Surrey Integrated Care Partnerships (ICPs) (East Surrey, Surrey Downs, Guildford & Waverley, North West Surrey) North West Sussex ICPs (Crawley, Horsham & Mid Sussex) & associated partner organisations

Evidence review for Surrey & North West Sussex Area Prescribing Committee (APC)

Medicine details	
Name, brand name	Semaglutide (Rybelsus)
Manufacturer	Novo Nordisk
Proposed indication	Oral semaglutide should be used as a secondline option to injectable GLP-1RA therapy when GLP-1 RA is suitable for the patient and injectable therapy is unacceptable to the patient. In the shorter term, during the Covid-19 pandemic, oral treatment may be used more to reduce numbers of patients having to attend injectionable initiation clinics.
Requested by	Diabetes Clinical Network

SUMMARY

Clinical Effectiveness

Oral semaglutide was studied in 10 trials prior to launch.[3-7,8-9,12, 17,18]

Six of the studies compared oral semaglutide to other antidiabetic agents commony used today: empagliflozin (an SGLT2 inhibitor), 2 trials with sitagliptin (a DPP4 inhibitor), liraglutide (the GLP-1 RA which was first licensed in the UK and is still commonly prescribed today) and dulaglutide (the most commonly prescribed weekly injectable GLP1-RA in the UK). The dulaglutide trial was completed in an exclusively Japanese population and used a lower dose of dulaglutide than recommended for use as an add-on treatment in the UK. This was unfortunate as a direct comparison with this product would have been very useful. There was also a second trial comparing oral semaglutide to liraglutide but again it was carried out exclusively in Japan and used a liraglutide dose which is not given in the UK.

In comparison to empagliflozin, oral semaglutide was significantly better at reducing HbA1c but about the same in terms of weight reduction at 26 weeks.

The first trial which compared oral semaglutide to **sitagliptin**, found that 7mg and 14mg doses were superior at lowering HbA1c at 26 weeks and this was sustained at 52 and 78weeks. It also led to significantly better weight loss at the same doses.The second trial produced similar results but used a more flexible regime to increase the doses of semaglutide which the patients received. At week 52, 9% of the oral semaglutide patients were receiving 3mg, 30% were on 7mg and 59% were on 14mg.

Compared to **liraglutide** there was not a clinically significant differance in HbA1c. However oral semaglutide did achieve significantly greater weight loss than liraglutide.

One study looked at the efficacy of oral semaglutide in patients with **renal impairment**. It was found that oral semaglutide was equally effective in this patient group and did not caue any further reduction in renal function.

Another trial looked at the incidence of CV events in patients treated with oral semaglutide compared to **placebo**. This study showed that oral semaglutide was non-inferior to

placebo but was not powered to demonstrate superiority or that oral semaglutide led to a reduction in major adverse cardiac events (which has been demonstrated for the injectable form of semagluide).

It must be noted that this compares unfavourably with injectable GLP-1 RAs, including injectable semaglutide, which have shown superiority v's placebo in terms of reduction of CV events. Indeed, sc semaglutide, seems to be the most potent of the injectable GLP-1 Ras currently on the market. This the main reason that oral semaglutide should be reserved for those patients unable to use injectable forms of treatment currently. There is another CV outcome trial looking at CV outcomes in oral semaglutide (SOUL) but that will not complete until 2024.

Finally oral semaglutide was trialled as an add on treatment for type 2 diabetic patients who were on **insulin**. They were found to have significantly reduced HbA1c, weight and insulin requirements after 52 weeks compared with those patients who were on the placebo arm of the trial.

Safety

The most common side effects with oral semaglutide are gastrointestinal symptoms, such as diarrhoea, nausea and vomiting. This is in line with the issues seen with the injectable form and was the most common reason for treatment discontinuation in the trials. The majority of adverse GI effects are seen during the initiation and dose escalation phase with oral semaglutide.

In patients with diabetic retinopathy treated with insulin and s.c. semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. This risk that cannot be excluded for orally administered semaglutide although no evidence of risk was found in the clinical trials for the oral product. Pre-existing retinopathy was an exclusion in all of the PIONEER studies.

Patients should have had a retinopathy screen within the year prior to starting treatment with oral semaglutide and caution should be exercised if starting oral semaglutide in a patient with a history of retinopathy. During the Covid Pandemic, some retinal screening has been delayed, so there is some discretion regarding this criterion and this requirement should be implemented on a case-by-case basis.

Caution should be exercised if starting semaglutide in a patient with a history of pancreatitis and all patients should be advised of the symptoms of acute pancreatitis and what to do if experienced.[1]

Patient factors

This is the first oral GLP-1 which makes it an option for patients who are unwilling or unable to self-inject glucose-lowering medications.

Although oral administration is a potential advantage with semaglutide, it must be taken correctly to ensure it is absorbed sufficiently (the oral bioavailability is about 1%) – tablet must be swallowed whole and on an empty stomach (30minutes before or 2 hours after food) with just a small amount of water (maximum of 120ml).

An injectable GLP-1 needs a considerable amout of clinician time to initiate. Semaglutide oral will require much less clinician time and save on resources – and this is also a considerable advantage during the current pandemic situation.

It should be noted that only about 5% of people in the efficacy trials were ≥ 75 years and there is no experience of the drug in severe renal failure.

Cost implications

Oral semaglutide costs about 9% more than semaglutide s.c. or dulaglutide s.c. weekly and a similar cost to weekly exenatide s.c, and 1.2mg daily liraglutide s.c.

In terms of budgetary impact, however, oral semaglutide availability will increase patient acceptability of GLP-1 treatment, as it can be expected that more patients will opt for this treatment rather than injectable alternatives – and possibly also earlier in their journey with the condition. This will increase the drug costs for the treatment of type 2 diabetes but hopefully also lead to reduced and delayed complications for the patient – so reducing the cost of diabetes complications. There is no data to confirm this currently.

It has been estimated that, if a 10% increase in the use of GLP-1 RAs was seen as a result of introduction of semaglutide oral within Surrey Heartlands, the cost of this drug group would increase by aproximately £250,000. More studies with long-term administration will be required before this can be elucidated.

The cost of oral semaglutide, may soon be higher relative to liraglutide as liraglutide comes off patent in Aug 2022, when biosimilar products may become available. Currently, there are no published plans for production of a generic version of liraglutide. Once it comes off patent, without a generic manufacturer to replace the branded product, there will be no change to the price of the injection.

Relevant guidance / reviews

The current NICE Guideline NG28: Type 2 diabetes in adults: management was published in December, 2015 and last updated in December 2020. It did not include any specific mention of semaglutide. Any recommendations for the GLP-1 analogues in this NG were made at drug class level and did not distinguish between them. The places identified in therapy for the drug class were as follows:

- If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who:
    - have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
    - have a BMI lower than 35 kg/m^2 **and**:
        - for whom insulin therapy would have significant occupational implications **or**
        - weight loss would benefit other significant obesity-related comorbidities.
- GLP-1 analogues should only be offered in combination with insulin with specialist care advice and ongoing support from a consultant and multidisciplinary team.
- GLP-1 analogue therapy should only be continued if the person has a beneficial metabolic response (reduction in HbA1c at least 11mmol.mol (1%) and a weight loss of at least 3% of initial body weight in 6 months).

Updated NICE clinical guidance for type 1 Diabetes was also published in December, 2020 but did not mention GLP-1 inhibitors at all. Updated NICE clinical guidance for diabetes in children (NG18) and pregnancy (NG3) were also published in December, 2020 but, again, did not contain any mention of GLP-1 receptor agonists.

In August 2020, the Scottish Medicines Commission acepted semaglutide tablets for restricted use in NHS Scotland as an alternative glucagon-like peptide-1 analogue option. It had previously accepted semaglutide injection use for the same indication (Jan, 2019). The summary highlighted that the effect of switching between oral and sc semaglutide could not be easily predicted because of the high variability in the bioavailability of oral semaglutide. The clinical effectiveness must be reviewed.

In September, 2020, the Northern Treatment Advisory Group made the following recommendation[19]:
Oral semaglutide is an option for patients with type 2 diabetes mellitus who require intensification of treatment, if use of a glucagon-like peptide 1 receptor agonist (GLP1RA) is clinically appropriate, in line with licensing and relevant guidance, and if an oral option is preferred. However, in patients with pre-existing cardiovascular disease or at high risk of cardiovascular (CV) events an agent with proven efficacy for CV risk reduction may be more suitable.

Likely place in therapy relative to current treatments

Oral semaglutide should be used in patients who have been assessed as suitable for a GLP1-RA but who are unable or unwilling to tolerate a weekly injection. They will have to understand the precise nature of how the tablets must be taken and why it is necessary. Currently, the CV risk reducation data is not strong for oral semaglutide and, for this reason, it remains a less preferred option compared to the injectable GLP-1 receptor agonists on Formulary.

Gastro-intestinal side effects do, however occur in a significant number of patients, particularly during the dose escalation phase of treatment. About 11% of patients discontinued treatment in the trials due to side effects which were mostly gastro-intestinal (usually nausea or diarrhoea). This compared to discontinuation rates of 4-6% for patients alternative antidiabetic agents(SGLT2 inhibitors or DPP4 inhibitors) and about 9% of liraglutide patients.

Liraglutide remains the first line GLP-1 for new patients who wish to have daily injections and dulaglutide is the preferred option for new patients requiring weekly injections. Semaglutide injection was also granted green status at the APC in December, 2020. Dulaglutide is the preferred injectable GLP-1 RA because it is no longer a ▼ drug and because the criticism of its potency has been addressed with the availability of 2 higher strengths (which have recently been launched).

Recommendation to APC

Oral semaglutide should be added to the formulary as a green drug, less preferred and as recommended in NICE NG28. i.e. It should be regarded as an alternative in patients who are suitable for this drug group but for whom injectable therapy is not acceptable (due to clinical reasons or patient preference).

Patients must be carefully counselled to ensure that it is taken correctly in relation to food.

The highest oral semaglutide dose is less potent than the highest dose of the semaglutide injection. All patients should be titrated to the highest tolerated oral dose in order to maximise benefit in terms of both reduction in HbA_{1c} and weight loss.

If the treatment does not achieve the NICE-recommended targets of 1% reduction in HbA_{1c} and 3% reduction in weight after 6 months on oral semaglutide at the maximum tolerated dose, the treatment should be reviewed with a view to discontinuing it and changing to another appropriate therapy.[14]

Oral semaglutide is not shown to give the same reduction in the risk of 3-point MACE (combination of the likelihood of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) as has been found with the injectable form, so must only be used in patients for whom injectable therapy is not suitable.

In the shorter term, during the Covid-19 pandemic, it may be useful to start some patients on semaglutide tablets in order to allow them to escalate treatment without having to attend clinic to learn how to take the injection.

If the APC approves the status of semaglutide then this means that the following documents currently on the PAD will need to be updated:

- Hypoglycaemic agents -Preferred choices - February 2018
- Diabetes Type 2 -Treatment Guidelines - February 2018
- GLP-1 patient agreement form - February 2018

Medicine details	
Name and brand name	Semaglutide (Rybelsus®▼) tablets 3mg, 7mg and 14mg
Licensed indication, formulation and usual dosage	The treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in combination with other medicinal products for the treatment of diabetes. No data in patients aged under 18 years. The tablets are oval and measure 7.5mm x 13.5mm. The starting dose of oral semaglutide is 3 mg once daily for one month. After one month, the dose should be increased to a maintenance dose of 7 mg once daily. After at least one month at this dose, the dose can be increased to a maintenance dose of 14 mg once daily if required to further improve glycaemic control. When semaglutide 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 or thiazolidinedione can be continued.[1] When semaglutide is used in combination with a sulfonylurea or with insulin, a reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia[1]. Oral semaglutide should be taken on an empty stomach, at any time of day. The tablet should be swallowed whole with a sip of water (no more than 120 mL). Tablets should not be split, crushed or chewed. Patients should wait at least 30 minutes before eating or drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of semaglutide. [1]
Summary of mechanism of action, and relevant pharmacokinetics	Semaglutide is a GLP-1 analogue which selectively binds to GLP-1 receptors. It has 94% same sequence as native GLP1. GLP1 is a physiological hormone that has multiple actions in glucose and appetitie regulation and the cardiovascular system. Semaglutide reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of semaglutide is independent of the route of administration.

	Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods. GLP-1 receptors are also found in the heart, vasculature, immune system and kidneys. Semaglutide has a beneficial effect on plasma lipids, lowers systolic blood pressure and reduces inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque **Pharmacokinetics** The absorption of semaglutide is about 1% when taken orally. It must be taken on an empty stomach and about 30 minutes before other medication. Despite this, absorption is highly variable. However it has a long half-life of about 1 week, so daily administration allows this variability to be smoothed out. It is about 99% bound to plasma proteins. If the treatment response with semaglutide is lower than expected, the treating physician should be aware that the absorption of semaglutide is highly variable and may be minimal (2-4% of patients will not have any exposure).[1] The effect of switching between oral and s.c. semaglutide cannot easily be predicted because of the high pharmacokinetic variability of oral semaglutide. Exposure after oral semaglutide 14 mg once daily is comparable to s.c. semaglutide 0.5 mg once weekly. An oral dose equivalent to 1.0 mg of s.c. semaglutide has not been established.[1] 14mg po daily is equivalent to 98mg weekly and this is stated to be equivalent to the 0.5mg weekly dose when given sc.[1] There is a 200 fold difference in the dose rate so, obviously, monitoring of response will be important if switching between oral and injectable forms. This also means that the 1mg dose is more potent than any available oral dose and may be needed if there is an inadequate response to the oral formulation. No dose adjustment is expected to be necessary for patients with either renal or hepatic impairment. This is because semaglutide is metabolised by proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain (probably by the membrane-bound enzyme, neutral endopeptidase). It is excreted in both urine and faeces. No dose adjustment required in the elderly.
Important drug interactions	As semaglutide delays gastric emptyling, it can affect the absorption of various drugs eg thyroxine (AUC increased by 33% following a single dose) and rosuvastatin (AUC increased by 41%). Rosuvastatin has a wide therapeutic index so the latter result is not considered clinically relevant. No clinically relevant change in AUC or C_{max} was seen in patients on digoxin, oral contraceptives (containing ethinylestradiol and levonorgestrel), metformin or furosemide was observed when concurrently administered semaglutide.

	Semaglutide did not change the AUC or c_{max} of a single dose of warfarin. It is however recommended to moitor INR frequently in patients on semaglutide.
Monitoring requirements	When semaglutide is used in combination with a sulfonylurea or with insulin, a reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Patients treated with semaglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects which in rare cases can lead to a deterioration of renal function. Patients should be warned to take precautions to avoid fluid depletion. Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised when using semaglutide in patients with diabetic retinopathy. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy Semaglutide delays gastric emptying which may influence the absorption of other oral medicinal products. Women of childbearing potential are recommended to use contraception when treated with semaglutide as animal studies have shown reproductive toxicity.
Prescribing considerations	Contraindications and cautions are the same as for other GLP-1RAs. - Semaglutide is contraindicated in type 1 diabetes mellitus, diabetic ketoacidosis and severe heart failure. - Caution needs to be exercised in patients with a history of pancreatitis and those with severe hepatic impairment, is no therapeutic experience with semaglutide in patients with bariatric surgery - 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. Patients need to have all existing blood glucose lowering medication optimised prior to starting a GLP-1RA.
Other considerations	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-hydroxylbenzoyl) 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.[2] Semaglutide is the first GLP-1 analogue which is available by the oral route. All of the others are given by sub-cutaneous injection. Semaglutide is also available by this route as a sub-cutaneous, once weekly injection. An oral preparation will mean that less clinician time will be needed to initiate this GLP-1 compared to an injectable GLP-1. Patients who are needle phobic, or refuse injectable therapy, will be able to have their treatment escalated appropriately to optimise blood glucose control. Hence, those patients' outcomes will be improved. NICE recommend that GLP-1 mimetic therapy should only be continued if the person with type 2 diabetes has had beneficial metabolic response (a reduction of at least 11 mmol/mol (1%) in HbA1c and a weight loss of at least 3% of initial body weight in 6 months [11]. This review will be important before longterm treatment is considered. There also needs to be guidance on what subsequent treatment to offer if the GLP1 treatment is not successful. Situations where the injection will be the best delivery route: • Patients who are unable to swallow the tablets whole • Patients who struggle with the need to take the tablets on an empty stomach - The SPC for oral semagultide states that patients should take the tablet at any time during the day, with up to 100ml of water and to then wait a further 30 minutes before eating or drinking or taking other oral medicinal products. This is important due to the low bioavailablity of this oral form of semaglutide, to encourage patients to take the tablet two hours after and 30minutes before eating and drinking, preferably first thing in the morning. • People who require assistance with medication for whom a once weekly injection makes that possible. • People who are acutely ill and unable to take medication orally. The Current formulary options for GLP-1 RAs are as follows: Liraglutide (Preferred daily injectable), dulaglutide (preferred weekly injectable) and semaglutide injection. Exenatide is also listed – both the BD and Weekly preparations. The inclusion of exenatide on the formulary will be reviewed in the chapter review which is currently being planned.

Potential patient group (if appropriate to include)	
Brief description of disease	Adults living with type II diabetes mellitus
Potential patient numbers per 100,000	The 2019 prevalence estimate for CCGs covered by APC is 7.7% (based on PHE prevalence estimate for CCG GP practice registered population[15]):97,924 residents over 16 with diabetes (type 1 and 2). Nationally, 90% of diabetic patients are estimated to have type 2 diabetes[16]. This is a prevalence of 5965 per 100,000 population.
Outcomes required	Patients should be reviewed after 6 months on oral semaglutide. NICE guidance specifies that it should only be continued in patients who have had a reduction in HbA1c of at least 1% and who have had a reduction in their weight of at least 3%[14]

Summary of current treatment pathway
Treatment Algorithm for blood glucose control in adults with type 2 diabetes in primary care on the Surrey PAD – accessed via the following link: PowerPoint Presentation (res-systems.net)

Evidence review

Current NICE guidance states that GLP-1 RAs can be considered clinically effective if, after 6 months on the therapy, the patient's HbA1c has fallen by 1% and their weight has reduced by 3%.[14]

See Appendix A for more detail on the clinical trial programme – the PIONEER studies- which was run by Novo-Nordisk to licence oral semaglutide. There are 10 multicentre, studies; the last 2 of which were solely conducted in Japan. PIONEER 9 has not been considered in this review because it compared oral semaglutide to a dose of liraglutide which is not used in the UK. PIONEER 10 compared oral semaglutide with dulaglutide. The primary endpoint was treatment-emergent

The remaining studies are briefly summarised below:

- **Treatment Naïve patients**. One study (n=703) looked at the response to semaglutide tablets of patients who had not received any previous antidiabetic medication.[3] It compared patients on 3mg, 7mg and 14mg with patients on placebo. By the above measure, the 3mg (-0.6%) and 7mg (-0.9%) doses did not produce a clinically significant reduction in HbA1c but the 14mg dose did achieve it (-1.1%). In terms of weight loss, there was a considerable placebo effect in this trial: 15.7% of placebo patients achieved a weight loss of ≥5%. This meant that only patients on 14mg oral semaglutide achieved a statistically significant weight loss compared with placebo with 44.3% achieving weight loss of ≥5% ($p<0.001$). A composite endpoint of HbA1c reduction of ≥ 1% and weight loss ≥ 3% was achieved in 11.3% patients on placebo, 20.1% patients on 3mg, 39% of patients on 7mg and 54.4% patients on 14mg oral semaglutide. In comparison with placebo, this was highly significant for the 7mg and 14mg doses of semalglutide tablets.
- **5 studies comparing semaglutide to other antidiabetic medication** as an add in for patients whose control was inadequate on their existing treatment regime:
    - V's Empagliflozin (SGLT2 inhibitor) (n=822)[4] – semaglutide found to be significantly better than empagliflozin in reducing HbA1c (-1.4% cf -0.9%, $p<0.001$) –all semaglutide patients aimed for the 14mg dose. Previous regime: metformin. The difference in reduction in weight at week 26 was not statistically or clinically significant for oral semaglutide compared to empagliflozin. The compsite endpoint of ≥1% reduction in HbA1c and ≥ 3% did, however, achieve significance ($p<0.0001$) in favour of oral semaglutide at both weeks 26 (OR 3.31, 95%CI 2.40, 4.56) and 52 (OR 2.39, 95%CI 1.74, 3.30).
    - V's sitagliptin (DPP4 inhibitor) (n=1864)[5] - HbA1c results favoured sitagliptin against 3mg semaglutide but favoured semaglutide for the 7mg and 14mg doses ($p<0.001$). These findings were sustained at 52 and 78 weeks. The difference in reduction of weight at 26 weeks was not significant for the 3mg dose of semaglutide compared to sitagliptin but did achieve statistical significance for the 7mg and 14mg doses. The compsite endpoint of ≥1% reduction in HbA1c and ≥ 3% did, however, achieve significance ($p<0.001$) in favour of oral semaglutide at all timepoints.Treatment allocation was 1:1:1:1 the doses of semaglutide and 100mg sitagliptin. Previous regime: metformin +/- sulphonylurea.
    - V's liraglutide (first licensed GLP1-RA) (n=711)[6]- The estimated treatment difference (ETD)in HbA1c between: semaglutide and placebo was -1.2% (95% Confidence interval -1.4 to -1.0%) which was highly statistically significant ($p<0.0001$). However,the ETD between semaglutide and liraglutide was -0.2% (95% confidence interval -0.3 to -0.1%). This difference was still statistically significant ($p=0.0056$) but did not achieve

clinical significance (p<0.0001). Weight loss at week 26 was significantly greater with oral semaglutide than with subcutaneous liraglutide (-1.5kg, 95% CI -2.2to -0.9; p<0.0001) and placebo (ETD -4.0kg, 95% CI -4.8 to -3.2; p<0.0001). The compsite endpoint of ≥1% reduction in HbA1c and ≥ 3% was not reported in the publication of this trial. All semaglutide patients aimed for 14mg. Previous regime: metformin +/- SGLT2 inhib.

- V's sitagliptin (DPP4 inhib) (n=504)[10] – 52 week primary endpoint. From a mean baseline HbA1c of 8·3% (SD 0·6%), a greater proportion of participants achieved an HbA1c of less than 7% with oral semaglutide than did with sitagliptin 63% [123 of 196] vs 28% [52 of 184]). This meant that the odds of achieving an HbA1c of less than 7% were significantly better with oral semaglutide than sitagliptin (OR 5·54, 3·54–8·68, p<0·0001). The mean body weight reduction at 52 weeks was 2.6kg for those on oral semaglutide and 0.7kg for the sitagliptin. This gave an ETD of -1.9kg (95%CI -2.6 to -1.2kg; p<0.0001). The odds of achieving the composite of decrease of HbA1c of 1% or more with a weight loss of 3% or more were significantly better with oral semaglutde than with stiagliptin (p<0.0001) – this last bit of data was not seen as it was included in an appendix to the report). Compared to flexible dosing of semaglutide to mimic use in practice. At week 52 9% of the oral semaglutide patients were receiving 3mg, 30% were on 7mg and 59% were on 14mg. Previous regime 1 or 2 anti-diabetic drugs with control no longer being adequate.
- V's dulaglutide 0.75mg weekly.[18] Primary endpoint was treatment emergent adverse effects. Change in HbA1c from baseline to week 52 was only statistically significantly higer for the highest dose of semaglutide vs dulaglutide (ETD 0.3%; 95% CI were -0.6 to -0.1%; p=0.0170). The results for 7mg semaglutide and dulaglutide were similar. (Note: The UK SPC recommends 1.5mg dulaglutide weekly when used as an add–on therapy and there are now also licensed doses of 3mg and 4.5mg dulaglutide). Treatment allocation was 1:1:1:0.5 for the doses of oral semaglutide and dulaglutide. Also, the study population was exclusively Japanese which is a gene-pool which may handle medication differently from that commonly seen in Europe. (summary from the SEL review – not originally considered for this evidence review.)

- **Efficacy in patients with moderate renal impairment.** One study (n=324) looked at the response to oral semaglutide in patients with moderate renal function (30-59ml/min/1.73m^2) [7]. The focus of this study was improvement in glucose control rather than effect on renal function and it did find that semaglutide led to a clinically and statistically significant drop in HbA1c of 1.1% p<0.0001 in this patient group. Overall renal function was unchanged for patients during this study (see summary of side effects in Appendix A for more detail). All semaglutide patients aimed for 14mg and patients were stratified by background medication.
- **Incidence of Cardiovascular events**. One study (n=3183) looked at the incidence of cardiovascular adverse events with oral semaglutide compared with placebo.[9] The study duration was until there had been 122 major cardiovascular events in the patient population. The mean time in the trial was 15.9 months and 75% of patients were in the trial for over 1 year. Major cardiovascular events occurred in 3.8% of semaglutide patients and 4.8% of patients in the placebo arm. This confirmed that oral semaglutide was non-inferior to placebo but the study was isufficiently powered to show CV benefits from treatment. Various other cardiovascular endpoints were examined (see appendix A) which similarly showed a trend towards improved outcomes in patients who were on semaglutide tablets. HbA1c levels decreased more in the oral semaglutide groups than in the placebo group (mean change from baseline to end of tria was -1.0% vs -0.3%), as did body

weight (mean change from baseline to end of tial, -4.2kg vs -0.8kg. The target dose of semaglutide was 14mg and 82.1% of patients were on this dose at the end of treatment visit. Background treatment was standard care with both the other anti-diabetc and cardiovascular drug doses being adjusted as necessary. 93.9% of patients were taking antihypertensive medication, 85.2% lipid-lowering medication and 79.4% antiplatelet or lipid lowering medication.

- **Patients on insulin**. One study (n=731) looked at the use of oral semaglutide in patients who were already on insulin treatment.[12] The reduction in HbA1c after 26 weeks was statistically significant for all three doses and clinically significant for those patients on 7mg or 14mg doses. After 52 weeks, these results were statistically significant for all 3 semaglutide doses but only the 14mg dose was still clinically significant (≥1% drop in HbA1c from baseline). At week 26, oral semaglutide patients had a mean body weight 0.9 (3mg), 2.5 (7mg) or 4.1kg (14mg) less than the patients who received placebo and these changes persisted after 52 weeks. All strengths or oral semaglutide resulted in statistically significantly reduced dose of insulin being required at week 52 when compared with placebo. Patients were randomised 1:1:1:1 to placebo or semaglutide 3mg, 7mg or 14mg. The patients were all taking insulin +/- metformin on study entry.

The **side effects** seen in all the studies above are summaried in a table at the end of Appendix A. In the PIONEER studies, 70-80% of semaglutide patients reported adverse effect(s) . They mostly occurred in the first 8 weeks when the dose was being escalated. About 11% of patients discontinued treatment due to the adverse effects which were mostly gastrointestinal in nature. This compared with 4-6% of patients on alternate antidiabetic agents (SGLT2 inhibitors and DPP4 inhibitors) and about 9% of liraglutide patients. The discontinuation rates were much lower for the 3mg and 7 mg strengths, where these were studied. In the study (PIONEER 7) which mimicked clinical dose titration more accurately, the discontinuation rate was still 9% for semaglutide.

The most commonly cited adverse events were **gastrointestinal** (GI) – mostly nausea and diarrhoea. And usually mild-moderate. However GI side effects were also the most reason for treatment discontinuation. This usually happened during the dose escalation phase of treatment in the 7mg and 14mg treatment groups. When semaglutide was compared to liraglutide, the increased occurrence of side effects was largely related to GI events.

Information on the incidence of **hypolgycaem**ia (blood glucose < 3.1mmol/L) was gathered in all of the studies. Often patients taking oral semaglutide who develop hypoglycaemia are also taking either a sulphonylura or insulin (both of which are themselves associated with causing hypoglycaemia). Thus it may be necessary to reduce the dose of the sulphonylurea or insulin when initiating oral semaglutide, to reduce this effect (as per SPC for oral semaglutide).

Patients were monitored for **diabetic retinopathy** in all the studies and no strong link was found with oral semaglutide therapy. It is a condition associated with diabetes and was picked up in routine eye examinations during the studies. It generally did not require any change to treatment. However all of the PIONEER studies excluded patients with a history of retinopathy, so there is no data on how oral semaglutide affects pre-existing retinopathy.

History of **pancreatitis** was an exclusion for participation in the clinical trials. However, no link was found between oral semaglutide and pancreatitis cases which were diagnosed during the studies. Two of the studies did find lincreased in lipase and amylase levels in patients taking oral semaglutide. Thus is is recommended that patients are monitored to

ensure early detection of any pancreatitis signs or symptoms. Caution is recommended if prescribing oral semaglutide to a patient with a history or pancreatitis.

Cardiac side effects have been looked at is a specific study (PIONEER 6) and monitored for in all the other studies. PIONEER 6 was, however, powered to assess whether oral semaglutide was non-inferior to placebo with respect to the occurrence of major adverse cardiovascular events (MACE, death from CV causes, non-fatal MI or non-fatal stroke), with the non-inferiority margin for the upper boundary of the 95% CI limit set a 1.8 (i.e. to ruling out an excess risk of ≥80%). In the other studies, it was noted that oral semaglutide may be associated with a slight increase in pulse rate (2-4 bpm) but no other changes in cardiac parameters were found.

PIONEER 6 was not powered to demonstrate superiority of semaglutide over placebo – i.e. wehether it was associated with a reduction in major adverse cardiac events (MACE), as has been demonstrated with subcutaneous semaglutide in the Sustain 6 trial. The European Public Assessment Report (EPAR) for oral semaglutide notes that, due to the large variability in exposure to the drug and the different route of administration, it remains uncertain if oral semaglutide exhibits the same cardiovascular effect. It may not be appropriate to extrapolate the results. A larger CV outcomes study of oral semaglutide v's placebo (SOUL) is currently underway (estimated study completion date is 2024).

The following is an extract from the minutes of the APC meeting in December 2020:
The SUSTAIN 6 trial was designed as a non inferiority study versus placebo. The trial showed cardiovascular safety demonstrating non-inferiority for Major Adverse Cardiovascular Events (MACE) against placebo as the primary outcome. Superiority was demonstrated as a statistically significant secondary outcome. The cautious wording of interpretation reflects the fact that superiority was a secondary outcome. After studying the findings, the US Federal Drugs Administration advised the manufacturer that a larger cardiovascular outcome study with semaglutide could be completed with the oral preparation only, and that the results of the SUSTAIN 6 trial could be used subsequently to justify a claim of cardiovascular superiority for the subcutaneous preparation, in the event of an equivalent finding with the oral preparation.

This has not, to date, been achieved with the oral semaglutide trails.

Renal function was monitored in all sutdyes and the PIONEER 5 study focussed on oral semaglutide in patients with moderate rnal failure. No association was found between the drug and deterioration in renal function in either this, or any of the other, studies.

In the studies, **deaths** were assessed independently to determine whether the study drug was implicated. No link was found. A few **malignancies** were identified in study participants in the course of the trials but no link to the dtudy drugs were identified and there was no clustering of type of malignancy.

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	3rd January, 2021 – a review of local formularies was conducted and the following information gathered: • **Frimley formulary** – semaglutide Injection green. Tablets are not listed. • **South East London Formulary** – semaglutide injection Amber 3. For specialist initiation only. Transfer of care after 3 months. They have a very good pathway for

	initiation and information on how to administer during Covid which should be adapted for our use. • **West Berkshire Formulary** – semaglutide injection is non-Formulary and the tablets are not listed. • **Brighton Joint Formulary** – semaglutide injection only – preferred weekly GLP-1. • **St Georges Hospital Formulary** – semaglutide injection only is listed. Amber drug • **Nottinghamshire Formulary** – semaglutide injection is formulary (Amber 2) and the tablets are non-Formulary as have not been considered as yet. • **Portsmouth and South East Hampshire** – semaglutide injection is green and the tablets are amber restricted for patients where sc semaglutide would be considered an option but where the sc route of administration is not tolerated or advisable. May be initiated on the advice of community specialist nurses. • **Coastal West Sussex formulary** – semaglutide injection is listed a green and third choice. Tablets are not listed. In summary, semaglutide tablets are not currently included in any of the Formularies which were checked
Recommendations from national / regional decision making groups	In 2019, NICE decided to not produce a NICE technology appraisal for semaglutide. It was considered alongside dulaglutide for appraisal. This is because there was already clear and effective guidance on the use of GLP-1 mimetics in NICE Clinical Guideline 28 (NG28) (Type 2 diabetes in adults: management) and they were the 6th and 7th GLP-1 inhibitors to come to market. It was felt that a NG update would be of more value, incorporating the positive effects of all GLP-1 mimetics on cardiovascular risk and renal dysfunction, once fully available. Novo Nordisk challenged this decision because it felt that semaglutide had clinical advantages over the 2nd and 3rd line therapies to treat type 2 diabetes. The current NICE Guideline NG28: Type 2 diabetes in adults: management was published in December, 2015 and last updated in December, 2020. It does not include any specific mention of semaglutide. Any recommendations for the GLP-1 analogues in this NG were made at drug class level and did not distinguish between them. The places identified in therapy for the drug class were as follows: • If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: o have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or** o have a BMI lower than 35 kg/m^2 **and**:

	▪ for whom insulin therapy would have significant occupational implications **or** ▪ weight loss would benefit other significant obesity-related comorbidities. • GLP-1 analogues should only be offered in combination with insulin with specialist care advice and ongoing support from a consultant and multidisciplinary team. • GLP-1 analogue therapy should only be continued if the person has a beneficial metabolic response (reduction in HbA1c at least 11mmol.mol (1%) and a weight loss of at least 3% of initial body weight in 6 months). Updated NICE clinical guidance for diabetes in children and pregnancy were published in December, 2020 along with updated Guidelines for type 1 diabetes in adults. These did not include any specific mention of GLP-1 receptor agonists at a group or semaglutide In August 2020, the Scottish Medicines Commission acepted semaglutide tablets for restricted use in NHS Scotland as an alternative glucagon-like peptide-1 analogue option. It had previously accepted semaglutide injection use in the same way as the tablets (Jan, 2019). The summary highlighted that the effect of switching between oral and sc semaglutide could not be easily predicted because of the high variability in the bioavailability of oral semaglutide. The clinical effectiveness must be reviewed. In September, 2020, the Northern Treatment Advisory Group (NTAG) made the following recommendation[19]: Oral semaglutide is an option for patients with type 2 diabetes mellitus who require intensification of treatment, if use of a glucagon-like peptide 1 receptor agonist (GLP1RA) is clinically appropriate, in line with licensing and relevant guidance, and if an oral option is preferred. However, in patients with pre-existing cardiovascular disease or at high risk of cardiovascular (CV) events an agent with proven efficacy for CV risk reduction may be more suitable. Unfortunately the detailed review that sits behind the decisions made by both the SMC and NTAG are no longer available for other areas to see, meaning that we had to conduct our own detailed review of oral semaglutide.
Stakeholder views	One comment received from Secondary Care Endocringology/Diabetes Consultants following circulation of this review prior to the APC meeting. The comment was in support of the application was from a Consultant setting up a tier 3 Obesity clinic at RSFT. No patient group engagement was sought.
CCG priorities	In line with QOF indicators DM007, DM008, DM009 which all relate to achievement of specific HbA1c targets. In line with the Surrey Heartlands Locally Commissioned Service

<table>
<tr><th colspan="2">Health economic considerations</th></tr>
<tr><td>Cost per year per patient</td><td>Annual cost of semaglutide is £942/patient and is additional to current costs. If offered to 5% of patients with HbA1c>58mmol/mol, additional cost in England could be £84,000 per 100,000 people/year.[7]</td></tr>
<tr><td>Alternative treatments cost per patient per year</td><td>Comparative costs for the GLP1RAs
<table>
<tr><th>Drug</th><th>Form</th><th>Strength and Form</th><th>Brand</th><th>Dose</th><th>Price per annum</th></tr>
<tr><td>Semaglutide</td><td>Tabs</td><td>3mg, 7mg and 14mg</td><td>Rybelsus▼</td><td>1 daily</td><td>954.84</td></tr>
<tr><td>Semaglutide</td><td>Inj</td><td>0.25mg ,0.5mg and 1.0mg Injection in a prefilled device (used for 4 doses)</td><td>Ozempic▼</td><td>1 weekly</td><td>879.00</td></tr>
<tr><td>Dulaglutide</td><td>Inj</td><td>0.75mg, 1.5mg, 3mg, and 4.5mg prefilled injections.</td><td>Trulicity</td><td>1 weekly</td><td>879.00</td></tr>
<tr><td>Liraglutide</td><td>Inj</td><td>6mg injection in a pre-filled device (used for 1 month)</td><td>Victoza</td><td>1 daily</td><td>1,020.24-1,530.76 (1.2-1.8mg daily)</td></tr>
<tr><td>Exenatide</td><td>Inj</td><td>5mcg and 10mcg injection in pre-filled pens (used for 30 days)</td><td>Byetta</td><td>1 twice daily</td><td>996.33</td></tr>
<tr><td>Exentatide</td><td>Inj</td><td>2mg injection</td><td>Bydureon</td><td>1 weekly</td><td>953.68</td></tr>
</table>
Prices were taken from the Drug Tariff April, 2021. NHS Electronic Drug Tariff (nhsbsa.nhs.uk) Date accessed 31/12/20. Semaglutide tablets are not yet listed in the drug tariff, so the price for these were taken from the BNF online version: SEMAGLUTIDE | Medicinal forms | BNF content published by NICE Date accessed 31/12/20.

Cost Trend in Surrey Heartlands – Spend on GLP-1 RAs 2014-2020 See Appendix B</td></tr>
</table>

Other financial considerations (if relevant)	The following information was taken from the SEL review of oral semaglutide (December 2020) and adapted with local ePACT data for Surrey Heartlands CCG. The cost of oral semaglutide is comparable to the injectable GLP-1 agonists already in use within Surrey Heartlands, with the advantage of nor requiring needles or sharps disposal. Therefore, during the pandemic when used an alternative to injectable therapy, the budget impact is cost neutral. However, in the longer-term, availability of an oral GLP-1 agonist is estimated to increase overall use by 10% (to include patients who may not have received a drug in this class e.g. due to needle phobia). Surrey Heartlands EPACT data shows the cost of GLP-1 therapy for Q2 2020/21 was approx. £560,000 items. If prescribing continued at a flat rate, the estimated annual spend for SE London equates to £2.24 million. However, based on prescribing continuing at the same rate as the previous year in Surrey Heartlands (i.e. an increase of 9.6% from Q2 2019 to Q2 2020 as per EPACT data), the estimated annual spend would be £2.5 million; and the 10% increase in GLP-1 therapy anticipated from oral semaglutide equates to approx. an additional £250,000 per annum for Surrey Heartlands (or £224,000 if prescribing continued at a flat rate).
Health economic data (if available)	None identified

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Prepared by:

Lynne Hargreaves, Medicines Optimisation Pharmacist, Guildford and Waverley ICP

Declaration of Interest:

None to declare

Date: 27/04/2021

Reviewed by:

Perminder Oberai, Lead Medicines Optimisation Pharmacist, Surrey Heartlands CCG

Declaration of Interest:

Received payment to provide training from a company that had received an educational grant from Novo Nordisk

DATE: 27/04/2021

In attendance:

Dr Ben Field, Clinical Reader in Diabetes and Endocrinology, University of Surrey and Honorary Consultant Endocrinologist, Surrey and Sussex Healthcare Trust

Declaration of interest:

Paid to attend conferences, advisory boards and provide training, by Novo Nordisk. Currently one of the investigators in the SOUL trial.

Date: 27/04/2021

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
v.1	*04/01/20*	*Lynne Hargreaves*	*Medicines Optimisation Pharmacist, Guildford and Waverley ICP*	*Out for comments to APC membership by 19th January, 2021.*
v.2.0	*09/04/21*	*Lynne Hargreaves*	*Medicines Optimisation Pharmacist, Guildford and Waverley ICP*	*In light of delay in taking the paper to APC due to Covid lockdown – updated paper sent to Clare Johns for comments from APC membership by 23rd April, 2021*
v.2.1	*23/04/21*	*Lynne Hargreaves*	*Medicines Optimisation Pharmacist, Guildford and Waverley ICP*	*Sent to Clare Johns for consideration at the May APC meeting.*
V3.0	*27/04/21*	*Lynne Hargreaves*	*Medicines Optimisation Pharmacist, Guildford and Waverley ICP*	*Updated version with declarations of interest and Dr Fields comments added.*

Appendix A Oral Semaglutide: The PIONEER Study Results

Study title	Number of Patients and Design
1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes[3]	703 patients Randomized, multi-centre, (93 centres in 9 countries), placebo-controlled, double-blind parallel group trial. Duration 26 weeks. Adult patients with type 2 diabetes were eligible if they had HbA1c in the range of 7.0–9.5% (53–80 mmol/mol) with management only by diet and exercise. All patients randomized 1:1:1:1 to oral semaglutide 3mg, 7mg or 14mg or placebo. All the semaglutide patients were initiated treatment with 3mg once daily with dose escalations every 4 weeks as in the SPC until the randomized maintenance dose was achieved. 5 week follow up period at the end. Doses were taken as per semaglutide SPC. Note: normal recommendation is to use metformin as first-line monotherapy. They went straight to semaglutide here as first-line drug.
2: Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin[4]	822 patients Randomised, open-label, multi-centre (108 sites in 12 countries). Patients were on a stable dose of metformin and had an HbA_{1c} of 7.0-10.5%. Duration 52 weeks with 5 week follow-up period. Patients were randomised 1:1 to receive either empagliflozin 25mg (SGLT2 inhib) or semaglutide oral 14mg daily. Semaglutide initiation was 3mg for 4 weeks, 7mg for 4 weeks and then 14mg. Semaglutide SPC – recommends only going up to 14mg if necessary. Empagliflozin was given at 10mg OD for 8 weeks and then escalated to 25mg OD. SPC only recommends 25mg if glycaemic control is not sufficient on 10mg.

Study title	Number of Patients and Design
3: Effect of additional oral semaglutide vs sitagliptin on HbA_{1c} in adults with type 2 diabetes uncontrolled with metformin alone or with sulphonylurea.[5]	1864 patients Randomized, double-blind, double-dummy, parallel-group, phase 3a trial (206 sites in 14 countries). Adults with type 2 diabetes uncontrolled (HbA1c 7.5-10.5%) with metformin with or without sulfonylurea. Patients were randomized 1:1:1:1 to once-daily oral semaglutide (3, 7, or 14 mg) or once-daily oral sitagliptin, 100 mg, for 78 weeks. Semaglutide was initiated as per SPC up to the randomized dose and sitagliptin was initiated at 100mg daily. Patients also received their pre-trial doses of metformin +/- sulphonylurea throughout the trial. Intensification of background treatment was allowed according to a randomized predefined protocol, based on fasting plasma glucose and/or HbA_{1c}. Patients were included in analysis if stopped taking the trial drug and/or received additional glucose-lowering medication.. However, they were not allowed to stop the trial medication and switch to a GLP1 RA or a DPP-4 inhibitor before the final follow-up visit.
4: Oral semaglutide versus sc lirglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial.	711 patients Randomised, double-blind, double-dummy trial (100 sites in 12 countries) over 52 weeks which had both active- and placebo-controls. Patients were ≥18 years old, with an HbA_{1c} of 7.0-9.5% on a stable dose of metformin with or without a SGLT2 inhibitor. Patients were assigned 2:2:1 to once daily oral semaglutide (dose escalated to 14mg over 8 weeks) or once-daily sc liraglutide (dose escalated to 1.8mg over 2 weeks), or placebo. They continued on the maximum tolerated dose for 52 weeks. This was in addition to existing background glucose-lowering medication. Treatment allocation was stratified by background glucose-lowering medication and country of origin (Japanese or non-Japanese) Participants received both a tablet (active or placebo) and an injection (active or placebo). For both oral semaglutide and subcutaneous liraglutide, the active and corresponding placebo products were visually identical to maintain masking of participants and site staff.

Study title	Number of Patients and Design
5: Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment.	324 patients Randomised, double-blind, phase 3a trial in 88 sites in 8 countries. Patients were ≥18 years, with type 2 diabetes, HbA_{1c} of 7.0-9.5%.and estimated glomerular filtration rate (eGFR) of 30-59ml/min per 1.73m^2. They had been receiving a stable dose of metformin or sulfonylurea, or both, or basal insulin with or without metformin for the past 90 days. Note: the size and duration of this trial was designed to assess glucose control in patients with moderate renal impairment and not renal safety and efficacy, which require further investigation. They were randomized 1:1 to receive semaglutide (escalated to 14mg) or matching placebo for 26 weeks, in addition to the background medication. Allocation was also stratified on the basis of which background medication the patient was receiving and their renal function. Dose escalation was as per SPC up to 14mg and no dose adjustment of the study drug was permitted during the trial. Dose was taken as per SPC for semaglutide Those receiving basal insulin were recommended to have the dose decreased by 20% after random assignment to treatment group to minimise the risk of hypoglycaemic episodes. Up-titration of basal insulin (to a dose not exceeding that at randomisation) was permitted in weeks 10–16, after the maximum dose of oral semaglutide was reached. Patients who prematurely discontinued their allocated treatment (eg, due to adverse events) were switched to an appropriate locally approved treatment selected at the investigator's discretion, excluding GLP-1 receptor agonists. All participants were asked to complete the protocol-specified visit schedule, regardless of premature discontinuation of allocated treatment or use of rescue medication, unless consent was withdrawn.

Study title	Number of Patients and Design
6: Oral semalgutide and cardiovascular outcomes in patients with type 2 diabetes	3183 patients An event-driven, randomized, double-blind, placebo-controlled trial, conducted at 214 sites in 21 countries . It involved patients at high cardiovascular risk (age of ≥50 years with established cardiovascular or chronic kidney disease, or age of ≥60 years with cardiovascular risk factors only). The trial was designed to rule out 80% excess cardiovascular risk as compared with placebo (noninferiority margin of 1.8 for the upper boundary of the 95% confidence interval for the hazard ratio for the primary outcome). The trial continued until 122 adverse events had occurred (no pre-defined minimum duration). Patients were randomly assigned (1:1) to receive once-daily oral semaglutide and stratified according to current treatment (target dose 14mg – reduced in patients unable to tolerate due to side effects. Re-escalation was considered in these patients, once the side effect was under control) or placebo, in addition to standard of care. Patients' existing glucose-lowering and cardiovascular medication was adjusted as necessary; in accordance with local and international guidelines. Randomisation was stratified according to evidence of established cardiovascular disease or chronic kidney disease or the presence of cardiovascular risk factors only.
7: Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes	504 patients A multicentre, open-label, randomised, phase 3a trial over 52 weeks. There were 82 sites in 10 countries. Patients were eligible if they were aged 18 years or older (19 years or older in South Korea), had type 2 diabetes (diagnosed ≥90 days before screening), HbA1c of 7·5–9·5% (58–80 mmol/mol), and were inadequately controlled on stable daily doses of one or two oral glucose-lowering drugs (for 90 days or more before screening). Participants were randomly assigned (1:1), stratified by whether or not they were taking a sulphonylurea at screening. They received oral semaglutide with flexible dose adjustments to 3, 7, or 14 mg once daily or sitagliptin 100mg once daily. To approximate treatment individualisation in clinical practice, oral semaglutide dose could be adjusted on the basis of prespecified HbA1c and tolerability criteria.

Study title	Number of Patients and Design
8: Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes. [11]	731 patients Randomized, double-blind, placebo-controlled, parallel-group trial, conducted at 111 sites in nine countries. Trial durations was 52 weeks with a 2 week run in and a 5 week follow-up. Patients were randomised 1:1:1:1 to once dialy oral semaglutide 3,7,or 14mg or placebo. Randomisation was stratified by country or origin (Japanese or non-Japanese) and background treatment (metformin or no metformin; basal, basal-bolus or premixed insulin). Insulin dose was reduced by 20% at randomisation and maintained to week 8, unless an increase was required to prevent acute metabolic deterioration. Insulin dose could then be adjusted up to a maximum of the pre-study dose until week 26. Thereafter, the dose could be adjusted freely at the investigatore discretion. Further detail is included in the study report. Patients were adults with type 2 diabetes diagnosed at least 90 days before enrolment. The patients had a baseline HbA1c of 7.0-9.5%, were on a stable regime of insulin and, if used, metformin for the previous 90 days. The dose escalation for semaglutide was as in the spc, with double-blinding of the step for patients randomised to the 7mg or 14 mg arms of the study.

A note on the recording of results in these trials:

The analysis of the results in these trials included estimands, as recommended by recent regulatory guidelines, to address different scientific questions of interest and to prespecify how intercurrent events and missing data were to be handled:

- The **treatment policy estimand**, which evaluates effect regardless of adherence to randomized treatment, may be relevant for understanding overall population-level effects, accounting for treatment effect, risks, adherence, and the addition of "rescue" medication. Reflects the 'intention to treat' principle. This estimand reflects the effect of initiating treatment with the trial treatment option whether followed by either discontinuation of study drug or addition of or switch to another glucose-lowering drug,or both.
- The **trial product estimand**, which estimates treatment effect for those who remain on treatment without rescue medication, to support clinical decision-making by describing the anticipated treatment effect. It assumes that all randomized patients remain on the trial product for the entire planned duration of the trial and did not use rescue medication. It, therefore, aims to compare the trial drugs, given for the duration of the trial. This measure is now commonly used in many phase 3a diabetes trials

A numerically greater HbA1c reduction was observed with placebo for the trial product estimand compared with the treatment policy estimand. This is likely due to the inclusion of patients who stopped receiving the trial drug, with modelling used to estimate the final treatment effect based on the effect seen at discontinuation – i.e. in general, how did those patients with a certain reduction in HbA1c fare by the end of the trial, if they continued for the full duration. However, in general, the two efficacy results were broadly consistent whether based on the treatment policy or trial product estimand, likely reflective of a high proportion of patients completing the trial with the vast majority completing on treatment.

For the purposes of this report – all the results shown are the trial product estimands. This was chosen because we are making a decision at a population level.

Results

<table>
<tr><th>Study title</th><th>Primary outcome</th></tr>
<tr><td>1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes[3]</td><td>Change from baseline (initial mean 8.0%, range 7.0-9.5%) in HbA_{1c} after 26 weeks of placebo (P) or oral semaglutide 3mg, 7mg or 14mg. Previous management diet and exercise. Average time from diagnosis of diabetes 3.5 years. The groups were randomised 1:1:1:1.

<table><tr><th>Dose</th><th>Placebo-adjusted reduction in HbA_{1c} (%)</th></tr><tr><td>3</td><td>-0.6</td></tr><tr><td>7</td><td>-0.9</td></tr><tr><td>14</td><td>-1.1</td></tr></table>The odds of achieving each target were statistically significantly greater with oral semaglutide than with placebo (p<0.001 for all doses)</td></tr>
<tr><td>2: Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin[4]</td><td>Change in HbA_{1c} from baseline to week 26.

<table><tr><th>Drug</th><th>Reduction in HbA_{1c} (%)</th></tr><tr><td>Semaglutide</td><td>-1.4</td></tr><tr><td>Empagliflozin</td><td>-0.9</td></tr></table>P<0.0001.

This also held for results at week 52.</td></tr>
</table>

<table>
<tr>
<td>3: Effect of additional oral semaglutide vs sitagliptin on HbA_{1c} in adults with type 2 diabetes uncontrolled with metformin alone or with sulphonylurea.[5]</td>
<td>Change in HbA_{1c} at week 26.

<table>
<tr><th>Dose of semaglutide (mg)</th><th>Difference in HbA1c (%) at Week 26 compared to sitagliptin (95% CI)</th></tr>
<tr><td>3</td><td>0.2 (0.1 to 0.4)</td></tr>
<tr><td>7</td><td>- 0.3 (- 0.4 to -0.2)</td></tr>
<tr><td>14</td><td>- 0.6 (- 0.7 to - 0.5)</td></tr>
</table>
The results favoured sitagliptin for the 3mg dose (p<0.001) but favoured semagutide for the 7mg and 14mg doses (p<0.001).</td>
</tr>
<tr>
<td>4: Oral semaglutide versus sc lirglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial.</td>
<td>Change in HbA_{1c} from baseline to week 26. (testing for non-inferiority vs liraglutide and superiority vs placebo and liraglutide)

<table>
<tr><th>Drug</th><th>HbA1c (%) at Week 26</th></tr>
<tr><td>Placebo</td><td>-0.1</td></tr>
<tr><td>Liraglutide</td><td>-1.1</td></tr>
<tr><td>Semaglutide</td><td>- 1.3</td></tr>
</table>
The estimated treatment difference (ETD) between:

semaglutide and placebo was -1.2% (95% Confidence interval -1.4 to -1.0%) highly statistically significant (p<0.0001)
semaglutide and liraglutide was -0.2% (95% confidence interval -0.3 to -0.1%). This was still statistically significant (p=0.0056)
</td>
</tr>
<tr>
<td>5: Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment.</td>
<td>Change from baseline to week 26 in HbA_{1c} of semaglutide compared to placebo:

Mean change in HbA1c –1·1 % versus –0·1 %
Estimated Treatment Difference –1·0 %,
95% CI –1·2 to –0·8; p<0·0001</td>
</tr>
</table>

<table>
<tr>
<td>6: Oral semalgutide and cardiovascular outcomes in patients with type 2 diabetes</td>
<td>Time-to-event analysis was the first occurrence of a major adverse cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke).

The primary outcome occurred in 3.8% patients receiving oral semaglutide and 4.8% patients receiving placebo. Thus, non-inferiority was confirmed for oral semaglutide compared with placebo, with a point estimate corresponding to a 21% difference in risk (Hazard ratio was 79%, 95% CI 0.57-1.11; p<0.001 for non-inferiority and p=0.17 for superiority).

Median time in the trial was 15.9 months; including follow-up (range 0.4-20 months). Approximately 75% patient were in the trial for over 1 year.</td>
</tr>
<tr>
<td>7: Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes</td>
<td>The primary endpoint was achievement of HbA1c of less than 7% at week 52.

From a mean baseline HbA1c of 8·3% (SD 0·6%), a greater proportion of participants achieved an HbA1c of less than 7% with oral semaglutide than did with sitagliptin 63% [123 of 196] vs 28% [52 of 184]). This meant that the odds of achieving an HbA1c of less than 7% were significantly better with oral semaglutide than sitagliptin (OR 5·54, 3·54–8·68, p<0·0001).</td>
</tr>
<tr>
<td>8: Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes. [11]</td>
<td>Mean baseline HbA1c was 8.2% and mean diabetes duration was 15.0 years.

Background metformin was used in 67.2% patients. 41.9% patients were on basal insulin, 38.9% were on basal-bolus and 17.6% were on premixed insulin.

<table>
<tr><th>Medication</th><th>Reduction in HbA1c (%) at week 26</th></tr>
<tr><td>Placebo</td><td>-0.0</td></tr>
<tr><td>3mg</td><td>-0.6</td></tr>
<tr><td>7mg</td><td>-1.0</td></tr>
<tr><td>14mg</td><td>-1.4</td></tr>
</table>
All of these results were statistically significant differences compared with placebo (p<0.0001) and clinically significant for the 7mg and 14 mg doses.</td>
</tr>
</table>

<table>
<tr><th>Study title</th><th>Secondary Outcomes</th></tr>
<tr><td>1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes[3]</td><td>Change in body weight from baseline to week 26.

<table><tr><td>Dose</td><td>Placebo-adjusted reduction in body weight (kg)</td></tr><tr><td>3</td><td>-0.1</td></tr><tr><td>7</td><td>-0.9</td></tr><tr><td>14</td><td>-2.3</td></tr></table>Significantly more patients achieved body weight loss of at least 5% with oral semaglutide 7mg and 14mg compared with placebo.

The proportion of patients who achieved a composite endpoint of ≥1% reduction in HbA_{1c} and ≥3% weight loss was also statistically significant with oral semaglutide 7mg and 14mg compared with placebo.</td></tr>
<tr><td>2: Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin[4]</td><td>Change in body weight from baseline to week 26.

<table><tr><td>Drug</td><td>Reduction in weight[c] (kg)</td></tr><tr><td>Semaglutide</td><td>-4.2</td></tr><tr><td>Empagliflozin</td><td>-3.8</td></tr></table>This difference was not statistically significant.

Of the additional secondary endpoints examined, the following were mentioned in the results section of the paper.

Weight loss was statistically significant at 52 weeks if the trial product estimand was used but not if the treatment policy estimand was used.</td></tr>
</table>

<table>
<tr><td></td><td>2 of the composite endpoints reached significance in favour of oral semaglutide vs empagliflozin at both weeks 26 and 52:
HbA1c <7% with no severe or symptomatic hypoglycaemia and no weight gain
Absolute reduction in HbA1c of ≥1.0% and body weight loss of ≥3%</td></tr>
<tr><td>3: Effect of additional oral semaglutide vs sitagliptin on HbA_{1c} in adults with type 2 diabetes uncontrolled with metformin alone or with sulphonylurea.[5]</td><td>Change in body weight at week 26.<table><tr><th>Dose of semaglutide (mg)</th><th>Difference body weight (kg) at Week 26 compared to sitagliptin (95% CI)</th></tr><tr><td>3</td><td>-0.5 (-1.0 to -0.1)</td></tr><tr><td>7</td><td>- 1.5 (- 2.0 to -1.1)</td></tr><tr><td>14</td><td>- 2.6 (- 3.1 to – 2.1)</td></tr></table>The results favoured semaglutide for all doses. The 3mg dose result was not highly significant (p=0.03) while the 7mg and 14mg doses were (p<0.001).

Additional secondary endpoints: change in HbA_{1c} and body weight at weeks 52 and 78.<table><tr><th>Dose of semaglutide (mg)</th><th>Difference in HbA_{1c} (%) at Week 52 compared to sitagliptin (95% CI)</th><th>Difference in HbA_{1c} (%) at Week 78 compared to sitagliptin (95% CI)</th></tr><tr><td>3</td><td>0.1 (0.0 to 0.3)</td><td>0.1 (-0.1 to 0.3)</td></tr><tr><td>7</td><td>- 0.4 (- 0.5 to -0.2)</td><td>- 0.3 (-0.4 to -0.1)</td></tr></table></td></tr>
</table>

14	- 0.7 (- 0.9 to – 0.6)	- 0.7 (-0.8 to -0.5)

The results favoured sitagliptin for the 3mg dose (but did not reach significance) but favoured semagutide for the 7mg and 14mg doses (p<0.001).

Dose of semaglutide (mg)	Difference in body weight (kg) at Week 52 compared to sitagliptin (95% CI)	Difference in body weight (kg) at Week 78 compared to sitagliptin (95% CI)
3	-0.7 (-1.3 to -0.1)	-0.8 (-1.4 to -0.1)
7	- 1.5 (- 2.1 to -0.9)	- 1.6 (-2.2 to -0.9)
14	- 2.9 (- 3.5 to – 2.3)	- 2.4 (-3.0 to -1.7)

The results favoured semaglutide for all doses. The 3mg dose result was not highly signifant (p=0.02 at wk 52 and p=0.03 at wk 78) while the 7mg and 14mg doses were (p<0.001).

Further secondary end points were: whether patients
achieved HbA1c levels below 7.0% (American Diabetes Association target) and at or below 6.5%; weight loss of at least 5% and at least 10%; composites of HbA1c below 7.0% without hypoglycemia (severe or whole-blood glucose–confirmed symptomatic hypoglycemia [<56 mg/dL {<3.1 mmol/L}]) and
without weight gain and (2) HbA1c reduction of at least 1%
and weight loss of at least 3%; and time to rescue medication
and additional glucose-lowering medication.

Of the secondary end-points, it was found that, compared with sitagliptin 100mg daily, significantly greater proportions of patients on semaglutide 7mg or 14mg achieved:

- HbA_{1c} levels lower than 7.0%
- body weight loss of 5% or greater
- time to rescue medication
- time to additional glucose-lowering medication

and the composite outcomes:

- HbA_{1c} <7.0% without hypoglycemia and without weight gain

<table>
<tr><td></td><td>
HbA_{1c} reduction ≥1% and weight loss ≥3%.
<table>
<tr><th rowspan="2">Dose of oral semaglutide (mg)</th><th colspan="3">• Estimated treatment difference (ETD) in patients achieving HbA_{1c} reduction ≥1% and weight loss ≥3% compared with sitagliptin 100mg (%)(95%CI)</th></tr>
<tr><th>26 weeks</th><th>52 weeks</th><th>78 weeks</th></tr>
<tr><td>3</td><td>3 (-2 to 7)</td><td>4 (-1 to 8)</td><td>4 (-1 to 9)</td></tr>
<tr><td>7</td><td>17 (12-22)</td><td>12 (7-17)</td><td>12 (6-17)</td></tr>
<tr><td>14</td><td>30 (25-36)</td><td>27 (21-32)</td><td>23 (17-28)</td></tr>
</table>
</td></tr>
<tr><td>4: Oral semaglutide versus sc lirglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial.</td><td>
Change in body weight from baseline to week 26. (testing for superiority vs placebo and liraglutide)
<table>
<tr><th>Drug</th><th>HbA1c (%) at Week 52</th></tr>
<tr><td>Placebo</td><td>+0.2</td></tr>
<tr><td>Liraglutide</td><td>-0.9</td></tr>
<tr><td>Semaglutide</td><td>- 1.2</td></tr>
</table>
The estimated treatment difference (ETD) between:

semaglutide and placebo was -1.4% (95% Confidence interval -1.6 to -1.2%) highly statistically significant (p<0.0001)
semaglutide and liraglutide was -0.3% (95% confidence interval -0.4 to -0.1%). This was still statistically significant (p=0.0012)

</td></tr>
<tr><td>5: Efficacy and safety of oral semaglutide in patients with type 2</td><td>Change from baseline to week 26 in body weight

Mean change in bodyweight –3·7 kg versus –1·1 kg ;</td></tr>
</table>

<table>
<tr>
<td>diabetes and moderate renal impairment.</td>
<td>Estimated Treatment Difference –2·7 kg, 95% CI –3·5 to –1·9; p<0·0001

The additional secondary endpoints which were reported in the results section of the trial publication were as follows: outcomes for fasting plasma glucose, BMI, and waist circumference favoured oral semaglutide over placebo, whereas they were similar between treatments for C-reactive protein and fasting lipids.

84 [67%] of 126 in semaglutide group vs 24 [19%] of 127 in placebo group with non-missing data who completed treatment without rescue medication and more achieved the targets of HbA1c of less 7·0% (89 [58%] of 154 vs 35 [23%] of 155) and 6·5% or more (60 [39%] vs 12 [8%]) with oral semaglutide than with placebo (treatment policy estimand; appendix pp 20–21). The odds of achieving both targets for both estimands were significantly higher with oral semaglutide than with placebo (p<0·0001).</td>
</tr>
<tr>
<td>6: Oral semalgutide and cardiovascular outcomes in patients with type 2 diabetes</td>
<td>The time from randomization to the first occurrence of the following:
- an expanded composite outcome consisting of the primary outcome plus unstable angina resulting in hospitalization or heart failure resulting in hospitalization. The result was similar to that for the primary outcome – events in 5.2% of patients who received semaglutide and 6.3% patients in the placebo group (HR0.82; 95% CI 0.61-1.10)
-a composite of death from any cause,
nonfatal myocardial infarction, or nonfatal stroke – events in 4.3% of patients receiving semaglutide and 5.6% of those on placebo (hazard ratio, 0.77; 95% CI, 0.56 to 1.05)
-the individual components of these composite outcomes:
<table>
<tr><th>Measure</th><th>Result –semaglutide first, then placebo</th></tr>
<tr><td>First event of angina resulting in hospitalisation</td><td>0.7% cf 0.4% (hazard ratio, 1.56; 95% CI, 0.60 to 4.01)</td></tr>
<tr><td>First event of heart failure resulting in hospitalisation</td><td>1.3% cf 1.5% (hazard ratio, 0.86; 95% CI, 0.48 to 1.55)</td></tr>
<tr><td>Death from cardiovascular causes</td><td>0.9% cf 1.9% (hazard ratio, 0.49; 95% CI, 0.27 to 0.92)</td></tr>
<tr><td>First events of Non-fatal myocardial infarction</td><td>2.3% cf 1.9% (hazard ratio, 1.18; 95% CI, 0.73 to 1.90)</td></tr>
<tr><td>First event of non-fatal stroke</td><td>0.8% cf 1.0% (hazard ratio, 0.74; 95% CI, 0.35 to 1.57)</td></tr>
<tr><td>Death from any cause</td><td>1.4% cf2.8% (hazard ratio, 0.51; 95% CI, 0.31 to 0.84)</td></tr>
</table>
</td>
</tr>
</table>

	Additional efficacy outcomes included the change from baseline to the end of the treatment period in: -the glycated haemoglobin level, -body weight -and lipid levels. 82.1% of patients in the oral semaglutide arm who completed the trial were on 14mg daily by the end-of-treatment visit. At baseline, most patients were taking metformin (2463 patients, 77.4%) or insulin (1930 patients, 60.6%); 1027 (32.3%) were taking sulfonylureas and 305 (9.6%) sodium–glucose cotransporter 2 (SGLT2) inhibitors In addition, 2988 patients (93.9%) were taking antihypertensive medication, 2712 (85.2%) lipid-lowering medication, and 2527 (79.4%) antiplatelet or antithrombotic medication During the trial, more patients initiated or intensified glucose-lowering therapy in the placebo group than in the oral semaglutide group, including greater use of SGLT2 inhibitors (111 patients [7.0%] vs. 50 [3.1%]). Glycated hemoglobin levels decreased more in the oral semaglutide group than in the placebo group (mean change from baseline to end of trial, –1.0 vs. –0.3 percentage points), as did body weight (mean change from baseline to end of trial, –4.2 kg vs. –0.8 kg). Systolic blood pressure decreased more in the oral semaglutide group than in the placebo group, and levels of low-density lipoprotein cholesterol and triglycerides were modestly lower in the oral semaglutide group

7: Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes	The odds of decreasing mean bodyweight from baseline to week 52 were higher with oral semaglutide than with sitagliptin: estimated mean change in bodyweight, –2·9 kg [SE 0·3] vs –0·8 kg [SE 0·3]. This gives an estimated mean treatment difference of –2·2 kg, –2·9 to –1·5; p<0.0001. Of the many secondary endpoints measured, the only one to be highlighted in the results section was the time to first dose of rescue medication: which was significantly longer with oral semagluditde than with sitagliptin (Hazard Ratio 0.18, 95% CI 0.09-0.39, p<0.0001) Supportive secondary efficacy endpoints were change from baseline to week 52 in HbA1c, fasting plasma glucose, BMI, bodyweight percentage, waist circumference, lipid profile, patient-reported outcomes (Diabetes Treatment Satisfaction Questionnaire [DTSQ]; Short Form-36 [SF-36] version 2 health survey [acute version]); and achievement of HbA1c less than or equal to 6·5% (48 mmol/mol),17 bodyweight loss of 5% or more or 10% or more by week 52, and time to use of rescue medication. Composite supportive secondary endpoints assessed achievement at week 52 of: • HbA1c of less than 7% without hypoglycaemia (treatment-emergent severe or confirmed by blood glucose concentration) • body weight loss of at least 3kg and decrease of HbA_{1c} of 1% or more. These were achieved in a significantly higher number of patients on semaglutide than sitagliptin (p<0.0001) 203 (40%) of 504 participants were receiving one concomitant glucose-lowering drug at baseline (primarily metformin), 299 (59%) were receiving two concomitant glucose-lowering drugs (mostly metformin plus a sulphonylurea), and two (<1%) was receiving 3 concomitant glucose-lowering drugs (protocol violation – these patients were included in the analysis). In the oral semaglutide group, 185 (73%) of 253 patients were escalated to the 7 mg dose at week 8 (appendix p 10). Of 212 participants on treatment at week 52, 19 (9%) were receiving 3 mg, 64 (30%) were receiving 7 mg, and 126 (59%) were receiving 14 mg of oral semaglutide. Dose information was missing for the remaining three [1%] patients at week 52, but the last known dose was 7 mg for one participant and 14 mg for two participants.

8: Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes. [11]

Mean baseline body weight was 85.9kg.

Change in body weight to week 26.

Medication	Mean change in body weight (kg)
Placebo	-0.4
3mg	-1.3
7mg	-3.0
14mg	-4.1

Change in body weight to week 52.

Medication	Mean change in body weight (kg)
Placebo	+0.6
3mg	-1.0
7mg	-2.9
14mg	-4.3

All results for 7mg and 14mg were statistically and clinically significant at both times.

Changes from baseline in HbA1c at week 52

Medication	Reduction in HbA1c (%)
Placebo	-0.0
3mg	-0.5
7mg	-0.8
14mg	-1.2

All of these results were statistically significant differences compared with placebo ($p<0.0001$) and clinically significant for the 14 mg dose.

The mean change from baseline in the daily insulin dose at weeks 26 and 52 was as follows:

Medication	Change at week 26 (units)	Change at week 52 (units)
Placebo	-4	+3
3mg	-7	-3
7mg	-7	-5
14mg	-10	-9

Statistical significance was achieved for these results at week 52 for all doses of semaglutide compared with placebo and for the 14mg dose at week 26.

However, it must be noted that many patients (mainly those on oral semaglutide 3 mg and placebo) increased their total daily insulin dosage from baseline by over 20% during the freely adjustable insulin treatment period (weeks 26–52). As this was considered rescue medication, this affected the results for this end point for the trial product estimand, where only data prior to initiation of rescue medication were used when estimating the results.

Of the combined outcoomes assessed, one was particularly noteworthy:
Observed proportion of patients achieving HbA1c <7.0% without hypoglycaemia and without body weight gain which was observed in 19.8%, 27.4% and 49.3% patients on the 3 semaglutide strengths compared with 2.5% of patients in the placebo arm of the study.

Of the supplementary secondary outcomes which were assessed, the proportions of patients achieving HbA1c <7.0% (53 mmol/mol) without hypoglycemia and without body weight gain were greater, and the odds of achieving the outcome statistically significantly greater, with oral semaglutide compared with placebo.

Oral semaglutide treatment tended to improve the fasting lipid profile from baseline. Reductions in total cholesterol were statistically significantly greater with all oral semaglutide doses compared with placebo at weeks 26 and 52, except for the 3-mg dose at week 52.

Summary of the adverse effects experienced in the trials:

Study	1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes[3]	2: Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin[4]	3: Effect of additional oral semaglutide vs sitagliptin on HbA_{1c} in adults with type 2 diabetes uncontrolled with metformin alone or with sulphonylurea.[5]	4: Oral semaglutide versus sc lirglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial.	5: Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment.	6: Oral semalgutide and cardiovascular outcomes in patients with type 2 diabetes	7: Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes	8: Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes. [11]
% patients with an adverse event	Placebo 55.6% Semaglutide 3 mg 53.1% Semaglutide 7mg 56.6% Semaglutide 14mg 56.6%	Similar number with both drugs and mostly mild-moderate in severity.	Any adverse event: Sitagliptin 83.3% Semaglutide 3 mg 79.4% Semaglutide 7mg 78.2% Semaglutide 14mg 79.6%	80% in the oral semaglutide group, 74% in the liraglutide group, and 67% in the placebo group. The proportion of	74% of oral semaglutide patients vs 65% of placebo patients	Serious adverse events occurred in 301 of 1591patients (18.9%) in the oral semaglutide group and 358 of 1592 (22.5%) in the placebo	Adverse events occurred in 78% participants in the oral semaglutide group versus 69% in the sitagliptin group. These adverse events were	Comparable proportions of patients experienced at least one adverse event while on treatment. These were classed as serious in

			Serious adverse event: Sitagliptin 12.4% Semaglutide 3 mg 13.7% Semaglutide 7mg 10.1% Semaglutide 14mg 9.5%	participants who had a serious adverse event was similar in the oral semaglutide and placebo groups, and lower in the liraglutide group.		group. Serious adverse events were varied and involved several organ systems.	mostly mild to moderate in nature. The semaglutide adverse events occurred mostly in the first 8 weeks of the trial, and few additional patients discontinued treatment after the main dose escalation timepoints	9.2% of patients on placebo, 13.6% on 3mg semaglutide, 10.5% on 7mg and 6.6% on 14mg. The serious adverse events were mostly gastrointestinal.
% patients who discontinued treatment due to an adverse event	2.3-7.4% with semaglutide (increasing with dose) v's 2.2% on placebo	10.7% of semaglutide patients vs 4.4% of empagliflozin patients. In 8.0% of semaglutide patients vs 0.7% of	5.6%, 5.8%, and 11.6% in the 3mg, 7mg, and 14mg semaglutide groups, respectively, and 5.2% for sitagliptin Often during the dose	31 (11%) participants in the oral semaglutide group, 26 (9%) in the liraglutide group, and five (4%) in the placebo group	15% of oral semaglutide patients vs 5% of placebo patients	Serious adverse events led to permanent discontinuation in 2.6% oral semaglutide patients and 3.0% placebo patients.	Adverse events resulted in discontinuation of the study drug in 9% of the patients taking semaglutide and 6% of those on sitagliptin.	2.7% of patients on placebo, 7.1% on 3mg semaglutide, 8.8% on 7mg and 13.3% on 14mg. The adverse events were mostly

		empagliflozin patients discontinuation was due to gastrointestinal symptoms and usually happened within the first 16 weeks.	escalation period for patients on the 7mg or 14mg doses of semaglutide.			Overall, 11.6% oral semaglutide patients vs 6.5% placebo patients permanently discontinued treatment.		gastrointestinal.
Number of deaths in trial and whether attributed to the treatment	0	Semaglutide 0 Empagliflozin 1 patient	12 – no pattern or clustering of causes of death.	8 – not judged to be treatment related by the investigator.	3 – not considered to be treatment related. 1 semaglutide patients and 2 placebo patients.	68 23 of 1591 in the oral semaglutide group and 45 of 1592 in the placebo group. No clustering of cause of death apart from cardiovascular (see below)	2 in the sitagliptin group – not judged to be linked to the study medication	3 All were on 14mg semaglutide. . The cause of death was infection for one patient and remained undetermined for the remaining 2 patients as their medical records were unavailable.
Gastric side effects	Mild to moderate GI side effects	Most common side effect in oral	Nausea was the most common side	The slightly higher occurrence of	The most frequent adverse	6.8% in the oral	Nausea (21% patients) and diarrhoea	Gastrointestinal disorders occurred most

	were the most common adverse events but also the most commonly associated with product discontinuation: Nausea in 8-16% patients in the semaglutide groups v's 5.6% placebo group Diarrhoea 5.5-8.6% in the semaglutide groups v's 2.2% placebo group Vomiting in 1.7-6.3% semaglutide patients (most	semaglutide patients was mild-moderate nausea. Prevalence was below 10% throughout the trial.	effect – mostly mild-moderate. However, gastric side effects were the most common cause of discontinuation in all treatment groups and discontinuation was usually during escalation to treatment dose in the 7mg and 14mg groups.	adverse events with oral semaglutide than with subcutaneous liraglutide was largely attributable to gastrointestinal events, with the most frequent being transient nausea and diarrhoea, which were generally mild to moderate in severity. Peak occurrence of nausea was earlier with subcutaneous liraglutide than with oral semaglutide (approximatel	events were mild-to-moderate gastrointestinal events, primarily nausea. Nausea was more common in patients who were given oral semaglutide who had stage 3A chronic kidney disease than in those with stage 3B disease. Gastrointestinal events (principally, nausea, vomiting, abdominal pain, and dyspepsia)	semaglutide group vs. 1.6% in the placebo group: Primarily nausea (2.9% vs.0.5%), vomiting (1.5% vs. 0.3%), and diarrhoea (1.4% v's 0.4%), mostly nonserious.	(22% patients) were the most common adverse events with oral semaglutide.	frequently in the oral semaglutide arms 3 mg, 39.1% 7 mg, 44.8% 14 mg, 50.3%

	in lower doses though) v's 3.4% placebo			y week 2 compared with week 8), before decreasing in both groups. Gastric adverse eents were the main reason for treatment discontinuatio n.	were the most common cause of treatment discontinuatio n.			
Hypoglycae mia (blood glucose <3.1mmol/L)	Severe or blood glucose-confirmed symptomatic hypoglycaemi a was seen in 5 patients on 3mg Semaglutide, 2 on 7mg semaglutide, 1 on 14mg semglutide	Incidence similar for both semaglutide and empagliflozin	Severe or whole-blood glucose–confirmed episodes of symptomatic hypoglycemia were experienced by 4.9%, 5.2%, and 7.7% of patients in the 3mg, 7mg, and 14mg	Severe or blood-glucose-confirmed symptomatic hypoglycaemi c events occurred in two (1%) participants in the oral semaglutide group, seven (2%) in the liraglutide	A symptomatic hypoglycaemi c episode confirmed by blood glucose concentration: 6% in the oral semaglutide group *vs* 2% in the placebo group). No severe hypoglycaemi	Despite improved glycemic control with oral semaglutide, the percentage of patients with severe hypoglycemia was 1.4%, as compared with 0.8% with placebo. All severe hypoglycemic	Proportions of participants who had symptomic hypoglycaemi a which was confirmed by blood glucose measurement was low and similar between treatment groups. Most individuals	Very few hypoglycaemi c episodes and the proportions were similar across the treatment arms.

	and 1 patient on placebo.		semaglutide groups, respectively, and by 8.4% in the sitagliptin group. These episodes mainly occurred in patients prescribed background metformin with sulfonylurea.	group, and three (2%) in the placebo group.	c events occurred.	events occurred in patients receiving concomitant insulin or sulfonylureas at the time of the event.	who experienced an episode were also taking a sulphonylurea . Twice as many participants were given additional glucose lowering drugs and more than four-times as many partipants were given rescue medication in the sitagliptin group compared with the oral semaglutide group	
Diabetic retinopathy		Identified in routine examination	Infrequent and similar across all	Eight [3%] in the oral semaglutide	All cases of retinopathy were non-	The percentage of patients with	Reported in 2% of patients in	Identified during routine examination

		during the study in 1.2% patients on empagliflozin and 3.4% patients on oral semaglutide	treatment groups. Mostly mild or moderate in severity, were reported at routine eye examinations, and did not require treatment.	group, four [1%] in the liraglutide group, and two [1%] in the placebo group.	serious and mild or moderate in severity, and none required treatment or led to discontinuation of study drug. Most of these events were discovered during routine end-of-treatment eye examination and were diagnosed as non-proliferative diabetic retinopathy.	adverse events related to diabetic retinopathy during the trial was 7.1% with oral semaglutide and 6.3% with placebo. Most cases were nonproliferative and were identified during routine examinations (92.5% of oral semaglutide cases and 85.5% of placebo cases). 75.7% resulted in no new treatment. In the placebo group, one case of serious retinopathy and one which lead to discontinuatio	both the oral semaglutide and sitagliptin groups.	for 40 patients (10 per treatment arm), and 8 patients required treatment. All events were mild or moderate in severity.

						n of the placebo were reported.		
Pancreatitis	No cases. However,mean lipase levels were significantly increased (13-34%) with semaglutide compared to placebo. Levels were more than 3 times ULN in 1.7-3.4% of semaglutide patients compared to 1.7% of placebo patients.	Not reported. Patients were not eligabile if had a history of pancreatitis. It was one of the criteria to be monitored during the trial.	No difference between treatment groups	2 cases – one in the liraglutide group and one in the placebo group. Lipase and amylase were generally similar between oral semaglutide and liraglutide but were significantly increased with oral semaglutide compared with placebo.	There was no record of any patients developing pancreatitis during this study in either the placebo or active treatment group.	1 confirmed case of acute pancreatitis in the oral semaglutide group and 3 in the placebo group	No cases reported. Mean lipase and amylase concentrations were increased in both treatment groups compared with baseline, with no difference between groups.	No cases of acute pancreatitis. No clinically relevant differences in laboratory parameters or other vital signs.

Cardiac SEs	At week 26, mean pulse rate increased significantly with oral semaglutide 14 mg (3 bpm; P = 0.003), but not with 3 or 7 mg, compared with placebo. There were no clinically relevant changes in blood pressure or other safety laboratory assessments.	None reported	No difference between treatment groups	No clinically relevant changes in physical examinations or ECG readings were recorded in any groups. Blood pressure and pulse rate changes from baseline were generally similar between treatment groups.	3% in semaglutide group and 2% in the placebo group.	Most frequent underlying cause of death – 10 of 23 in the oral semaglutide group and 23 or 45 in the placebo group. Mean pulse rate increased by 4bpm in the oral semaglutide group (unchanged in placebo patients)	No clinically relevant changes in blood pressure or pulse rate	Low and similar incidence across treatment arms. Compared with placebo, pulse rate increased for the oral semaglutide arms, with an estimated treatment difference of 2–4 beats/min at week 26 (all groups P , 0.05) and 1–2 beats/min at week 52 (P , 0.05 for oral semaglutide 14 mg only) while on treatment.

Renal function	Not reported in the write up but renal function was to be monitored throughout.	Patients were excluded if GFR <60ml/min and AKI was checked for by the external validation committee. No specific concerns re results were raised in the write-up.	No difference between treatment groups	Stable in all treatment groups	Overall, renal function was unchaged throughout the trial period in both treatment groups. Median eGFR ratios (at week 31 compared to baseline) were 1.02 (range 0.27-1.96) for oral semaglutide and 1.00 (range 0.68-2.17) for placebo. 2 patients in the oral semglutide group had 3 non-serious events of acute kidney injury (stage1, recovered or	Excluded if eGFR<30ml/min. AKI in 2% semaglutide patients vs 2.3% placebo patients.	No clinically relevant difference in eGFR were reported.	Incidence of acute kidney injury events were low and similar incidence across treatment arms.

					recovering while remaining on study drug). One patient in the placebo group had a non-serious event of acute kidney injury (stage 2) and recovered.			
Malignancy	Monitored for but none reported.	Malignant neoplasms were seen in 0.5% of empaglilozin patients and 1.7% of oral semaglutide patients. There was no trend in type or organ affected.	No difference between treatment groups	Monitored for but none reported.	Screened for and monitored for but none reported.	Malignant neoplasms were recorded in 2.6% of semaglutide patients and 3.0% of placebo patients	3% of participants in the oral semaglutide group and in 1% in the sitagliptin group. There was no clustering of malignancies to specific organ systems.	Few patients – no other comment in publication.

Miscellaneous reports		It was found that mild-moderate female and male genital mycotic infections occurred in 8.5% empagliflozin patients compared with 2.0% oral semaglutide patients (at week 26).	Infestations were the most common reason for discontinuation in the 3mg and 7mg semaglutide groups and in the sitagliptin group.	One participant in the oral semaglutide group tested positive for anti-semaglutide antibodies at baseline, but not at any measurements thereafter; the single positive sample was negative for cross-reacting antibodies and in-vitro neutralising effect.				Infections and infestations were the most commonly reported side effect in the placebo (43.5% of participants) and the 3mg semaglutide (39.7% of participants) arms. There was one pregnancy in the 7mg semaglutide arm of the study. The participant elected to have a termination.

Appendix B -Items trend analysis for GLP1 RAs in Surrey Heartlands Jan 2014-Sep 2020