutide does not currently have Marketing Authorisation in the EU for any indication.<sup>5</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

Type 2 diabetes mellitus (T2D) is a lifelong condition which constitutes 90% of all diabetes cases. Normally, the pancreas will release insulin in response to increased blood glucose levels which allows the body's cells to absorb glucose.<sup>6</sup> In T2D, insulin resistance and/or deficiency in insulin secretion by the pancreas results in abnormal carbohydrate, fat and protein metabolism.<sup>7</sup>

There are several factors which increase the risk of developing T2D. These include:<sup>7</sup>

- obesity - which accounts for 80-85% of the overall risk of developing T2D
- Physical Inactivity
- Family history - risk of developing T2D is 15% if one parent has T2D and 75% if both parents have T2D
- Ethnicity - people of Asian and African ethnicity are two to four times more likely to develop T2D than those of Caucasian ethnicity
- History of gestational diabetes
- Poor dietary habits - low fibre, high GI diets
- The use of certain drugs e.g. statins, corticosteroids and thiazide diuretic plus a beta-blocker combinations
- Polycystic ovarian syndrome
- Metabolic syndrome
- Low birth weight for gestational age

Symptoms of T2D include increased need to urinate, constant thirst, weight fluctuations, feeling extremely tired, blurred vision and regular genito-urinary infections.<sup>8</sup>

If T2D is not adequately controlled, this may result in hyperglycaemia, which in itself has numerous associated complications. These can include kidney failure, nerve damage, damage to vision (sometimes even causing blindness), heart disease, stroke, peripheral arterial disease, foot ulcers (which can eventually lead to foot or lower leg amputation), persistent or regular infections (e.g. skin or urine infections) and dementia. Very rarely, blood glucose can reach dangerously high levels, leading to a condition called hyperosmolar hyperglycaemic state in which people become very dehydrated and lose consciousness.

Hypoglycaemia can also be a complication of T2D where blood glucose levels become too low (which can be caused by not eating enough carbohydrate while taking insulin, missing meals or medications, drinking too much alcohol or doing more physical activity than usual). Symptoms of hypoglycaemia include feeling hungry, increased sweating, heart palpitations, anxiety and irritability, tingling lips, feeling tired and confused and blurred vision. If hypoglycaemia is not treated, this can result in fits, loss of consciousness and death.<sup>8</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

In England in 2016-2017 the prevalence of diagnosed cases of diabetes was 3,116,399. If 90% of these cases are T2D, the prevalence of T2D in England in 2016-2017 was 2,804,759.<sup>9</sup> In England in 2015, there were 194,640 newly diagnosed cases of T2Ds.<sup>10</sup>

When T2D is not well managed, it can be associated with many serious complications. By the time of diagnosis, half of people with T2Ds will show signs of complications. Complications may begin five to

six years before diagnosis and the actual onset of diabetes may be ten years or more before clinical diagnosis. These complications can include:<sup>11</sup>

- Cardiovascular disease (CVD) - accounting for 52% of fatalities in people with T2D. T2D also increases risk of various CVD including a 2 fold increased risk of stroke, 75.7% and 55.1% increased risk of hospital admissions due to angina and myocardial infarction respectively.
- Kidney Disease – Approximately 20% people with diabetes will develop kidney disease requiring treatment during their lifetime. Kidney disease accounts for 11% of deaths in T2D.
- Diabetic neuropathy - accounts for approximately 7% of people registered blind in England and Wales and within 20 years of diagnosis approximately 60% people with T2D have some degree of retinopathy.
- Amputation - Diabetes is the most common cause of lower limb amputation with over 100 amputations per week performed in people with diabetes. Amputations are generally preceded by foot ulceration and approximately 2.5% people with diabetes have foot ulcers at any given time, equating to approximately 80,000 people with foot ulcers across the UK.
- Depression – People with diabetes are two times more likely to suffer an episode of depression. Also people who suffer with depression are 60% more likely to develop T2D
- Neuropathy – affect up to 50% of patients with diabetes. Chronic painful neuropathy is estimated to affect up to 26% of people with diabetes.
- Pregnancy complications – babies born to diabetic women are five times more likely to be stillborn, three times more likely to die in their first months of life and three to six times more likely to have a major congenital anomaly. Women with diabetes are also five times more likely to have a pre-term baby compared to women without diabetes and three times more likely to have caesarean section delivery. Dementia – people with T2D are at 1.5-2.5 fold increased risk of dementia

In England and Wales, people with T2D have 34.5% greater risk of mortality compared to the general population. For T2D, life expectancy for someone diagnosed in their 50s is reduced by an average of 6 years. It is currently estimated that 10% of NHS budget is spent on diabetes which equates to about £10 billion. The total cost (including direct and indirect costs) associated with diabetes in the UK is currently £23.7 billion and this is expected to rise to 39.8 billion in 2035/2036.<sup>11</sup>

## PATIENT TREATMENT PATHWAY

### PATIENT PATHWAY

Treatment of T2D usually takes into account personal treatment preferences, co-morbidities and potential polypharmacy. The main aim of T2D treatment is to control blood glucose levels. This may include lifestyle changes and medication.<sup>7,8</sup>

Self-help strategies are usually tried first to control blood glucose levels which include eating a balanced, healthy diet and taking part in regular exercise to maintain a healthy weight and reduce risk of high blood pressure and high cholesterol levels. Medication is usually used for those where lifestyle changes do not control blood glucose. Insulin injections are usually used for those in whom lifestyle changes and medications cannot control blood glucose levels.<sup>8</sup>

### CURRENT TREATMENT OPTIONS

- Lifestyle advice – encourage healthy balanced diet, increased physical activity and weight loss (where appropriate)<sup>7</sup>
- Anti-diabetic medication:<sup>7</sup>
  - First line - standard release metformin
  - First line (if metformin is contraindicated/not tolerated) – gliptin, pioglitazone, a sulfonylurea or a sodium-glucose cotransporter 2 inhibitor (SGLT-2i)
  - Second line – dual therapy of metformin plus gliptin, pioglitazone, a sulfonylurea and a SGLT-2i
  - Second line (if metformin is contraindicated/not tolerated) - gliptin plus pioglitazone or a sulfonylurea, or pioglitazone plus a sulfonylurea, or a SGLT-2i instead of a gliptin if a sulfonylurea or pioglitazone is not appropriate
  - Third line – triple therapy with metformin, a gliptin and a sulfonylurea or pioglitazone and a sulfonylurea or triple therapy with metformin, pioglitazone or a sulfonylurea and an SGLT-2i, or insulin-based treatment
  - Fourth line - combination treatment with metformin, a sulfonylurea, and a glucagon-like peptide-1(GLP-1) mimetic or insulin plus GLP-1.

## PLACE OF TECHNOLOGY

If licenced, oral semaglutide could be the first oral GLP-1 analogue for the treatment of T2D, as all currently licensed GLP-1 analogues are delivered by subcutaneous injection.<sup>4,12</sup>

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	PIONEER 1, <a href="#">NCT02906930</a> , 2015-005622-19, U1111-1177-5112; oral semaglutide vs placebo; phase III
<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	Published
<b>Source of Information</b>	Publication, <sup>13</sup> , Press Release <sup>14</sup> , Trial registry <sup>15</sup>
<b>Location</b>	5 EU countries (not incl UK), USA, and other countries
<b>Design</b>	Randomised, placebo-controlled, parallel assignment, double blinded
<b>Participants</b>	n=703; aged 18 years and older; diagnosed type 2 diabetes
<b>Schedule</b>	Participants were randomised to one of four study arms: <ol style="list-style-type: none"> <li>1. 3mg oral semaglutide once daily</li> <li>2. 7mg oral semaglutide once daily</li> <li>3. 14mg oral semaglutide once daily</li> <li>4. oral placebo once daily</li> </ol>
<b>Follow-up</b>	Follow up – up to 31 weeks
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in glycated haemoglobin (HbA1c) [Time Frame: Week 0, Week 26]</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in Body weight (kg) [Time Frame: Week 0, Week 26]</li> <li>• Change in Fasting plasma glucose [Time Frame: Week 0, Week 26]</li> <li>• HbA1c below 7.0% (53 mmol/mol) [Time Frame: At week 26]</li> <li>• Number of treatment-emergent adverse events [Time Frame: Weeks 0-31]</li> </ul>

	<ul style="list-style-type: none"> <li>Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes [Time Frame: Weeks 0-31]</li> </ul>
<b>Key Results</b>	<p>Applying the intention-to-treat principle, the trial achieved its primary objective by demonstrating that people treated with any of the three doses of oral semaglutide achieved significant HbA1c reductions compared to placebo (<math>p &lt; 0.001</math> for all estimated treatment differences [ETD] in A1C for oral semaglutide vs placebo). Furthermore, applying the intention to treat principal, people treated with 14 mg oral semaglutide achieved significant reductions (<math>p &lt; 0.001</math>) in weight vs placebo while weight reductions with 7 mg and 3 mg doses did not reach statistical significance. When applying the on-treatment principle, from a mean baseline A1C of 8.0%, people treated with 3, 7 and 14 mg oral semaglutide achieved A1C reductions of 0.8%, 1.3% and 1.5%, respectively, compared to 0.1% with placebo (<math>p &lt; 0.001</math> vs placebo for ETD of oral semaglutide vs placebo). In addition, applying the on-treatment principal, 59%, 72% and 80% of people respectively treated with oral semaglutide achieved the ADA treatment target of A1C below 7%, compared to 34% treated with placebo (<math>p &lt; 0.001</math> for odds for achieving the target).<sup>14</sup></p> <p>When applying the on-treatment principle, people treated with 3, 7 and 14 mg oral semaglutide experienced a weight loss of 1.7 kg (3.7 lb), 2.5 kg (5.5 lb) and 4.1 kg (9.0 lb), respectively, compared to 1.5 kg (3.3 lb) with placebo (<math>p &lt; 0.001</math> for ETD of oral semaglutide 14 mg vs placebo, <math>p &lt; 0.05</math> for oral semaglutide 7 mg vs placebo, oral semaglutide 3 mg vs placebo was not statistically significant). Moreover, applying the on-treatment principal, 21%, 29% and 44% of people treated with oral semaglutide achieved a weight reduction of 5% or more compared to 16% with placebo.<sup>14</sup></p>
<b>Adverse effects (AEs)</b>	<p>The most common adverse events (&gt;5%) were transient, mild or moderate nausea, which occurred in 5–16% of people treated with oral semaglutide compared with 6% in those treated with placebo. Overall, adverse events were reported by 58%, 53% and 57% of people treated with 3, 7 and 14 mg oral semaglutide, respectively, and in 56% of people treated with placebo. Treatment discontinuation due to adverse events ranged from 2% to 7% for people treated with oral semaglutide, compared to 2% for people treated with placebo.<sup>14</sup></p>
<b>Expected reporting date</b>	-

<b>Trial</b>	PIONEER 2, <a href="#">NCT02863328</a> , 2015-005209-36, U1111-1176-6006; oral semaglutide vs empagliflozin; phase III
<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	Published
<b>Source of Information</b>	Press Release, <sup>16</sup> Trial registry <sup>17</sup>
<b>Location</b>	7 EU countries (not incl UK), USA, Argentina, Brazil, Russia, Thailand
<b>Design</b>	Randomised , active-controlled, parallel assignment, open label

<b>Participants</b>	n=827; aged 18 years and older; stable daily dose of metformin; diagnosed type 2 diabetes
<b>Schedule</b>	Participants were randomised to one of two treatment arms: <ol style="list-style-type: none"> <li>1. Experimental arm: 14mg oral semaglutide administered orally once daily</li> <li>2. Active comparator: 25mg empagliflozin administered orally once daily</li> </ol>
<b>Follow-up</b>	Follow-up for up to 52 weeks
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in glycosylated haemoglobin (HbA1c) [Time Frame: Week 0, Week 26]</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in Body weight (kg) [Time Frame: Week 0, Week 26, Week 52]</li> <li>• Change in Fasting plasma glucose [Time Frame: Week 0, Week 26, Week 52]</li> <li>• HbA1c below 7.0 % (53 mmol/mol) [Time Frame: At week 26 and 52]</li> <li>• Number of treatment-emergent adverse events [Time Frame: Weeks 0-57]</li> <li>• Number of treatment-emergent severe symptomatic hypoglycaemic episodes [Time Frame: Weeks 0-57]</li> <li>• Number of treatment-emergent severe blood glucose-confirmed symptomatic hypoglycaemic episodes [Time Frame: Weeks 0-57]</li> </ul>
<b>Key Results</b>	<p>When applying the on treatment principal, people treated with 14 mg oral semaglutide achieved a statistically significant improvement in HbA<sub>1c</sub> of 1.4% at 26 weeks and 1.3% at 52 weeks, compared to an improvement in HbA<sub>1c</sub> of 0.9% and 0.8% with 25 mg empagliflozin at 26 and 52 weeks, respectively. When applying the on-treatment principal, the 14 mg dose of oral semaglutide demonstrated weight loss of 4.2 kg at 26 weeks and 4.7 kg at 52 weeks versus 3.8 kg with 25 mg empagliflozin at both 26 weeks and 52 weeks. The increased weight loss with oral semaglutide was statistically significant compared to empagliflozin at the 52-week time point.<sup>16</sup></p> <p>In addition, applying the on-treatment principal, the American Diabetes Association (ADA) treatment target of HbA<sub>1c</sub> below 7.0% was achieved by 72% of people treated with 14 mg oral semaglutide compared with 47% of people treated with 25 mg empagliflozin at 52 weeks.<sup>16</sup></p>
<b>Adverse effects (AEs)</b>	The most common adverse event for oral semaglutide was mild to moderate nausea, which diminished over time. In PIONEER 2, 20% of people treated with oral semaglutide experienced nausea during the trial. The proportion of subjects who discontinued treatment due to adverse events was 11% for people treated with 14 mg oral semaglutide compared to 4% for people treated with 25 mg empagliflozin. <sup>16</sup>
<b>Expected reporting date</b>	-

<b>Trial</b>	PIONEER 3, <a href="#">NCT02607865</a> , 2015-001351-71, U1111-1168-4339; oral semaglutide vs sitagliptin; phase III
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<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	Published
<b>Source of Information</b>	Press Release, <sup>3</sup> Trial registry <sup>1</sup>
<b>Location</b>	6 EU countries (incl the UK), USA and other countries
<b>Design</b>	Randomised, active-controlled, double blind, parallel assignment
<b>Participants</b>	n=1864; aged 18 years and older; stable daily dose of metformin alone or in combination with sulfonylurea; diagnosed type 2 diabetes
<b>Schedule</b>	Participants were randomised into one of 4 treatment arms: <ol style="list-style-type: none"> <li>1. 3mg oral semaglutide administered orally once daily</li> <li>2. 7mg oral semaglutide administered orally once daily</li> <li>3. 14mg oral semaglutide administered orally once daily</li> <li>4. 100mg sitagliptin administered orally once daily</li> </ol>
<b>Follow-up</b>	Follow-up for up to 78 weeks
<b>Primary Outcomes</b>	Change in HbA1c (glycosylated haemoglobin) [Time Frame: Week 0, week 26]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in body weight (kg) [Time Frame: Week 0, week 26]</li> <li>• Change in FPG (fasting plasma glucose) [Time Frame: Week 0, week 26]</li> <li>• Subjects who achieve HbA1c below 7.0% (53 mmol/mol), American Diabetes Association (ADA) target (yes/no) [Time Frame: At week 26]</li> <li>• Subjects who achieve HbA1c below 7.0% (53 mmol/mol), American Diabetes Association (ADA) target (yes/no) [Time Frame: At week 52]</li> <li>• Subjects who achieve HbA1c below 7.0% (53 mmol/mol), American Diabetes Association (ADA) target (yes/no) [Time Frame: At week 78]</li> <li>• Change in HbA1c [Time Frame: Week 0, Week 52]</li> <li>• Change in HbA1c [Time Frame: Week 0, Week 78]</li> <li>• Change in body weight (kg) [Time Frame: Week 0, Week 52]</li> <li>• Change in body weight (kg) [Time Frame: Week 0, Week 78]</li> <li>• Change in FPG [Time Frame: Week 0, Week 52]</li> <li>• Change in FPG [Time Frame: Week 0, Week 78]</li> </ul>
<b>Key Results</b>	The trial achieved its primary objective according to the intension to treat principal by demonstrating statistically significant and superior reductions in HbA <sub>1c</sub> with oral semaglutide 7 and 14 mg compared to sitagliptin at week 26. Furthermore, people treated with oral semaglutide 7 and 14 mg achieved statistically significant and superior reductions in body weight compared to sitagliptin at week 26. When applying the on treatment principal for week 26

	and week 78, respectively, people treated with 7 and 14 mg oral semaglutide experienced statistically significantly greater reductions in HbA <sub>1c</sub> of 1.1% and 0.7% with 7 mg oral semaglutide, 1.4% and 1.1% with 14 mg oral semaglutide compared to 0.8% and 0.4% with sitagliptin. Reductions in HbA <sub>1c</sub> with 3 mg oral semaglutide at 26 and 78 weeks were 0.5% and 0.3%, respectively, and the reduction was statistically significantly less than sitagliptin at 26 week, but was not statistically different at week 78. Reductions in body weight from baseline were statistically significantly greater with 3, 7 and 14 mg oral semaglutide at week 26 and 78, respectively, with reductions of 1.2 and 1.9 kg for 3 mg oral semaglutide, 2.2 and 2.7 kg for 7 mg oral semaglutide and 3.3 and 3.5 kg for 14 mg oral semaglutide compared to 0.7 and 1.1 kg with sitagliptin. <sup>3</sup>
<b>Adverse effects (AEs)</b>	The most common adverse event for oral semaglutide was mild to moderate nausea, which diminished over time. In PIONEER 3, 7-15% of people treated with oral semaglutide experienced nausea, compared to 7% of people treated with sitagliptin. The proportion of people who discontinued treatment due to adverse events was 6-12% for people treated with oral semaglutide compared to 5% with sitagliptin. <sup>3</sup>
<b>Expected reporting date</b>	-

<b>Trial</b>	PIONEER 4, <a href="#">NCT02863419</a> , 2015-005210-30, U1111-1176-6029; oral semaglutide vs liraglutide vs placebo; phase III
<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	Published
<b>Source of Information</b>	Press Release, <sup>18</sup> Trial registry <sup>19</sup>
<b>Location</b>	8 EU countries (not incl UK), USA, Japan, Puerto Rico, South Africa, United Arab Emirates,
<b>Design</b>	Randomised, placebo-controlled, active-controlled, double blinded, parallel assignment
<b>Participants</b>	n=711; aged 18 years and older; stable daily dose of metformin alone or in combination with a stable daily dose of a SGLT-2 inhibitor; diagnosed with type 2 diabetes
<b>Schedule</b>	Participants were randomised to one of three treatment arms: <ol style="list-style-type: none"> <li>1. Experimental arm: semaglutide administered orally once daily</li> <li>2. Active comparator: liraglutide administered by subcutaneous injection once daily</li> <li>3. Placebo arm: placebo administered once daily</li> </ol>
<b>Follow-up</b>	Follow-up for up to 57 weeks
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in HbA<sub>1c</sub> [Time Frame: Week 0, week 26]</li> </ul>

<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in HbA1c [Time Frame: Week 0, week 52]</li> <li>• Change in body weight (kg) [Time Frame: Week 0, Week 26, Week 52]</li> <li>• Change in Fasting plasma glucose [Time Frame: Week 0, Week 26, Week 52]</li> <li>• HbA1c below 7.0 % (53 mmol/mol) [Time Frame: At week 26 and 52]</li> <li>• Number of treatment-emergent adverse events [Time Frame: Weeks 0-57]</li> <li>• Number of treatment-emergent severe symptomatic hypoglycaemic episodes [Time Frame: Weeks 0-57]</li> <li>• Number of treatment-emergent blood glucose-confirmed symptomatic hypoglycaemic episodes [Time Frame: Weeks 0-57]</li> </ul>
<b>Key Results</b>	<p>PIONEER 4 achieved its primary objective according to the intension to treat principal approach by demonstrating a non-inferior reduction in HbA<sub>1c</sub> and statistically significant and superior weight loss at 26 weeks with oral semaglutide compared to liraglutide. Furthermore, oral semaglutide provided statistically significant and superior reductions in HbA<sub>1c</sub> and weight compared to placebo.<sup>18</sup></p> <p>When applying the on treatment principal for week 26 and week 52, respectively, people treated with oral semaglutide experienced a reduction in HbA<sub>1c</sub> of 1.3% and 1.2% compared to 1.1% and 0.9% with liraglutide whereas placebo declined by 0.1% and increased by 0.2%. Reductions in HbA<sub>1c</sub> were statistically significantly greater with oral semaglutide compared to both liraglutide and placebo. Reduction in body weight from baseline was statistically significantly greater with oral semaglutide at 4.7 and 5.0 kg at 26 and 52 weeks, respectively, compared to 3.2 and 3.1 kg with liraglutide, and 0.7 and 1.2 kg with placebo. The American Diabetes Association (ADA) treatment target of HbA<sub>1c</sub> below 7.0% was achieved by 69% of people treated with oral semaglutide, 63% of people treated with liraglutide and 18% of people treated with placebo after 52 weeks; the difference between oral semaglutide and placebo was statistical significant.<sup>18</sup></p>
<b>Adverse effects (AEs)</b>	<p>The most common adverse event for oral semaglutide was mild to moderate nausea which diminished over time. In PIONEER 4, 20% of people treated with oral semaglutide experienced nausea, compared to 18% of people treated with liraglutide and 4% of people treated with placebo. The proportion of people who discontinued treatment due to adverse events was 11% for people treated with oral semaglutide compared to 9% for people treated with liraglutide and 4% for people receiving placebo.<sup>18</sup></p>
<b>Expected reporting date</b>	<p>-</p>
<b>Trial</b>	<p>PIONEER 5, <a href="#">NCT02827708</a>, 2015-005326-19, U1111-1176-9230; oral semaglutide vs placebo; phase III</p>

<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	Complete but unpublished
<b>Source of Information</b>	Trial registry <sup>20</sup>
<b>Location</b>	5 EU countries (incl UK), USA, Israel and Russian Federation
<b>Design</b>	Randomised, placebo-controlled, double blinded, parallel assignment
<b>Participants</b>	n=324; aged 18 years and older; diagnosed with type 2 diabetes; moderate renal impairment; stable daily dose of 1-2 oral antidiabetic drugs: metformin, sulfonylurea, basal insulin alone, metformin in combination with basal insulin
<b>Schedule</b>	Participants were randomised into one of two treatment arms: <ol style="list-style-type: none"> <li>1. Experimental arm: semaglutide administered orally once daily</li> <li>2. Placebo arm: placebo administered orally once daily</li> </ol>
<b>Follow-up</b>	Follow-up for up to 31 weeks
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in glycosylated haemoglobin (HbA1c) [Time Frame: Week 0, Week 26]</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in body weight (kg) [Time Frame: Week 0, Week 26]</li> <li>• Change in fasting plasma glucose [Time Frame: Week 0, Week 26]</li> <li>• HbA1c below 7.0% [Time Frame: At week 26]</li> <li>• Number of treatment-emergent adverse events [Time Frame: Weeks 0-31]</li> <li>• Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes [Time Frame: Weeks 0-31]</li> </ul>
<b>Key Results</b>	Not reported
<b>Adverse effects (AEs)</b>	Not reported
<b>Expected reporting date</b>	Previously reported as August 2018

<b>Trial</b>	PIONEER 6, <a href="#">NCT02692716</a> , 2015-003563-10, U1111-1173-0750; oral semaglutide vs placebo; phase III
<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	ongoing – not recruiting
<b>Source of Information</b>	trial registry <sup>21</sup>
<b>Location</b>	8 EU countries (including UK), 2 countries in South America, 2 countries in Africa, 6 countries in Asia, Mexico, Canada, USA

<b>Design</b>	Randomised, placebo-controlled, double blinded, parallel assignment
<b>Participants</b>	n=3176 (planned); aged 50 years and older; diagnosed with type 2 diabetes; aged at least 50 years old and presence of cardiovascular disease or aged at least 60 years old and presence of at least one cardiovascular risk factor
<b>Schedule</b>	Participants were randomised to one of two treatment arms: <ol style="list-style-type: none"> <li>1. Experimental arm: oral semaglutide administered orally once daily</li> <li>2. Placebo arm: placebo administered orally once daily</li> </ol>
<b>Follow-up</b>	Follow up for up to 19 months
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke [Time Frame: From randomisation up to 19 months]</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• From randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure [Time Frame: From randomisation up to 19 months]</li> <li>• Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint [Time Frame: From randomisation up to 19 months]</li> <li>• Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke [Time Frame: From randomisation up to 19 months]</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Study completion date reported as September 2018.

<b>Trial</b>	PIONEER 7, <a href="#">NCT02849080</a> , 2015-005593-38, U1111-1177-5103; oral semaglutide vs sitagliptin; phase III
<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	ongoing – not recruiting
<b>Source of Information</b>	Press Release, <sup>18</sup> trial registry <sup>22</sup>
<b>Location</b>	3 EU countries (excluding UK), Argentina, Brazil, Egypt, Republic of Korea, Switzerland, Turkey, USA
<b>Design</b>	Randomised, active-controlled, parallel assignment
<b>Participants</b>	n=500 (planned); aged 18 years or older; diagnosed with type 2 diabetes; stable daily doses of 1-2 anti-diabetic drugs: metformin (= or > 1500mg or maximum

	tolerated dose), sulfonylureas (= or above half the maximum approved dose), thiazolidinediones (= or above half the maximum approved dose)
<b>Schedule</b>	Participants were randomised to one of two treatment arms: <ol style="list-style-type: none"> <li>1. Experimental arm: oral semaglutide flexible dosing (3, 7 or 14mg) administered orally once daily</li> <li>2. Active comparator: 100mg sitagliptin administered orally once daily</li> </ol>
<b>Follow-up</b>	Follow-up up to 57 weeks
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Main phase: Glycosylated haemoglobin (HbA1c) below 7% (53 mmol/mol) American Diabetes Association target (yes/no) [Time Frame: After week 52]</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Main phase: Change in body weight (kg) [Time Frame: Week 0, week 52]</li> <li>• Main phase: Change in HbA1c [Time Frame: Week 0, week 52]</li> <li>• Main phase: Change in fasting plasma glucose (FPG) [Time Frame: Week 0, week 52]</li> <li>• Main phase: Number of treatment-emergent adverse events during exposure to trial product [Time Frame: Week 0 - week 52]</li> <li>• Main phase: Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product [Time Frame: Week 0 - week 52]</li> <li>• Ext. phase (sustainability): HbA1c below 7% (53 mmol/mol) American Diabetes Association target (yes/no) [Time Frame: After week 104]</li> <li>• Ext. phase (sustainability): Change in body weight (kg) [Time Frame: Week 0, week 104]</li> <li>• Ext. phase (sustainability): Change in HbA1c [Time Frame: Week 0, week 104]</li> <li>• Ext. phase (sustainability): Change in FPG [Time Frame: Week 0, week 104]</li> <li>• Ext. phase (sustainability): Number of treatment-emergent adverse events during exposure to trial product [Time Frame: Week 0 - week 109]</li> <li>• Ext. phase (sustainability): Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product [Time Frame: Week 0 - week 109]</li> <li>• Ext. phase (switch): HbA1c below 7% (53 mmol/mol) American Diabetes Association target (yes/no) [Time Frame: After week 104]</li> <li>• Ext. phase (switch): Change in body weight (kg) [Time Frame: Week 52, week 104]</li> <li>• Ext. phase (switch): Change in HbA1c [Time Frame: Week 52, week 104]</li> <li>• Ext. phase (switch): Change in FPG [Time Frame: Week 52, week 104]</li> </ul>

	<ul style="list-style-type: none"> <li>• Ext. phase (switch): Number of treatment-emergent adverse events during exposure to trial product [Time Frame: Week 52 - week 109]</li> <li>• Ext. phase (switch): Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product [Time Frame: Week 52 - week 109]</li> </ul>
<b>Key Results</b>	<p>The trial achieved its primary objective according to the intension to treat principal by demonstrating that oral semaglutide was statistically significant and superior to sitagliptin 100 mg in the proportion of people achieving the American Diabetes Association (ADA) treatment target of HbA<sub>1c</sub> below 7% at week 52. Oral semaglutide also demonstrated statistically significant and superior reductions in body weight versus sitagliptin.<sup>18</sup></p> <p>When applying the on-treatment principal, people treated with oral semaglutide experienced a statistically significant reduction in HbA<sub>1c</sub> of 1.4% compared to 0.7% with sitagliptin at week 52. From a baseline HbA<sub>1c</sub> of 8.3%, 63% of people treated with oral semaglutide achieved the target HbA<sub>1c</sub> below 7% after 52 weeks of treatment compared to 28% of people treated with sitagliptin, and the difference was statistically significant. The reduction in body weight of 2.9 kg with oral semaglutide was statistically significantly greater at week 52 compared to 0.8 kg with sitagliptin. After 52 weeks of treatment, approximately 9% of the people receiving oral semaglutide treatment were receiving 3 mg oral semaglutide, while approximately 31% and 60% were receiving 7 mg and 14 mg oral semaglutide, respectively.<sup>18</sup></p>
<b>Adverse effects (AEs)</b>	<p>In the trial, oral semaglutide was well-tolerated and with a profile consistent with GLP-1-based therapy. The most common adverse event for oral semaglutide was mild to moderate nausea, which diminished over time. In PIONEER 7, 21% of people treated with oral semaglutide experienced nausea, compared to 2% of people treated with sitagliptin. The proportion of people who discontinued treatment due to adverse events was 9% for people treated with oral semaglutide compared to 3% for people treated with sitagliptin.<sup>18</sup></p>
<b>Expected reporting date</b>	Previously reported as March 2018

<b>Trial</b>	PIONEER 8, <a href="#">NCT03021187</a> , 2016-000988-16, U1111-1180-3637; oral semaglutide vs placebo; phase III
<b>Sponsor</b>	Novo Nordisk A/S
<b>Status</b>	Ongoing – not recruiting
<b>Source of Information</b>	Trial registry <sup>23</sup>
<b>Location</b>	3 EU countries (not incl UK), Canada, USA and other countries
<b>Design</b>	Randomised, placebo-controlled, double blinded, parallel assignment

<b>Participants</b>	n=720 (planned); aged 18 years and older; diagnosed with type 2 diabetes, stable treatment with insulin regimes: basal insulin alone, basal and bolus insulin in any combination or premixed insulin including combinations of soluble insulins
<b>Schedule</b>	Participants were randomised to one of four treatment arms: <ol style="list-style-type: none"> <li>1. 3mg oral semaglutide administered orally once daily for 52 weeks as an add on to the subjects pre-trial insulin treatment</li> <li>2. 3mg and 7mg oral semaglutide administered orally (3mg followed by 7mg) once daily for 52 weeks as an add on to the subjects pre-trial insulin treatment</li> <li>3. 3mg and 7mg and 14mg oral semaglutide administered orally (3mg followed by 7mg and finally 14mg) once daily for 52 weeks as an add on to the subjects pre-trial insulin treatment</li> <li>4. Placebo administered orally once daily for 52 weeks as an add on to the subjects pre-trial insulin treatment</li> </ol>
<b>Follow-up</b>	Follow-up 52 weeks
<b>Primary Outcomes</b>	Change in HbA1c [Time Frame: Week 0, week 26]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in body weight [ Time Frame: Week 0, week 26 ]</li> <li>• Change in HbA1c [ Time Frame: Week 0, week 52 ]</li> <li>• Change in body weight [ Time Frame: Week 0, week 52 ]</li> <li>• Change in fasting plasma glucose (FPG) [ Time Frame: Week 0, week 26, week 52 ]</li> <li>• Number of treatment-emergent adverse events (TEAEs) during exposure to trial product [ Time Frame: Assessed up to approximately 57 weeks ]</li> <li>• Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product [ Time Frame: Assessed up to approximately 57 weeks ]</li> <li>• Change in 7-point self-measured plasma glucose (SMPG) profile - Mean 7-point profile [ Time Frame: Week 0, week 26, week 52 ]</li> <li>• Change in 7-point self-measured plasma glucose (SMPG) profile - Mean postprandial increment (over all meals) [ Time Frame: Week 0, week 26, week 52 ]</li> <li>• Change in body weight (%) [ Time Frame: Week 0, week 26, week 52 ]</li> <li>• Change in body mass index (BMI) [ Time Frame: Week 0, week 26, week 52 ]</li> <li>• Change in waist circumference [ Time Frame: Week 0, week 26, week 52 ]</li> <li>• Change in fasting lipid profile - total cholesterol [ Time Frame: Week 0, week 26, week 52 ]</li> </ul>

- Change in fasting lipid profile - low density lipoprotein [LDL]  
[ Time Frame: Week 0, week 26, week 52 ]
- Change in fasting lipid profile - high density lipoprotein [HDL]  
[ Time Frame: Week 0, week 26, week 52 ]
- Change in fasting lipid profile - triglycerides [ Time Frame: Week 0, week 26, week 52 ]
- Change in patient-reported outcome (PRO) - Short Form (SF)-36v2(TM) (acute version) health survey [ Time Frame: Week 0, week 26, week 52 ]
- Change in patient-reported outcome (PRO) - Impact of Weight on Quality of Life (IWQOL) [ Time Frame: Week 0, week 26, week 52 ]
- Change in patient-reported outcome (PRO) - Diabetes Treatment Satisfaction Questionnaire (DTSQs) [ Time Frame: Week 0, week 26, week 52 ]
- Achievement of HbA1c less than 7.0% (53 mmol/mol) (American Diabetes Association (ADA) target) (yes/no) [ Time Frame: Week 26, week 52 ]
- Achievement of HbA1c less than or equal to 6.5% (48 mmol/mol) (American Association of Clinical Endocrinologists (AACE) target) (yes/no) [ Time Frame: Week 26, week 52 ]
- Achievement of HbA1c reduction greater than or equal to 1%-point (10.9 mmol/mol) (yes/no) [ Time Frame: Week 26, week 52 ]
- Achievement of weight loss greater than or equal to 3% (yes/no) [ Time Frame: Week 26, week 52 ]
- Achievement of weight loss greater than or equal to 5% (yes/no) [ Time Frame: Week 26, week 52 ]
- Achievement of weight loss greater than or equal to 10% (yes/no) [ Time Frame: Week 26, week 52 ]
- Achievement of HbA1c below 7.0% (53 mmol/mol) without hypoglycaemia (treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemia) and no weight gain (yes/no) [ Time Frame: Week 26, WEEK 52 ]
- Achievement of HbA1c reduction greater than or equal to 1.0%-point (10.9 mmol/mol) and weight loss greater than or equal to 3% (yes/no) [ Time Frame: Week 26, Week 52 ]
- Time to rescue medication [ Time Frame: Week 0 - week 57 ]
- Change in total daily insulin dose (IU) [ Time Frame: Week 0, week 26, week 52 ]

	<ul style="list-style-type: none"> <li>• Number of treatment-emergent adverse events (TEAEs) during exposure to trial product [ Time Frame: Assessed up to approximately 26 weeks ]</li> <li>• Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product [ Time Frame: Assessed up to approximately 26 weeks ]</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Study completion date reported as August 2018

## ESTIMATED COST

The cost of oral semaglutide is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance in development. Ertugliflozin as monotherapy and in dual therapy for treating type 2 diabetes [ID1158]. Expected publication date 26 June 2019.
- NICE technology appraisal guidance in development. Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160]. Expected publication date 26 June 2019.
- NICE technology appraisal guidance. Dapagliflozin in triple therapy for treating type 2 diabetes (TA418). November 2016.
- NICE technology appraisal guidance. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (TA390). May 2016.
- NICE technology appraisal guidance. Empagliflozin in combination therapy for treating type 2 diabetes (TA336). March 2015.
- NICE technology appraisal guidance. Canagliflozin in combination therapy for treating type 2 diabetes (TA315). June 2014.
- NICE technology appraisal guidance. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (TA390). June 2013. Last updated 2016.
- NICE technology appraisal guidance. Dapagliflozin in combination therapy for treating type 2 diabetes (TA288). June 2013. Last updated November 2016.
- NICE guideline. Type 2 diabetes in adults: management (NG28). December 2015. Last updated May 2017.
- NICE guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). August 2015. Last updated November 2016.
- NICE quality standard. Diabetes in adults (QS6). March 2011. Last updated August 2016.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Insulin-Resistant Diabetes Services (All Ages). A03/S(HSS)/b

## OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network. Management of diabetes (SIGN: 116). March 2010. Last updated November 2017.<sup>24</sup>
- NICE clinical knowledge summaries. Diabetes – type 2. Last updated August 2017.<sup>7</sup>

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