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Review

Will oral semaglutide be a game-changer in the management of type 2 diabetes in primary care?

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ABSTRACT

GLP-1 receptor agonists (GLP-1RAs) are recommended for patients with type 2 diabetes (T2D), particularly those at high cardiovascular risk. Oral semaglutide is the first oral GLP-1RA. In clinical trials, oral semaglutide 14 mg reduced mean HbA_{1c} by approximately 1.1–1.5% and reduced body weight by up to 5 kg. These changes were significantly greater compared with empagliflozin, sitagliptin and liraglutide ($p < 0.05$ for estimated treatment differences at 52 weeks in patients on treatment without rescue medication use). The most common side effects were gastrointestinal, mainly mild-to-moderate and transient nausea. Oral semaglutide may change the paradigm of T2D treatment in primary care.

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1. Introduction

Patients with type 2 diabetes (T2D) require treatment to be tailored to the individual course of their disease in order to maintain glycaemic control, reduce the risk of diabetes-related comorbidities and improve their prognosis [1–3]. However, in practice, treatment intensification may be delayed despite inadequate improvements in patients' blood glucose levels [4–6]. This may partly be due to the challenge that physicians face in having to navigate complex treatment algorithms and multiple drug classes to provide personalised plans for each patient based on individual clinical factors [7–9]. In addition, patients and physicians alike may be reluctant to initiate injectable therapy [10,11].

In general, patients requiring add-on therapy to metformin are recommended to receive one of a: glucagon-like peptide-1 receptor agonist (GLP-1RA); sodium glucose cotransporter-2 inhibitor (SGLT2i); dipeptidyl peptidase-4 inhibitor (DPP-4i); sulphonylurea (SU) or thiazolidinedione (TZD) [7,8]. GLP-1RAs or SGLT2is are recommended for patients with indicators of high cardiovascular risk or established cardiovascular disease (CVD), chronic kidney disease (CKD) or heart failure, regardless of glycated haemoglobin (HbA_{1c}) [9,10]. Of the available treatments, GLP-1RAs are considered among the most effective because they exert multi-organ effects to lower blood glucose, discourage overeating (potentially resulting in body weight reductions) [11] and may reduce cardiovascular risk [12–17]. DPP-4is also upregulate GLP-1 by blocking the enzyme responsible for its elimination [18], but with more modest effects on blood glucose, no effect on body weight [19] and with a neutral effect on cardiovascular outcomes [20–22]. SGLT2is inhibit the action of the transporter largely responsible for glucose reuptake in the kidney and, like GLP-1RAs, improve glucose control, reduce body weight and have cardiovascular benefits [23]. TZDs and SUs are effective for glycaemic control and are often preferred when cost is an issue, but are both associated with weight gain and hypoglycaemia, as well as concerns about cardiovascular safety with some (but not all) drugs in these classes [7].

Despite their efficacy, global use of GLP-1RAs is low [24–27]. In some cases, cost and lack of reimbursement may contribute to this. However, in primary care in particular, a further barrier may be the reluctance of some injection-naïve patients to accept a subcutaneously administered medication [28]. Such patients also need to be trained properly in injection technique, which could have implications for primary healthcare providers' time and resource [29–31]. In contrast, DPP-4is, SGLT2is, SUs and TZDs are all administered orally, and there is evidence that adherence to oral therapy is greater than that for injectables [32]. Indeed, since their introduction in 2013, use of oral SGLT2i therapy has been greater than that for injectable GLP-1RAs [24,25], suggesting a preference for oral therapies. The unmet need for an oral GLP-1RA has led to the development of oral semaglutide. This is a coformulation of semaglutide (the subcutaneous formulation of which was more effective than other GLP-1RAs including exenatide [33], dulaglutide [34] and liraglutide [35]) with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) [36] in a tablet. SNAC protects semaglutide from degradation in the stomach and helps to increase its absorption [36] (Fig. 1), thus overcoming two of the main barriers to the oral delivery of a peptide-based molecule [37]. Once administered, either orally or by injection, semaglutide has a half-life of approximately one week [36]. However, because of greater variation in drug exposure between individuals with oral versus subcutaneous administration [36], oral semaglutide is dosed once daily rather than the once-weekly schedule used with subcutaneous semaglutide [38,39]. Oral semaglutide may be an attractive option for use by primary-care providers (PCPs) and their patients, potentially encouraging earlier and more adherent use of GLP-1RAs to enhance glycaemic control [40].

This article reviews the efficacy and safety of oral semaglutide compared with other recommended glucose-lowering medications and offers practical information on managing oral semaglutide for PCPs, referring to clinical data from the phase 3 PIONEER clinical trial programme.

2. The phase 3 clinical trial programme for oral semaglutide

Oral semaglutide was tested in a series of eight global phase 3 clinical trials [41–48]. The programme included patients at different stages of the T2D treatment journey, from those managed by diet and exercise alone, through to people already receiving other oral glucose-lowering drugs and/or insulin, as well as patients with comorbidities such as CVD and CKD [37–44] (Table 1). In general, patients were eligible for the studies if they were aged ≥18 years, had been diagnosed with T2D at least 90 days before screening and had a HbA_{1c} of ≥7% (53 mmol/mol), i.e. above the American Diabetes Association (ADA) target [49]. Exclusion criteria varied by trial but generally encompassed disorders including a familial or personal history of certain cancers, including thyroid carcinoma, a history of pancreatitis, and proliferative retinopathy or maculopathy [41–48].

Early clinical trials showed that absorption of oral semaglutide was affected by food and water intake [36]. Therefore, to ensure adequate absorption, oral semaglutide was dosed in the morning on an empty stomach with no more than 120 mL water, and at least 30 min before any other oral medication, food or other drink [41–48]. Based on a phase 2 trial [50], the dose was escalated in 4-week increments, starting at 3 mg once daily, to mitigate potential gastrointestinal (GI) side effects, which are the most common type of adverse event with GLP-1RAs [33–35].

Data from the PIONEER trials were analysed using two sets of prespecifications (called estimands) to provide an estimated treatment effect based on whether or not data from patients who discontinued treatment or required rescue (i.e. additional glucose-lowering) medication during the trial were included in the efficacy analyses [51]. Here, we present efficacy data without the confounding effects of treatment discontinuation or rescue medication use (called the trial product estimand in the PIONEER trials), i.e. showing the best efficacy achievable with oral semaglutide [51].

3. Efficacy of oral semaglutide in patients who require treatment intensification

The European Association for the Study of Diabetes (EASD) and ADA joint consensus report [7] states that patients without a high cardiovascular risk, inadequately controlled on metformin, should receive one of a DPP-4i, GLP-1RA, SGLT2i, SU or TZD as add-on therapy. Glucose-lowering drugs from other classes can then be added as needed (with some restrictions) to achieve further HbA_{1c} reductions [7]. However, there is little guidance regarding the order in which medications should be added [7]. Four of the PIONEER trials were designed with this clinical choice in mind, evaluating oral semaglutide against commonly used oral DPP-4i and SGLT2i medications, as well as a subcutaneously administered GLP-1RA [42–44,47].

3.1. Oral semaglutide vs SGLT2i

In PIONEER 2, oral semaglutide 14 mg once daily was compared against empagliflozin 25 mg once daily in patients receiving metformin who had an average T2D duration of approximately 7 years, a mean HbA_{1c} of 8.1% and a baseline body weight of approximately 92 kg [42]. Oral semaglutide provided significantly greater reductions in HbA_{1c} at 26 weeks compared with empagliflozin (−1.4% vs

Table 1
Overview of the design and key efficacy results of the global PIONEER trials.

Trial name (N patients)	Design	Comparators	Key inclusion criteria	Baseline characteristics	Change in HbA_{1c}[a]	Change in body weight[a]
PIONEER 1 (703) [41]	• Double blind • 26 weeks	• Oral semaglutide 3, 7, 14 mg OD • Placebo	• Background diet and exercise only • HbA_{1c} 7.0–9.5%	• Age: 55 y • T2D duration: 3.5 y • HbA_{1c}: 8.0% • Weight: 88.1 kg	• HbA_{1c} (wk 26): −0.8%*, −1.3%*, −1.5%* (oral semaglutide 3, 7, 14 mg) vs −0.1% (placebo)	• Body weight (wk 26): −1.7 kg*, −2.5 kg*, −4.1 kg* (oral semaglutide 3, 7, 14 mg) vs −1.5 kg (placebo)
PIONEER 2 (822) [42]	• Open label • 52 weeks	• Oral semaglutide 14 mg OD • Empagliflozin 25 mg OD	• Background metformin • HbA_{1c} 7.0–10.5%	• Age: 58 y • T2D duration: 7.4 y • HbA_{1c}: 8.1% • Weight: 91.6 kg	• HbA_{1c} (wk 26): −1.4%* (oral semaglutide 14 mg) vs −0.9% (empagliflozin)	• Body weight (wk 26): −4.2 kg (oral semaglutide 14 mg) vs −3.8 kg (empagliflozin)
PIONEER 3 (1864) [43]	• Double blind • 78 weeks	• Oral semaglutide 3, 7, 14 mg OD • Sitagliptin 100 mg OD	• Background metformin ± SU • HbA_{1c} 7.0–10.5%	• Age: 58 y • T2D duration: 8.6 y • HbA_{1c}: 8.3% • Weight: 91.2 kg	• HbA_{1c} (wk 26): −0.5%, −1.1%*, −1.4%* (oral semaglutide 3, 7, 14 mg) vs −0.8%† (sitagliptin)	• Body weight (wk 26): −1.2 kg*, −2.2 kg*, −3.3 kg* (oral semaglutide 3, 7, 14 mg) vs −0.7 kg (sitagliptin)
PIONEER 4 (711) [44]	• Double blind • 52 weeks	• Oral semaglutide 14 mg OD • Liraglutide 1.8 mg OD • Placebo	• Background metformin ± SGLT2i • HbA_{1c} 7.0–9.5%	• Age: 56 y • T2D duration: 7.6 y • HbA_{1c}: 8.0% • Weight: 94.0 kg	• HbA_{1c} (wk 26): −1.3%* (oral semaglutide 14 mg) vs −1.1% (liraglutide) and −0.1% (placebo)	• Body weight (wk 26): −4.7 kg* (oral semaglutide 14 mg) vs −3.2 kg (liraglutide) and −0.7 kg (placebo)
PIONEER 5 (324) [45]	• Double blind • 26 weeks	• Oral semaglutide 14 mg OD • Placebo	• Moderate renal impairment[b] • Background metformin ± SU or insulin ± metformin • HbA_{1c} 7.0–9.5%	• Age: 70 y • T2D duration: 14.0 y • HbA_{1c}: 8.0% • Weight: 90.8 kg	• HbA_{1c} (wk 26): −1.1%* (oral semaglutide 14 mg) vs −0.1% (placebo)	• Body weight (wk 26): −3.7 kg* (oral semaglutide 14 mg) vs −1.1 kg (placebo)
PIONEER 6 (3183) [46]	• Double blind	• Oral semaglutide 14 mg OD	• ≥50 y with CVD/CKD or ≥60 y with CV risk factors	• Age: 66 y	• HbA_{1c}[c]: −1.0% (oral semaglutide 14 mg) vs −0.3% (placebo)	• Body weight[c]: −4.2 kg (oral semaglutide 14 mg) vs −0.8 kg (placebo)

Table 1 (*Continued*)

Trial name (N patients)	Design	Comparators	Key inclusion criteria	Baseline characteristics	Change in HbA_{1c}[a]	Change in body weight[a]
	• Event driven	• Placebo	• Background standard of care	• T2D duration: 14.9 y • HbA_{1c}: 8.2% • Weight: 90.9 kg		
PIONEER 7 (504) [47]	• Open label	• Oral semaglutide 3, 7 or 14 mg flexibly dosed OD	• 1–2 background glucose-lowering therapies	• Age: 57 y	• HbA_{1c} (wk 52): −1.4%* (oral semaglutide) vs −0.7% (sitagliptin)	• HbA_{1c} (wk 52): −2.9 kg* (oral semaglutide) vs −0.8 kg (sitagliptin)
	• 52 weeks[d]	• Sitagliptin 100 mg OD	• HbA_{1c} 7.5–9.5%	• T2D duration: 8.8 y • HbA_{1c}: 8.3% • Weight: 88.6 kg		
PIONEER 8 (731) [48]	• Double blind	• Oral semaglutide 3, 7 or 14 mg OD	• Background insulin	• Age: 61 y	• HbA_{1c} (wk 26): −0.6%*, −1.0%*, −1.4%* (oral semaglutide 3, 7, 14 mg) vs −0.0 (placebo)	• Body weight (wk 26): −1.3 kg*, −3.0 kg*, −4.1 kg* (oral semaglutide 3, 7, 14 mg) vs −0.4 kg (placebo)
	• 52 weeks	• Placebo	• HbA_{1c} 7.0–9.5%	• T2D duration: 15.0 y • HbA_{1c}: 8.2% • Weight: 85.9 kg		

CKD, chronic kidney disease; CV(D), cardiovascular (disease); HbA_{1c}, glycated haemoglobin; OD, once daily; SGLT2i, sodium glucose cotransporter-2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes; wk, week; y, year.

* $p < 0.05$ for estimated difference between treatments favouring oral semaglutide vs comparator.

† $p < 0.05$ estimated difference between treatments favouring comparator vs oral semaglutide 3 mg.

[a] Data assuming all patients remained on treatment without using rescue medication.

[b] Estimated glomerular filtration rate 30–59 mL/min/1.73 m^2.

[c] Median time in trial: 15.9 months; difference in outcomes not analysed statistically.

[d] With a further 52-week extension trial (results not yet reported).

−0.9%; $p < 0.0001$) (Table 1). Importantly, significantly better glycaemic control with oral semaglutide was maintained at 52 weeks (−1.3% vs −0.8%; $p < 0.0001$) (Fig. 2), and 72% of patients receiving oral semaglutide (vs 48% on empagliflozin) had a HbA_{1c} <7% at the end of treatment ($p < 0.0001$) [42]. Both treatments led to a decrease in body weight at 26 weeks (−4.2 kg vs −3.8 kg; $p = 0.1358$) (Table 1), but whereas weight did not decrease further in patients receiving empagliflozin, those taking oral semaglutide had a further reduction at week 52 (−4.7 kg vs −3.8 kg; $p = 0.0114$ vs empagliflozin) (Fig. 3) [42].

3.2. Oral semaglutide vs DPP-4i

Three doses of oral semaglutide (3, 7 and 14 mg once daily) and a flexible dosing approach were compared against sitagliptin 100 mg once daily in patients uncontrolled on 1–2 oral glucose-lowering medications [43,47]. Patients in these two trials (PIONEER 3 and 7) had T2D for 8–9 years, with HbA_{1c} 8.3% and body weight of approximately 90 kg at baseline [43,47]. Compared with sitagliptin (−0.8%), there were significant HbA_{1c} reductions from baseline with oral semaglutide 7 mg (−1.1%; $p < 0.001$) and 14 mg (−1.4%; $p < 0.001$), but not oral semaglutide 3 mg (−0.5%; $p < 0.001$ favouring sitagliptin), at week 26 in PIONEER 3 (Table 1). Significant reductions in HbA_{1c} versus sitagliptin were maintained at week 78 for the 7 and 14 mg doses (Fig. 2) [43]. When oral semaglutide was flexibly dosed in PIONEER 7, 63% of patients reached the HbA_{1c} target of <7% compared with sitagliptin (28%; $p < 0.0001$) after 52 weeks [47]. Oral semaglutide 7 mg (−2.2 kg) and 14 mg (−3.3 kg) significantly reduced body weight from baseline versus sitagliptin (−0.7 kg) at week 26 ($p < 0.001$) (Table 1), with the difference conserved at week 78 (Fig. 3) [43]. Flexibly dosed oral semaglutide also led to significantly greater body weight loss than sitagliptin after 52 weeks (−2.9 kg vs −0.8 kg; $p < 0.0001$) (Table 1) [47].

3.3. Oral semaglutide vs injectable GLP-1RA

In PIONEER 4, people with T2D uncontrolled on metformin with or without an SGLT2i received either oral semaglutide 14 mg once daily or the injectable GLP-1RA liraglutide escalated to 1.8 mg once daily [44]. There was also a placebo arm. Participants had a T2D duration of approximately 7–8 years, mean HbA_{1c} 8.0% and body weight 94 kg at baseline [44]. At 26 weeks, patients receiving oral semaglutide had a significantly greater reduction from baseline in HbA_{1c} (−1.3%) than those receiving liraglutide (−1.1%; $p = 0.0056$) (Table 1) and a significant difference between treatments remained at week 52 (Fig. 2) [44]. Similarly, body weight loss from baseline with oral semaglutide was significantly greater than with liraglutide (−4.7 kg vs −3.2 kg and −5.0 kg vs −3.1 kg at weeks 26 and 52, respectively, $p < 0.0001$ for both weeks) (Table 1, Fig. 3) [44].

4. Efficacy of oral semaglutide in patients with long-standing T2D and comorbidities

The EASD/ADA consensus report and the European Society of Cardiology guidelines state that, independent of the target HbA_{1c}, people with T2D and atherosclerotic CVD or CKD should

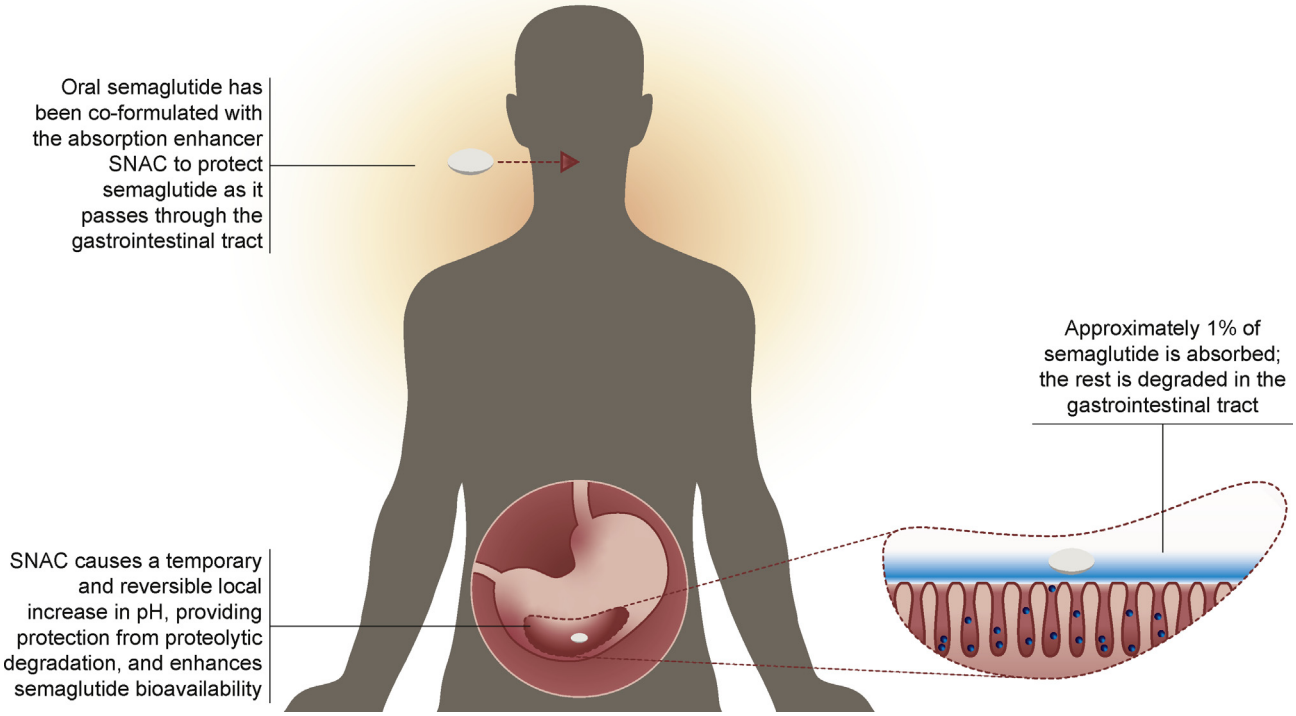

Fig. 1. Mechanism of absorption for oral semaglutide [36]. SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.

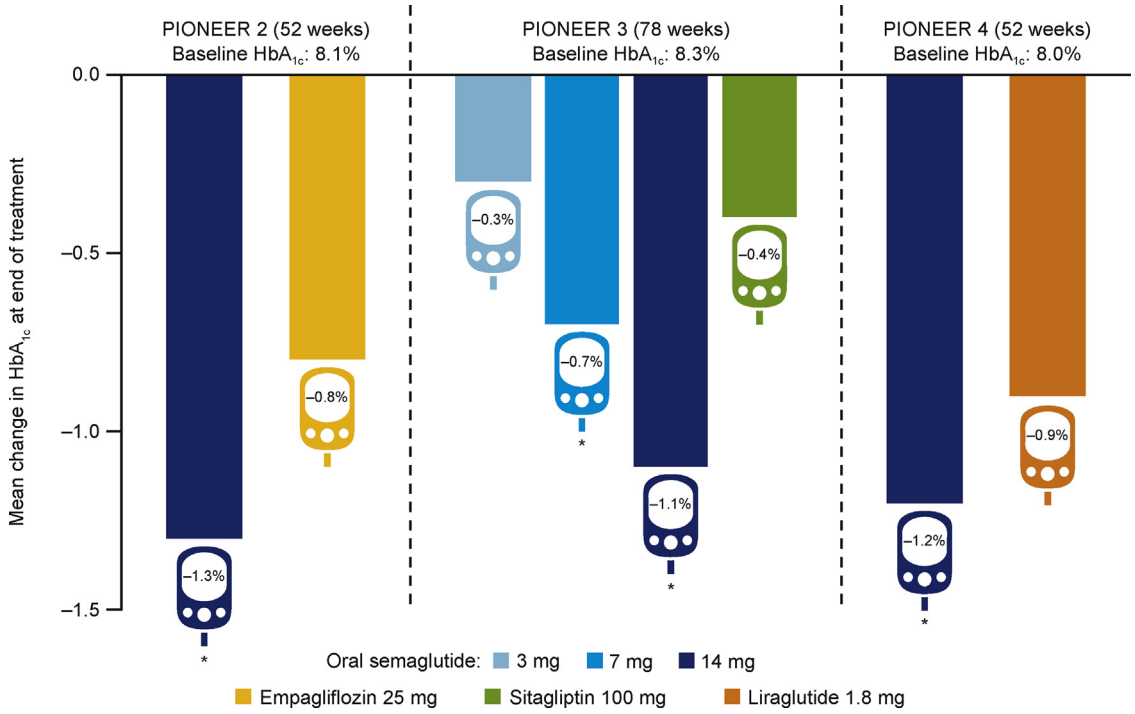

Fig. 2. Change in HbA_{1c} with oral semaglutide and active comparators at end of treatment (PIONEER 2, 3 and 4) [42–44].
Data analysed assuming patients remained on treatment without use of rescue medication. *$p < 0.05$ favouring oral semaglutide versus comparator for estimated treatment difference. HbA_{1c}, glycated haemoglobin.

preferentially receive a GLP-1RA with proven benefit in reducing cardiovascular risk and/or CKD progression [9,10]. An SGLT2i may also be considered. Further medications that do not increase cardiovascular risk can be added in a stepwise fashion (as in other patients) when increased glycaemic control is required [9,10]. SGLT2is are preferred over GLP-1RAs in patients with heart failure and/or CKD (and both drug classes can be combined if clinically appropriate) [9,10]. Unlike SGLT2is, there is no restriction for use of GLP-1RAs in patients with renal impairment [9,10]. If glycaemic control continues to decline in patients

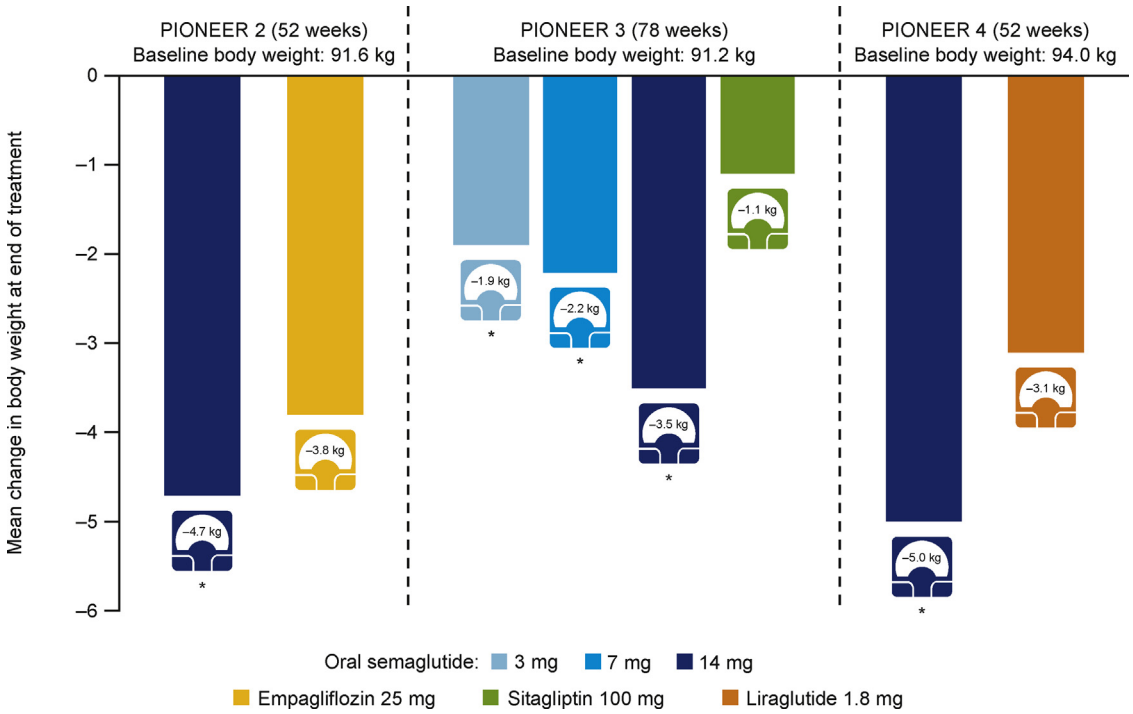

Fig. 3. Change in body weight with oral semaglutide vs active comparators at end of treatment (PIONEER 2, 3 and 4) [42–44].
Data analysed assuming patients remained on treatment without use of rescue medication. *$p < 0.05$ favouring oral semaglutide versus comparator for estimated treatment difference.

taking multiple glucose-lowering therapies, insulin can be added [9,10].

Three PIONEER trials were designed to study oral semaglutide in patients with CVD and/or CKD, and in those taking insulin [45,46,48]. In PIONEER 5, in patients with moderate renal impairment (estimated glomerular filtration rate 30–59 mL/min/1.73 m^2) who were taking other glucose-lowering drugs and/or insulin, oral semaglutide had significantly greater efficacy for HbA_{1c} and body weight reduction compared with background medication alone (Table 1) [45]. Coadministration with oral semaglutide also led to reductions in insulin doses in PIONEER 8 [48]. There were also reductions in HbA_{1c} and body weight with oral semaglutide added on to standard of care in patients who had established CVD or were at high cardiovascular risk, compared with standard care alone in PIONEER 6 (Table 1) [46].

5. Safety of oral semaglutide in the PIONEER programme

In the PIONEER trials, oral semaglutide had a tolerability profile consistent with that seen for other GLP-1RAs, including once-weekly subcutaneous semaglutide [41–48,52]. The most common adverse events were GI-related, mainly nausea, vomiting and diarrhoea, which generally occurred early in treatment, and mostly resolved after continuous use (Table 2) [41–48]. When flexible dose adjustment of oral semaglutide was employed, with dose reduction permitted if gastrointestinal tolerability warranted (PIONEER 7), most patients were on an effective oral semaglutide dose (either 7 mg [30% of patients] or 14 mg [59% of patients]) at the end of treatment [47] (Table 2). There were no unexpected safety concerns across the PIONEER trials, including in patients with moderate renal impairment (PIONEER 5) [45]. Additionally, across the PIONEER trials, there was a low incidence of severe or blood glucose-confirmed symptomatic hypoglycaemia (1.7% in PIONEER 2 and 0.7% in PIONEER 4), although the incidence was higher in patients receiving concomitant SU and insulin, both of which are associated with hypoglycaemia [41–48]. Patients with active diabetic retinopathy were excluded from the trials, and the incidence of diabetic retinopathy in-trial was low (<8% and not related to dose) [41–48]. Most cases were not symptomatic and were found by routine eye inspections.

GLP-1RAs or SGLT2is are recommended for patients at high cardiovascular risk, regardless of HbA_{1c} [10]. PIONEER 6 was a pre-approval trial specifically designed to evaluate the cardiovascular safety of oral semaglutide when added to standard of care, compared with standard care alone [46]. Patients were either aged ≥50 years with established CVD and/or CKD, or ≥60 years with cardiovascular risk factors. Over a median 15.9 months of study, adding oral semaglutide to standard care was shown to be as safe as standard care alone. There was no increase in the risk of major adverse cardiovascular events (defined as first instance of cardiovascular death, nonfatal stroke or nonfatal myocardial infarction) with versus without oral semaglutide (3.8% vs 4.8%, $p < 0.001$ for noninferiority) [46]. With subcutaneous semaglutide, as well as liraglutide, dulaglutide and albiglutide, a benefit of adding GLP-1RA to standard of care has been seen in terms of reductions in the risk of major adverse cardiovascular events [14–17]. The 5-year SOUL trial (NCT03914326) is now underway to determine whether oral semaglutide also has a cardiovascular benefit in people with T2D and CVD or CKD.

6. Practical considerations for oral semaglutide use in the primary care setting

A practical algorithm for PCPs who are considering prescribing oral semaglutide, based on international recommendations, is provided in Fig. 4.

6.1. Patients requiring improved glycaemic control

Oral semaglutide may encourage more PCPs and their patients to consider GLP-1RA therapy as an add-on to metformin when treatment intensification is needed. Although international recom-

Table 2
Summary of safety results for the PIONEER studies.

Trial name (N patients)	Any AE (%)	Most common GI AEs (%)	AEs leading to treatment discontinuation (%)	On-treatment hypoglycaemia[a] (%)	In-trial CV events (%)
PIONEER 1 (703) [41]	• 58%, 53%, 57% (oral semaglutide 3, 7, 14 mg) vs 56% (placebo)	• Nausea: 8%, 5%, 16% vs 6% • Diarrhoea: 9%, 5%, 5% vs 2% • Vomiting: 3%, 5%, 7% vs 2%	• Any: 2%, 4%, 7% vs 2% • GI: 2%, 2%, 5% vs 1%	• 3%, 1%, 1% vs 1%	• 2%, 3%, 1% vs 3%[b]
PIONEER 2 (822) [42]	• 70% (oral semaglutide 14 mg) vs 69% (empagliflozin)	• Nausea: 20% vs 2% • Diarrhoea: 9% vs 3% • Vomiting: 7% vs 2%	• Any: 11% vs 4% • GI: 8% vs 1%	• 2% vs 2%	• 1% vs 2%[b]
PIONEER 3 (1864) [43]	• 79%, 78%, 80% (oral semaglutide 3, 7, 14 mg) vs 83% (sitagliptin)	• Nausea: 7%, 13%, 15% vs 7% • Diarrhoea: 10%, 11%, 12% vs 8% • Vomiting: 3%, 6%, 9% vs 4%	• Any: 6%, 6%, 12% vs 5% • GI: 2%, 3%, 7% vs 3%	• 5%, 5%, 8% vs 8%	• 3%, 2%, 1% vs 2%[b]
PIONEER 4 (711) [44]	• 80% (oral semaglutide 14 mg) vs 74% (liraglutide) and 67% (placebo)	• Nausea: 20% vs 18% and 4% • Diarrhoea: 15% vs 11% and 8% • Vomiting: 9% vs 5% and 2%	• Any: 11% vs 9% and 4% • GI: 8% vs 6% and 2%	• 1% vs 2% and 2%	• 1% vs 1% and 1%[b]
PIONEER 5 (324) [45]	• 74% (oral semaglutide 14 mg) vs 65% (placebo)	• Nausea: 19% vs 7% • Constipation: 12% vs 4% • Vomiting: 12% vs 1%	• Any: 15% vs 5% • GI: 12% vs 2%	• 6% vs 2%	• 3% vs 2%[b]
PIONEER 6 (3183)[c] [46]	• NR	• NR	• Any: 12% vs 7% • GI: 7% vs 2%	• NR	• 4% vs 5%[d]
PIONEER 7 (504) [47]	• 78% (oral semaglutide flex) vs 69% (sitagliptin)	• Nausea: 21% vs 2% • Diarrhoea: 9% vs 3% • Vomiting: 6% vs 1%	• Any: 9% vs 3% • GI: 6% vs 1%	• 6% vs 6%	• 1% vs 2%[b]
PIONEER 8 (731) [48]	• 74%, 78%, 83% (oral semaglutide 3, 7, 14 mg) vs 76% (placebo)	• Nausea: 11%, 17%, 23% vs 7% • Diarrhoea: 9%, 12%, 15% vs 6%	• Any: 7%, 9%, 13% vs 3% • GI: 5%, 7%, 10% vs 1%	• 28%, 26%, 27% vs 29%	• 2%, 3%, 3% vs 3%[b]

Table 2 (*Continued*)

Trial name (N patients)	Any AE (%)	Most common GI AEs (%)	AEs leading to treatment discontinuation (%)	On-treatment hypoglycaemia[a] (%)	In-trial CV events (%)
		• Vomiting: 6%, 8%, 10% vs 4%			

Proportions are percentages of patients with at least one event.
AE, adverse event; CV, cardiovascular; flex, flexibly dosed; GI, gastrointestinal; NR, not recorded.
[a] Considered severe by American Diabetes Association criteria, symptomatic and/or confirmed by blood glucose <3.1 mmol/L (56 mg/dL).
[b] Confirmed by an independent adjudication committee.
[c] Patients in PIONEER 6 were at high CV risk.
[d] First major CV AE, i.e. CV death, non-fatal myocardial infarction or nonfatal stroke.

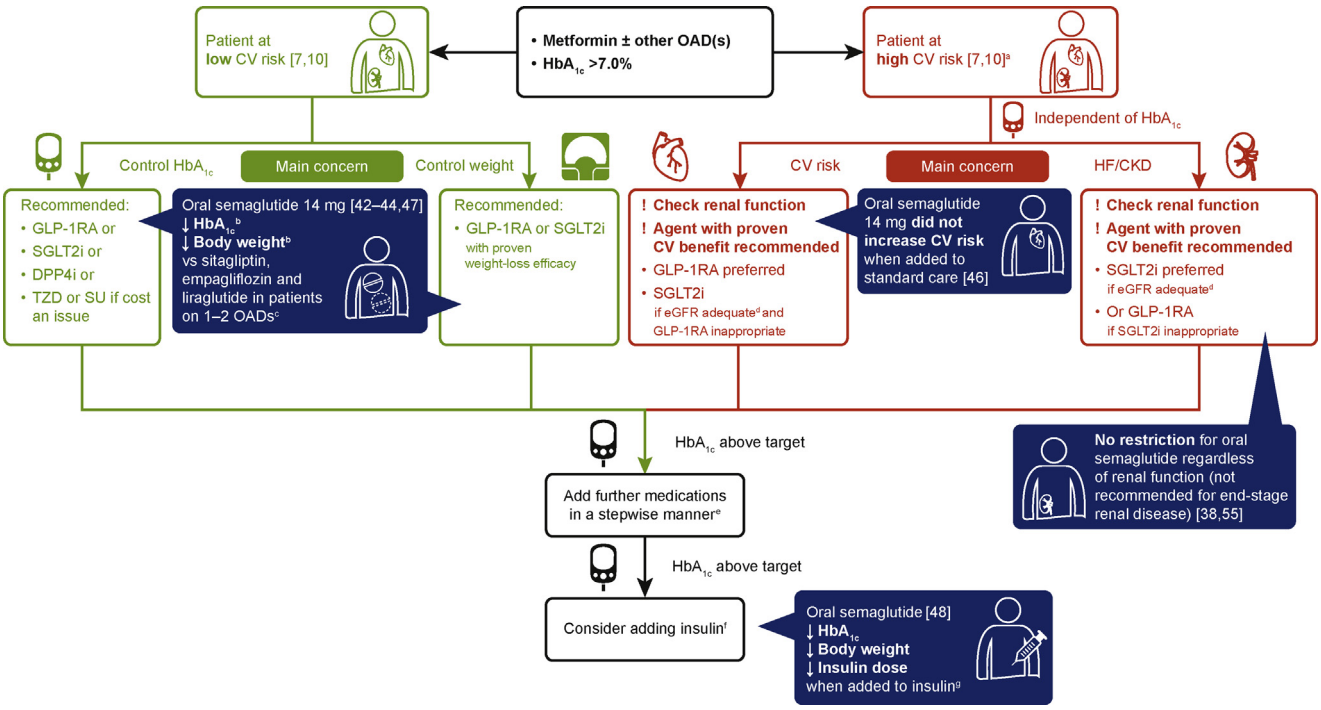

Fig. 4. Potential place of oral semaglutide in international treatment recommendations for people with T2D.
[a]With established CV disease, CKD or risk factors; [b]At end of treatment in patients who remained on treatment and did not use rescue medication in PIONEER 2–4 [42–44]; [c]Metformin alone in PIONEER 2 [42], metformin ± SU in PIONEER 3 [43], metformin ± SGLT2i in PIONEER 4 [44] and 1–2 of metformin, SU, TZD or SGLT2i in PIONEER 7 [47]; [d]Guidance varies by drug and region; [e]GLP-1RAs and DPP4is are not recommended to be used in combination; [f]Consider basal insulin with lower risk of hypoglycaemia; [g]Basal, bolus and premix insulin.
CKD, chronic kidney disease; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HF, heart failure; OAD, oral anti-diabetes (glucose-lowering) drug; SGLT2i, sodium glucose cotransporter-2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes; TZD, thiazolidinediones.

mendations give limited guidance as to which drug class to choose first in this case [7], the results of the PIONEER trials suggest that oral semaglutide is as effective as an injectable GLP-1RA, and physicians could consider adding oral semaglutide before an SGLT2i or DPP-4i because of greater HbA_{1c} reductions in head-to-head trials [42–44,47]. Equally, many patients in PIONEER 7 were already taking an SGLT2i and/or TZD [47], supporting the addition of oral semaglutide to these regimens. Because of the overlap in their modes of action, the combination of oral semaglutide and a DPP-4i was not tested, and indeed is not advocated by recommendations [7].

6.2. Patients requiring improved body weight control

For patients at low cardiovascular risk, for whom body weight control or reduction and intensification of glycaemic control are important, the EASD/ADA consensus is to add a GLP-1RA or SGLT2i with proven weight-loss efficacy as second line to metformin [7]. Oral semaglutide was more effective than liraglutide for weight loss in PIONEER 4 [44]. When compared head-to-head in PIONEER 2, both oral semaglutide and the SGLT2i empagliflozin helped to reduce body weight by approximately 4 kg after 26 weeks' treatment [42]. However, whereas weight loss plateaued with empagliflozin, it continued decreasing with oral semaglutide up to week 52 in patients who continued on treatment without needing rescue medication, at which point it approached an average of approximately 5 kg [42]. Therefore, oral semaglutide can be considered as an effective option for patients in this situation.

6.3. Patients at high cardiovascular risk or with established CVD/CKD

The situation in people with T2D and concomitant CVD and/or CKD, or who are considered at increased cardiovascular risk is somewhat nuanced. Unless considered inappropriate, and regardless of HbA_{1c} target, such patients are recommended to receive a

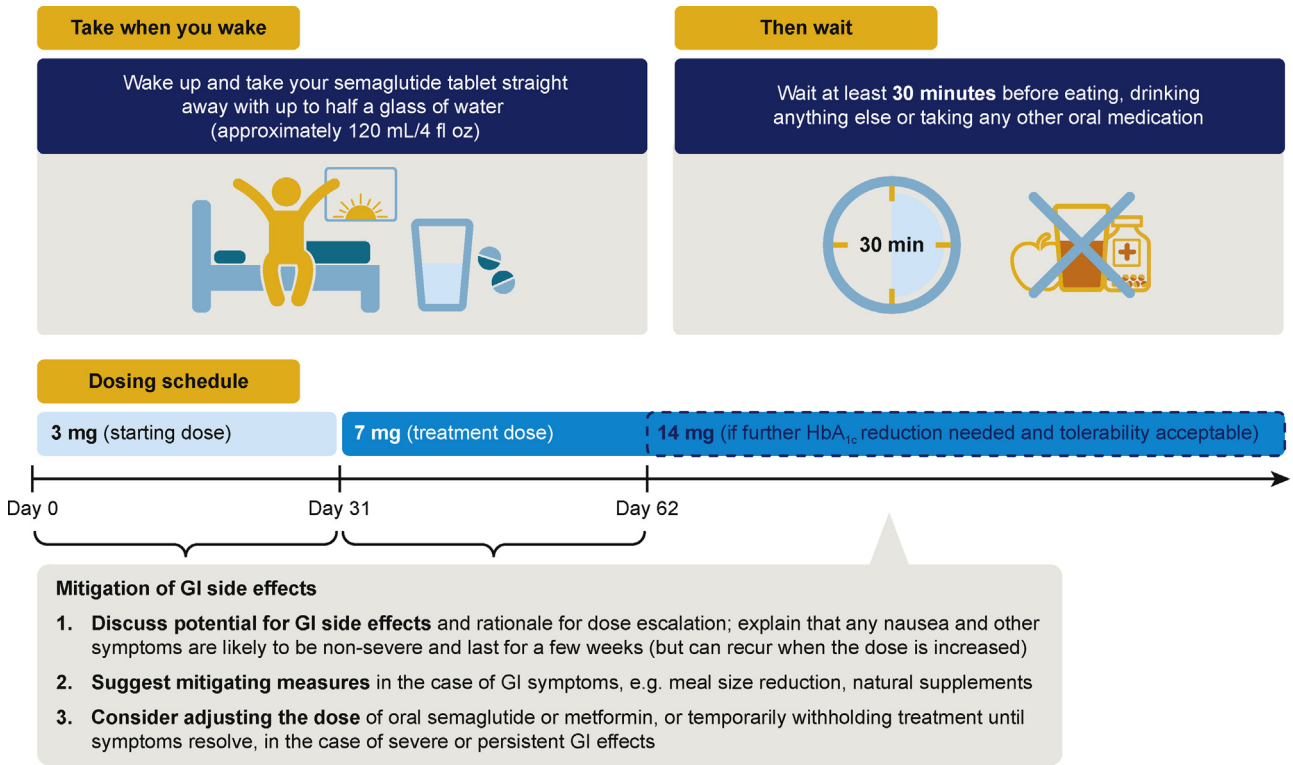

Fig. 5. Treatment algorithm for oral semaglutide [38,55,68,69].

GI, gastrointestinal; HbA_{1c}, glycated haemoglobin.

GLP-1RA with proven cardiovascular benefit [9,10], which in practice means subcutaneous semaglutide, dulaglutide or liraglutide [14,15,17]. Oral semaglutide demonstrated cardiovascular safety in high-risk patients [46], and conclusive evidence of a benefit over current standard of care will come with the completion of the long-term SOUL trial. Therefore, PCPs considering oral semaglutide in patients at high cardiovascular risk will have to weigh up their patients' preferences for an oral versus injectable therapy against the current evidence and the option to use an injectable GLP-1RA or oral SGLT2i with proven cardiovascular benefit instead [9,10].

6.4. Patients with comorbidities

It should be noted that oral semaglutide does not require dose adjustment in patients with hepatic or renal impairment (including people receiving dialysis) [53–55]. In contrast, SGLT2is have adjustments and restrictions for use in patients with impaired liver and/or kidney function [56–59]. There were no clinically significant drug–drug interactions between oral semaglutide and commonly coadministered drugs (digoxin, lisinopril, metformin, warfarin and the combined oral contraceptive) [60,61]. Moreover, coadministration of a proton pump inhibitor (omeprazole) did not affect oral semaglutide exposure to a clinically relevant extent [62]. However, exposure to levothyroxine was increased by 33% when coadministered with oral semaglutide (see dosing instructions below) [63]. The presence of upper GI disease did not affect the pharmacokinetics of oral semaglutide [64].

The US prescribing information states to avoid oral semaglutide in patients with a personal or familial history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 [55]. Oral semaglutide should be discontinued in cases of suspected pancreatitis, and renal function should be monitored in patients with renal impairment reporting severe adverse GI reactions [55]. Patients with a history of diabetic retinopathy should also be monitored closely with regular screening for progression of diabetic retinopathy. The incidence of hypoglycaemia was noticeably higher when oral semaglutide was combined with insulin [48], so consideration should be given to lowering the insulin dose in this circumstance [55].

6.5. Dosing instructions

Patients should be instructed to take oral semaglutide in the morning upon waking (i.e. in a fasted state) with no more than 120 mL/4 fl oz (half a glass) of water, and to wait at least 30 min before eating breakfast, consuming any further liquid or taking any other oral medication (Fig. 5) [38,55]. This approach ensures clinically relevant semaglutide exposure [65,66]. If patients are taking comedications with similar dosing instructions (such as thyroid hormone), consideration should be given as to whether these medications can be taken at a different time of day (potentially at bedtime [67]). Compliance with the dosing conditions for oral semaglutide with monitoring of thyroid parameters is strongly advised, as is treatment of hypothyroidism according to local guidelines.

As in the PIONEER trials, patients should start on an oral semaglutide dose of 3 mg once daily, escalated to 7 mg after 30 days. If further glycaemic control is needed, the dose can be increased to 14 mg once daily after a further 30 days (Fig. 5) [38,55]. The 14 mg once-daily oral dose is considered equivalent to the 0.5 mg once-weekly subcutaneous dose [38,55]. The US prescribing information for oral semaglutide recommends that patients currently treated with subcutaneous semaglutide 0.5 mg once weekly can be switched to oral semaglutide by starting oral semaglutide 7 mg or 14 mg once daily up to 7 days after the last semaglutide injection [55]. There is no equivalent oral dose to the subcutaneous 1 mg dose of semaglutide. If a patient treated with oral semaglutide 14 mg needs to transition to subcutaneous semaglutide, perhaps to achieve greater glycaemic efficacy, the US prescribing information

recommends starting injections, initially at 0.5 mg once weekly, on the day after the last oral semaglutide dose [55].

6.6. Managing potential GI side effects

GI side effects were dose-dependent in the PIONEER trials, but at the highest dose fewer than 25% of patients experienced nausea; diarrhoea and vomiting tended to occur at incidences <15% [41–45,47,48]. In PIONEER 3, such events tended to occur early in treatment and when the dose was escalated; nausea associated with oral semaglutide 14 mg lasted for a median 21 days, whereas diarrhoea lasted 9 days and vomiting 2 days [43]. It is therefore recommended that patients are advised of the possibility of these events occurring during the first weeks of oral semaglutide treatment, and also potentially when the dose is escalated (Fig. 5). Patients should be reassured that, in most cases, these symptoms are not severe and will resolve on their own after a few weeks, and that they should continue their treatment. If needed, nausea may be relieved by use of natural supplements such as ginger or peppermint, avoiding fried or fatty foods or by reducing meal portion size (Fig. 5) [68]. Nevertheless, if symptoms are severe or persistent, patients should be encouraged to inform their PCP and consideration could be given to temporary dose adjustment or withdrawal of either metformin (which is also associated with GI issues [69]) or oral semaglutide until symptoms resolve (Fig. 5). Notably, oral semaglutide was effective when flexible dose adjustment was used [47] and in the absence of metformin [41].

7. Conclusion

In clinical trials, oral semaglutide 14 mg reduced mean HbA_{1c} by approximately 1.1–1.5% and reduced body weight by up to 5 kg. The most common side effects were gastrointestinal, mainly mild-to-moderate and transient nausea. Oral semaglutide may offer a practical and effective means of managing people living with T2D who require treatment intensification, and may change the paradigm of care in the primary care setting.

Conflicts of interest

SS reports personal fees from Amgen, AstraZeneca, NAPP, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi-Aventis and Boehringer Ingelheim, grants from AstraZeneca, Sanofi-Aventis, Servier and Janssen, outside the submitted work.

LM reports personal fees from Novo Nordisk, outside the submitted work.

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Role of the funding source

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