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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipgm20

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To cite this article: Frank Lavernia & Lawrence Blonde (2020): Clinical review of the efficacy and safety of oral semaglutide in patients with type 2 diabetes compared with other oral antihyperglycemic agents and placebo, Postgraduate Medicine, DOI: 10.1080/00325481.2020.1798638

To link to this article: https://doi.org/10.1080/00325481.2020.1798638

Published online: 08 Sep 2020.

POSTGRADUATE MEDICINE
https://doi.org/10.1080/00325481.2020.1798638

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SUPPLEMENT: INTRODUCING ORAL SEMAGLUTIDE AND THE PIONEER PROGRAM TO PRIMARY CARE

Clinical review of the efficacy and safety of oral semaglutide in patients with type 2 diabetes compared with other oral antihyperglycemic agents and placebo

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ABSTRACT

Oral semaglutide is a tablet formulation of a glucagon-like peptide-1 receptor agonist (GLP-1RA), recently approved in the USA and other countries. This paper reviews data from clinical trials (PIONEER 1, 2, 3, and 7) comparing oral semaglutide (once-daily doses of 3, 7, or 14 mg) with either once-daily placebo, empagliflozin 25 mg, or sitagliptin 100 mg. After 26 weeks in PIONEER 1, patients randomized to 3, 7, or 14 mg doses of oral semaglutide monotherapy had statistically significant reductions in glycated hemoglobin (HbA_{1c}) of 0.9%, 1.2%, and 1.4%, respectively, versus 0.3% with placebo. In the active-comparator studies, oral semaglutide 14 mg provided better glycemic control than empagliflozin or sitagliptin after 26 weeks, with durable effects. Body weight reductions were significantly greater with oral semaglutide than with placebo and sitagliptin. However, body weight reductions with oral semaglutide 14 mg versus empagliflozin 25 mg were not significantly different. Gastrointestinal adverse events (AEs) with oral semaglutide were mostly mild-to-moderate, occurred early in the course of treatment, and abated over time. Across these trials, 5–13% and 15–20% of patients experienced nausea with oral semaglutide 7 and 14 mg, respectively, and 2.3–3.4% and 5.1–8.0%, respectively, discontinued treatment due to gastrointestinal AEs. Severe or blood glucose-confirmed symptomatic hypoglycemia occurred infrequently with oral semaglutide and was seen most often in patients taking concomitant sulfonylureas. Findings from these trials indicate that the addition of oral semaglutide reduces HbA_{1c} and body weight and is associated with a low risk of hypoglycemia. Oral semaglutide represents an additional option for treating people with type 2 diabetes in primary care, with the potential to expand the numbers of patients benefiting from GLP-1RAs beyond that currently seen with injectable formulations.

ARTICLE HISTORY
Received 1 June 2020
Accepted 17 July 2020

KEYWORDS
Oral semaglutide; sitagliptin; empagliflozin; comparative studies; treatment intensification; type 2 diabetes

Article overview and relevance to your clinical practice

- The first oral formulation of a glucagon-like peptide-1 receptor agonist, oral semaglutide, has recently been introduced for the treatment of type 2 diabetes (T2D) and presents an additional option for primary care clinicians treating people with T2D.
- This article reviews trials from the PIONEER program that: 1) established the efficacy, safety, and tolerability of oral semaglutide compared with placebo; and 2) compared oral semaglutide to some other oral antihyperglycemic agents, specifically the sodium-glucose co-transporter-2 inhibitor, empagliflozin, and the dipeptidyl peptidase-4 inhibitor, sitagliptin.
- The paper also discusses the implications of these data for primary care practice, focusing on attainment of glycemic control and durability of effect, changes in body weight, safety and tolerability profile, and patient satisfaction when oral semaglutide is compared with these commonly used oral antihyperglycemic agents.

1. Oral antihyperglycemic agents for treating type 2 diabetes

A well-known quote by C. Everett Koop MD, past US Surgeon General, cautioned that: 'Drugs don't work in patients who don't take them' [1]. This encapsulates an important challenge for the care of the estimated 90% of people with type 2 diabetes (T2D) in the US who are managed by primary care clinicians (as of 2010) [2]. Antihyperglycemic therapy selection for people with T2D encompasses the need to: achieve glycemic targets; avoid weight gain or, if necessary, attain and maintain weight loss; reduce cardiovascular disease (CVD) risk; ensure safety and tolerability; align with patient preference; and consider access and cost [3]. Accomplishing these goals could potentially encourage better medication adherence.

Although metformin is recommended by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) as first-line antihyperglycemic therapy for many patients with T2D, some patients may benefit from an initial combination of agents with complementary mechanisms of action [3,4]. Indeed, the AACE/ACE specifically recommends this course of action for most patients presenting with HbA_{1c} >7.5%

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[4]. Since T2D is a progressive disease, most patients will eventually require two or more antihyperglycemic agents to attain and/or maintain glycemic control. Guideline recommendations for second-line oral antihyperglycemic agents may include sulfonylureas (SUs), sodium-glucose co-transporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, or thiazolidinediones (TZDs). Injectable therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) or basal insulins, are also options [3,4].

SGLT2 inhibitors cause renal glucosuria that results in decreased hyperglycemia and body weight [4]. GLP-1RAs mimic natural endogenous GLP-1, enhancing glucose-dependent insulin secretion and suppression of excess glucagon release, while also delaying gastric emptying and increasing satiety, which can result in weight loss [5,6]. In addition, some GLP-1RAs and SGLT2 inhibitors have shown cardiovascular and renal benefits [3,7–12]. By contrast, DPP-4 inhibitors constrain the DPP-4 enzyme that deactivates a variety of bioactive peptides including GLP-1 and glucose-dependent insulinotropic polypeptide, enhancing their endogenous levels and thereby increasing glucose-dependent insulin secretion and decreasing glucagon secretion, like GLP-1RAs [5]. However, DPP-4 inhibitors do not convey the same magnitude of effect as GLP-1RAs. They have only intermediate antihyperglycemic efficacy, are not associated with significant weight loss, and have a neutral effect on cardiovascular events [3].

Until recently, all GLP-1RAs required subcutaneous injection because they are peptide-based drugs. However, the injectable route of administration can be a barrier for some clinicians and patients, perhaps owing to the need to take time to teach/learn injection technique, fear (or perceived dislike) of needles and their resultant discomfort, concerns about self-administration, and a belief that the necessity for escalation to injectable therapy represents the failure of prior efforts [13]. It is therefore not surprising that some studies have indicated that many, if not most, patients prefer oral to injectable therapies [14,15].

To overcome some of the barriers associated with injectable therapy, an oral formulation of the GLP-1RA, semaglutide, was developed and has been approved in the US, Canada, and Europe for treating adults with T2D [16–18]. Oral semaglutide presents an additional option, which, by obviating the injectable barrier for patients and healthcare providers, may increase the timely use of a GLP-1RA in people with T2D.

As described in the first manuscript in this supplement [19], the clinical efficacy and safety of oral semaglutide were evaluated in an extensive clinical trial program, Peptide InnOvatioN for Early diabEtes tReatment (PIONEER), comprising 10 trials involving over 9,500 patients from across a broad spectrum of individuals with T2D. This paper will review data from the PIONEER trials that evaluated the efficacy and safety of oral semaglutide compared with:

- placebo (PIONEER 1) [20];
- the SGLT2 inhibitor, empagliflozin (PIONEER 2) [21];
- the DPP-4 inhibitor, sitagliptin (PIONEER 3 and PIONEER 7) [22,23].

We will also explore the implications of the results of these trials for primary care clinicians. Data from trials assessing oral semaglutide compared with (or in addition to) injectable therapies, and in patients with CVD and/or other comorbidities, are reviewed in the subsequent manuscripts in this supplement by Wright and Aroda [24] and Mosenzon et al. [25], respectively.

2. Clinical evidence for oral semaglutide versus placebo and other oral antihyperglycemic agents

2.1. Study designs

The phase 3a PIONEER 1, 2, 3, and 7 studies tested oral semaglutide in settings ranging from monotherapy in patients previously treated only with medical nutrition therapy and appropriately prescribed physical activity to those with inadequate control on one or two oral antihyperglycemic agents. Key aspects of each study design are summarized in Figure 1.

PIONEER 1 was a 26-week randomized, double-blind, placebo-controlled, parallel-group trial comparing oral semaglutide (3, 7, or 14 mg once daily) with placebo in 703 individuals with T2D who were insufficiently controlled with diet and exercise [20]. PIONEER 2 was an open-label, parallel-group trial in which 822 patients with T2D uncontrolled on metformin were randomized to once-daily oral semaglutide 14 mg or empagliflozin 25 mg for 52 weeks [21]. PIONEER 3 was a 78-week, randomized, double-blind, double-dummy, parallel-group trial involving 1,864 patients with T2D uncontrolled with metformin, with or without an SU [23]. Patients were randomized to oral semaglutide (3, 7, or 14 mg) once daily or sitagliptin 100 mg once daily [23]. PIONEER 7 was a 52-week, randomized, open-label, parallel-group trial in 504 patients taking one or two antihyperglycemic agents (metformin, SU, TZD, or SGLT2 inhibitor), comparing a flexible dose-adjustment regimen for oral semaglutide with sitagliptin 100 mg once daily [22].

2.1.1. Study drugs

In PIONEER trials 1–3, oral semaglutide treatment was initiated at 3 mg once daily, with dose escalation every 4 weeks until the randomized dose was achieved [20,21,23]. By contrast, in PIONEER 7, a flexible dose adjustment regimen for oral semaglutide was used, as follows [22]. Patients began treatment with the 3 mg dose for 8 weeks. At this point, and every 8 weeks thereafter, dose adjustment could be performed, based on glycemic control and gastrointestinal tolerability: if HbA_{1c} was <7%, the dose level was maintained; if HbA_{1c} was ≥7%, the dose was escalated to 7 mg (and subsequently could be further increased to 14 mg). However, if moderate-to-severe nausea or vomiting was reported for three or more days in the week before the next scheduled study visit, the dose was maintained or decreased at the investigator's discretion [22]. In each study, rescue medication was added for persistent or unacceptable hyperglycemia (according to pre-specified criteria) at the investigator's discretion [20–23].

In all trials, patients were instructed to take oral semaglutide with no more than 4 fluid ounces (120 mL) of plain water in the morning in a fasted state and at least 30 minutes before eating, drinking, or taking any other oral medication [20–23].

2.1.2. Eligible patients

Aside from concomitant therapy, the studies generally used consistent inclusion and exclusion criteria. Male or female

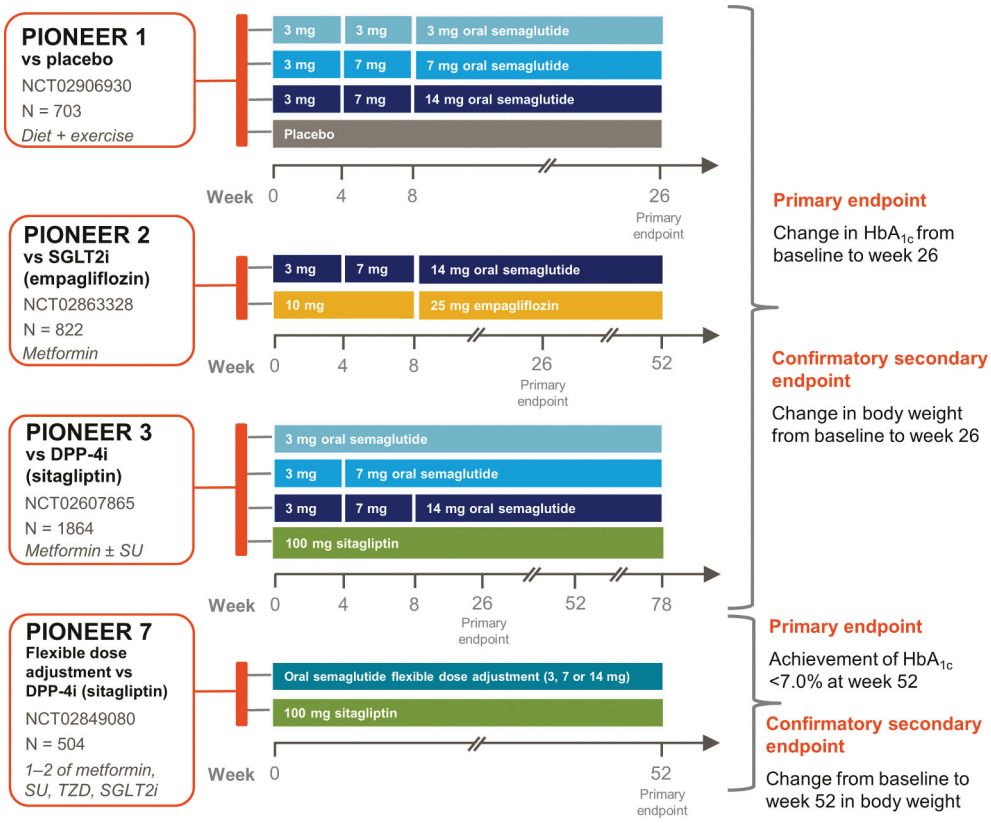

Figure 1. Overview of study designs of PIONEER trials 1, 2, 3, and 7 [20–23]. *Text in italics indicates permitted background medication*. All trials shown here included a 2-week screening period and 5-week follow-up period (for those not continuing into an extension phase [not shown] in PIONEER 7). Changes in other parameters of efficacy, safety and tolerability were evaluated in all trials. DPP-4i, dipeptidyl peptidase-4 inhibitor; HbA_{1c}, glycated hemoglobin; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

adult patients (generally ≥18 years of age but ≥19 or ≥20 in some countries) with T2D diagnosed ≥30 days (PIONEER 1) or ≥90 days (PIONEER 2, 3, and 7) before screening were eligible for inclusion if they had a baseline HbA_{1c} of 7.0–9.5% (PIONEER 1), 7.0–10.5% (PIONEER 2 and 3), or 7.5–9.5% (PIONEER 7). Key exclusion criteria were a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2), or a history of pancreatitis. Patients with diabetic retinopathy were included in the studies, however, patients with proliferative retinopathy or maculopathy requiring acute treatment were excluded [20–23].

2.1.3. Endpoints

Primary and confirmatory secondary endpoints are shown in Figure 1; other secondary endpoints included change in HbA_{1c} and body weight from baseline to week 52 (PIONEER 2) and week 78 (PIONEER 3). The studies also used two composite endpoints: 1) HbA_{1c} <7.0% without severe or blood glucose-confirmed symptomatic hypoglycemia (<56 mg/dL [<3.1 mmol/L]) and without weight gain, and 2) HbA_{1c} reduction of ≥1% with body weight loss ≥3% [20–23].

Patient-reported outcomes (PROs) are of increasing clinical importance, as they identify how patients feel and function during treatment. In addition to measures of quality of life, treatment satisfaction is a PRO of interest evaluating both the patient's expectations and their actual experiences with the trial product [26]. Treatment satisfaction with oral semaglutide and sitagliptin was assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) in PIONEER 7 [22]. Other PROs assessed were: the 36-item Short-Form Health Survey version 2 (SF-36) in PIONEER 2, 3, and 7; Control of Eating Questionnaire in PIONEER 2 and 3; and Impact of Weight on Quality of Life-Lite questionnaire Clinical Trial Version (IWQOL-Lite-CT) in PIONEER 3 [21–23].

2.1.4. New statistical analytics leveling the field

Over the 5 years prior to this manuscript, a new concept regarding clinical trial design, measurement, and interpretation (known as an estimand) has been introduced by regulatory authorities. Although trials are designed to show an appropriate measure of treatment effect in a given population, this may not account for the effect of post-randomization events, such as dropout or the addition of rescue medication(s). Such events can introduce ambiguity to the interpretation of the treatment effect [27]. An estimand accounts for these intercurrent events [27], ensuring alignment of the objectives with the design, conduct, and analysis of a trial. For a more detailed overview of the estimands concept, see Aroda et al., 2019 [27].

In the PIONEER trials, two different scientific questions were addressed through two efficacy-related estimands [27]:

- The ***treatment policy*** estimand assessed the treatment effect for all randomly assigned participants regardless of premature treatment discontinuation or use of rescue medication (defined as the addition of antihyperglycemic medication while the patient remained on their assigned trial drug; regardless of the use of rescue medication, all patients were followed up for the entire study duration). It was also designated to be the primary estimand for all efficacy endpoints and reflects the intention-to-treat principle [21–23].
  - This estimand provides the perspective of the treatment effect in the population of patients with T2D and so aims to reflect the average effect expected across patients seen in clinical practice.
- The ***trial product*** estimand assessed the treatment effect for all randomly assigned participants under the assumption that all participants remained on treatment for the entire planned duration of the trial and did not use rescue medication.
  - This estimand aims to reflect the anticipated effect of the medication as it was intended to be used, in the absence of potentially confounding factors (treatment discontinuation and/or rescue medication use).

Efficacy outcomes in this article, and the other articles in this supplement, are primarily reported based on the ***treatment policy*** estimand.

2.2. Study results

Within each study, baseline demographics and disease characteristics were similar between treatment groups [20–23]. Across the four trials, mean age was 55–58 years, mean HbA_{1c} was 8.0–8.3%, mean duration of diabetes was 3.5–8.8 years, mean body weight was 88–92 kg, and mean body mass index was 32–33 kg/m^2 Table 1 [20–23]. The majority of patients were white (71–86%), 5–9% were Black or African American, and 6–17% were Asian, with slightly greater proportions of male than female patients [20–23]. The proportion of patients completing these studies without the use of rescue medications was relatively high (77%, 62%, and 78% in PIONEER 2, 3, and 7, respectively; data not reported for PIONEER 1).

2.2.1. Glycemic control

In all studies discussed in this paper, statistically significantly greater reductions in HbA_{1c} versus comparators were achieved with oral semaglutide 7 and 14 mg, and when flexibly dosed, and dose-dependent reductions in HbA_{1c} were maintained until the end of treatment Figure 2. For PIONEER 1, 2, and 3, the primary endpoint was the change from baseline in HbA_{1c} to week 26. After 26 weeks in PIONEER 1, patients randomized to oral semaglutide monotherapy 3, 7, or 14 mg once daily had superior HbA_{1c} reductions from baseline of 0.9%, 1.2%, and 1.4%, respectively, versus 0.3% with placebo ($p < 0.05$ for all doses) [20]. In PIONEER 2, reductions in HbA_{1c} after 26 weeks were superior with oral semaglutide 14 mg versus empagliflozin 25 mg (1.3% versus 0.9%; $p < 0.05$) and remained significantly greater after 52 weeks (1.3% versus 0.9%; $p < 0.05$) [21]. After a 26-week treatment period in PIONEER 3, noninferiority of oral semaglutide 3 mg (0.6% reduction) to sitagliptin was not demonstrated. However, oral semaglutide 7 mg (HbA_{1c} reduction of 1.0%) and 14 mg (1.3% reduction) were superior to sitagliptin 100 mg (0.8% reduction; $p < 0.05$) [23]. Significantly greater reductions persisted with oral semaglutide over sitagliptin after 52 weeks for the 7 and 14 mg doses, and after 78 weeks for the 14 mg dose [23]. Results of the treatment policy and trial product estimands were broadly consistent [20,21,23].

In PIONEER 7, more than twice as many participants achieved the primary endpoint of HbA_{1c} <7% after 52 weeks when treated with oral semaglutide using flexible dose-adjustment (58%) versus sitagliptin 100 mg (25%; p value for the estimated odds ratio [EOR] < 0.05) [22]. Flexibly dosed oral semaglutide also reduced HbA_{1c} significantly more than sitagliptin after 52 weeks, which was a secondary endpoint of the study (1.3% versus 0.8%; $p < 0.05$) Figure 2 [22]. Similar results were gained using the trial product estimand [22].

Additional data relating to the proportion of patients achieving HbA_{1c} <7.0% or ≤6.5% during the PIONEER 1, 2, 3, and 7 trials are shown in Table 1. Across these trials, 42–77% of patients achieved HbA_{1c} <7.0% after 26 weeks' treatment with oral semaglutide 7 or 14 mg [20,21,23]. The odds of achieving HbA_{1c} <7.0% were significantly greater with oral semaglutide 14 mg versus placebo (p value for EOR < 0.001) and the active comparators empagliflozin (p value for EOR < 0.0001) and sitagliptin (p value for estimated treatment difference [ETD] < 0.001) by the end of treatment [20,21,23].

2.2.2. Body weight

The change in body weight from baseline in each study is shown in Figure 3. In PIONEER 1, oral semaglutide 14 mg resulted in superior weight loss versus placebo after 26 weeks' treatment (3.7 versus 1.4 kg; $p < 0.05$) [20]. Reductions in body weight were similar between oral semaglutide and empagliflozin in PIONEER 2 after 26 weeks (3.8 versus 3.7 kg, respectively) [21]. A recent network meta-analysis of clinical trials involving GLP-1RAs or SGLT2 inhibitors suggested that long-acting GLP-1RAs, particularly subcutaneous semaglutide, are associated with greater reductions in body weight than SGLT2 inhibitors [28]. No significant differences in body weight reductions were found between oral semaglutide and empagliflozin in PIONEER 2 after 26 or 52 weeks for the treatment policy estimand. However, investigators reported a significantly greater reduction in body weight with oral semaglutide versus empagliflozin after 52 weeks for the trial product estimand (4.7 versus 3.8 kg, respectively; $p < 0.05$) [21]. Greater reductions in body weight were achieved in PIONEER 3 after 26 weeks with oral semaglutide versus sitagliptin, with ETDs of 1.6 and 2.5 kg for oral semaglutide 7 and 14 mg, respectively ($p < 0.001$ for both doses versus sitagliptin) [23]. In PIONEER 7, the mean body weight reduction over a 52-week period was 2.6 kg for oral semaglutide with flexible dose-adjustment versus 0.7 kg for sitagliptin, an ETD of −1.9 kg ($p < 0.05$) [22]. Body weight reductions were maintained at the end of treatment in the

Table 1. Selected secondary efficacy endpoints for PIONEER trials 1, 2, 3, and 7.

Trial (N randomized)	Background regimen/trial duration/time of primary end point	Mean baseline characteristics	Treatment arms	% of patients attaining				
				HbA_{1c} <7.0%	HbA_{1c} ≤6.5%	Body weight loss ≥5%	HbA_{1c} <7.0% without hypoglycemia[†] and without weight gain	HbA_{1c} reduction ≥1% and body weight loss ≥3%
PIONEER 1 (N = 703) [20]	Diet and exercise/ 26 weeks/week 26	Age: 55 years HbA_{1c}: 8.0% Diabetes duration: 3.5 years Body weight: 88.1 kg BMI: 31.8 kg/m^2 eGFR: 98 mL/min/1.73 m^2	Oral semaglutide 3 mg (n = 175)	55*	36*	20	37*	18
			Oral semaglutide 7 mg (n = 175)	69*	48*	27*	57*	37*
			Oral semaglutide 14 mg (n = 175)	77*	64*	41*	69*	51*
			Placebo (n = 178)	31	18	15	23	11
PIONEER 2 (N = 822)[‡] [21]	MET/ 52 weeks/week 26	Age: 58 years HbA_{1c}: 8.1% Diabetes duration: 7.4 years Body weight: 91.6 kg BMI: 32.8 kg/m^2 eGFR: 95 mL/min/1.73 m^2	Oral semaglutide 14 mg (n = 411)	67*	47	41	61*	45*
			Empagliflozin 25 mg (n = 410)	40	17	36	36	28
PIONEER 3 (N = 1,864) [23]	MET ± SU/ 78 weeks/week 26	Age: 58 years HbA_{1c}: 8.3% Diabetes duration: 8.6 years Body weight: 91.2 kg BMI: 32.5 kg/m^2 eGFR: 95–96 mL/min/1.73 m^2[§]	Oral semaglutide 3 mg (n = 466)	27	13	13	20	13
			Oral semaglutide 7 mg (n = 465)	42*	26*	19*	34*	26*
			Oral semaglutide 14 mg (n = 465)	55*	36*	30*	46*	37*
			Sitagliptin 100 mg (n = 467)	32	14	10	20	9
PIONEER 7 (N = 504) [22]	1–2 of: MET, SU, TZD, SGLT2 inhibitor/ 52 weeks/week 52	Age: 57 years HbA_{1c}: 8.3% Diabetes duration: 8.8 years Body weight: 88.6 kg BMI: 31.5 kg/m^2 eGFR: 95–97 mL/min/1.73 m^2[§]	Oral semaglutide (flexible 3, 7, or 14 mg)(n = 253)	58*	33*	27*	45*	35*
			Sitagliptin 100 mg (n = 251)	25	12	12	15	11

Note: efficacy outcomes are shown at the time of the primary endpoint for the treatment policy estimand, which evaluated the treatment effect for all randomized patients regardless of trial product discontinuation or the use of rescue medication (estimated by a pattern mixture model using multiple imputation to handle missing data).

*$p < 0.05$ for the estimated odds ratios favoring oral semaglutide over placebo or active comparator; [†]severe or blood glucose-confirmed symptomatic hypoglycemia; [‡]data from one patient was excluded due to duplication (already enrolled in the trial at another site); [§]stated range is the range of mean values reported across the treatment groups.

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; MET, metformin; SGLT2, sodium-glucose co-transporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

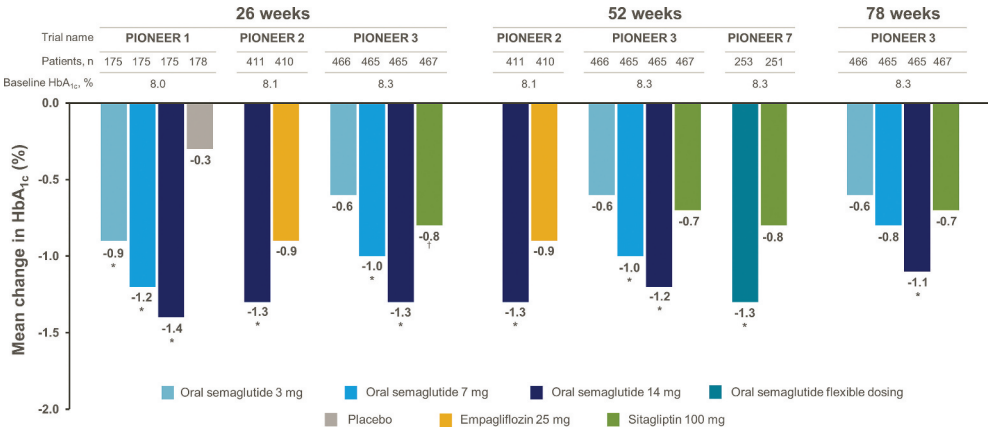

Figure 2. Mean change in HbA_{1c} from baseline in PIONEER 1, 2, 3, and 7 [20–23].*p < 0.05 for ETD for oral semaglutide versus comparator; †p < 0.05 for ETD for sitagliptin versus oral semaglutide 3 mg. ETD, estimated treatment difference; HbA_{1c}, glycated hemoglobin.

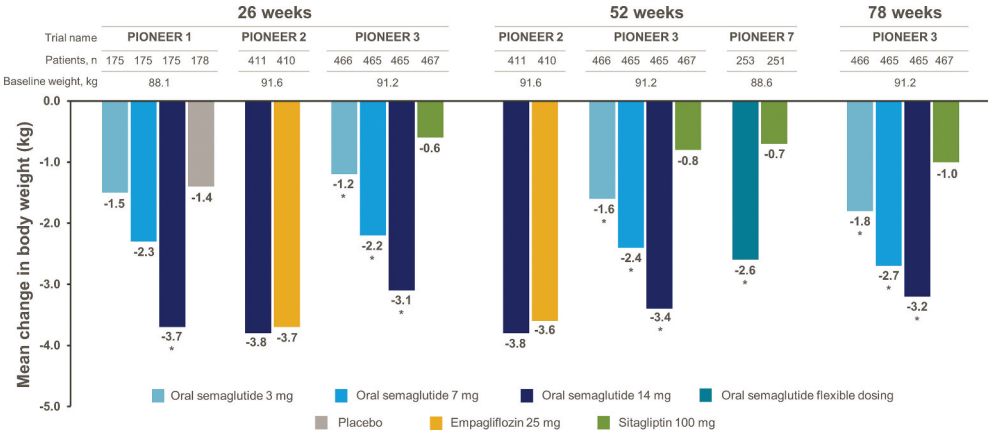

Figure 3. Mean change in body weight from baseline in PIONEER 1, 2, 3, and 7 [20–23]. *p < 0.05 for estimated treatment difference for oral semaglutide versus comparator.

studies with durations of 52 (PIONEER 2 [21]) or 78 weeks (PIONEER 3 [23]) Figure 3.

Significantly more patients achieved body weight reductions of ≥5% after 26 weeks' treatment with oral semaglutide 7 and 14 mg versus placebo in PIONEER 1 (27% and 41%, respectively, versus 15%; p value for the EOR < 0.05) and versus sitagliptin in PIONEER 3 (19% and 30%, respectively, versus 10%; p value for the ETD < 0.001) [20,23]. This was also the case with flexibly dosed oral semaglutide versus sitagliptin in PIONEER 7 after 52 weeks' treatment (27% versus 12%; p value for the EOR < 0.05) [22]. A similar proportion of patients achieved body weight reductions of ≥5% after 26 weeks with oral semaglutide and empagliflozin in PIONEER 2 (41% versus 36%, p value for the EOR = 0.1500) [21] Table 1.

2.2.3. Composite endpoints

After 26 weeks' treatment with oral semaglutide 7 or 14 mg, 34–69% of patients achieved HbA_{1c} <7.0% without severe or blood glucose-confirmed hypoglycemia or weight gain across the PIONEER 1–3 trials, and 26–51% had HbA_{1c} reduction ≥1% with body weight loss ≥3% [20,21,23] Table 1.

Key clinical take-home points: efficacy

- Oral semaglutide 7 and 14 mg provided HbA_{1c} reductions superior to those of sitagliptin after 26 weeks (1.0%, 1.3%, and 0.8%, respectively; p-value for ETD < 0.001 for both doses of oral semaglutide versus sitagliptin); this was maintained after 78 weeks for the 14 mg dose (PIONEER 3).
- Oral semaglutide 14 mg provided greater HbA_{1c} reductions than empagliflozin after 26 weeks (1.3% versus 0.9%, respectively; p-value for ETD < 0.0001), with significantly greater reductions still present after 52 weeks (PIONEER 2).
- Oral semaglutide was associated with significantly greater body weight loss than sitagliptin (ETDs −1.6 kg and −2.5 kg for the 7 and 14 mg doses, respectively; p < 0.001 for both doses versus sitagliptin) after 26 weeks of treatment, and this was maintained after 78 weeks (PIONEER 3).
- Body weight loss was similar with oral semaglutide 14 mg compared with empagliflozin for the treatment policy estimand (3.8 kg versus 3.7 kg after 26 weeks, and 3.8 kg versus 3.6 kg after 52 weeks, respectively [PIONEER 2]).

2.2.4. Patient-reported outcomes

In general, PROs were similar between oral semaglutide and active comparators [21–23], although there were some notable differences. Treatment satisfaction is an important PRO given the oral semaglutide dosing instructions. After 52 weeks, DTSQ scores for questionnaire items 'satisfaction with treatment,' 'convenience of treatment,' and 'flexibility of treatment' with oral semaglutide were similar to those reported for sitagliptin [22,29]. This suggests that patients did not find flexibly dosed oral semaglutide any more burdensome than sitagliptin [22,29].

Overall, SF-36 version 2 health survey responses were broadly similar between treatment groups in these studies. However, the more targeted questionnaires provided some interesting outcomes. One of the effects of GLP-1RA therapy is a reduction in appetite [5,6]. In PIONEER 2, the Control of Eating Questionnaire domains 'craving control' (weeks 26 and 52) and 'craving for savory' (week 52) were significantly improved with oral semaglutide 14 mg versus empagliflozin [4,21].

Control of calorie intake and HbA_{1c} increased physical activity, and associated weight loss can have positive psychological and physical benefits for patients [30]. After 52 weeks in PIONEER 3, the IWQOL-Lite-CT domains 'psychosocial' and 'physical function' were significantly improved with oral semaglutide 7 mg versus sitagliptin, and the domains 'physical' and 'physical function' were improved with oral semaglutide 14 mg versus sitagliptin [23]. However, further studies are needed to fully assess the association between glycemic control and weight loss with oral semaglutide and patients' psychological and physical quality of life.

2.2.5. Summary of adverse events

In the individual trials, including the 78-week PIONEER 3 trial, the safety profile of oral semaglutide was consistent with that of other GLP-1RAs [20–23]. Key safety data for the PIONEER trials described in this paper are summarized in Table 2. In general, the proportion of patients reporting adverse events (AEs) in these trials was similar for oral semaglutide and placebo or the active comparators (Table 2). As often seen with GLP-1RAs [3,31], the most common AE for oral semaglutide was nausea, which was generally mild-to-moderate and transient and occurred in 15–20% of patients treated with oral semaglutide 14 mg (7 mg, 5–13%) across PIONEER trials 1–3. Around 7–12% of patients discontinued oral semaglutide 14 mg due to AEs in these trials (7 mg, 4–6%), with the primary cause of discontinuation being gastrointestinal AEs (5–8% of patients with oral semaglutide 14 mg, and 2–3% with oral semaglutide 7 mg). Similar rates of discontinuation occurred with flexible dosing of oral semaglutide in PIONEER 7 [20–23].

GLP-1RAs have a low risk for hypoglycemia, which increases if administered in combination with agents that are known to cause hypoglycemia (e.g. SUs or insulin). Across the PIONEER trials featured here, severe (defined according to the ADA classification as requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) or blood glucose-confirmed (<3.1 mmoL/L [56 mg/dL]) symptomatic hypoglycemic episodes occurred infrequently in 1–8% of patients in the oral semaglutide groups across the four studies [20–23]. In PIONEER 3 and 7, such episodes occurred most often in patients taking concomitant SUs [22,23]. The incidence of severe hypoglycemic episodes was very low, affecting ≤1 patient in each oral semaglutide group in the four studies [20–23].

Across the four studies, deaths were infrequent in all treatment groups, with no clustering of causes observed [20–23]. Consistent with the known effects of GLP-1RAs [19], small increases in pulse rate (typically 1–2 beats per minute) were observed with oral semaglutide [20–23]. Patients on-treatment with oral semaglutide experienced mean reductions of 2–5 mmHg in systolic blood pressure and 1–2 mmHg in diastolic blood pressure at study end [20–23].

2.2.6. Adverse events of specific interest

The studies also assessed the incidence of AEs of specific interest, such as thyroid C-cell tumors, MTC, retinopathy complications, and pancreatitis, which are included as warnings and precautions in the prescribing information for oral semaglutide [18].

Consistent with some GLP-1RAs, the prescribing information for oral semaglutide includes a boxed warning relating to thyroid C-cell tumors, and treatment is therefore contraindicated in those with personal or family history of MTC or MEN 2 [18]. In the PIONEER studies described herein, there were no adjudication committee-confirmed reports of thyroid C-cell tumors, including in PIONEER 3, which involved the largest number of patients and the longest treatment duration [20–23].

The prescribing information states that treatment with oral semaglutide should be discontinued promptly if pancreatitis is suspected [18]. There were no external adjudication committee (EAC)-confirmed reports of acute pancreatitis in PIONEER 1 and 7 [20,22]. In PIONEER 2, there was one EAC-confirmed case of acute pancreatitis in each of the groups randomized to oral semaglutide 14 mg (0.2%) and empagliflozin (0.2%) [21]. EAC-confirmed acute pancreatitis occurred in one patient (0.2%) in each treatment group (oral semaglutide versus sitagliptin) in PIONEER 3 [23]. Meta-analyses, as well as information collected from cardiovascular outcomes trials (CVOTs) involving the long-term follow-up of thousands of patients, have consistently found insufficient evidence to support an increased risk of acute pancreatitis associated with GLP-1RAs as a class [7–10,12,32,33].

The prescribing information for oral semaglutide notes that across all placebo-controlled trials, cholelithiasis was reported in 1% of patients with oral semaglutide 7 mg, but was not reported in patients receiving oral semaglutide 14 mg [18] and there was no mention of cholelithiasis in the active-controlled PIONEER 2, 3, and 7 trials [21–23]. While a risk of cholelithiasis with oral semaglutide thus remains uncertain, an increased risk of cholelithiasis has previously been reported for GLP-1RAs in a meta-analysis of trials with these agents [34].

Diabetic retinopathy is a common complication of T2D [35]. In the SUSTAIN 6 CVOT of subcutaneous semaglutide, an increase in diabetic retinopathy complications was seen in the semaglutide arm compared with placebo, although most of these patients had diabetic retinopathy at baseline [8]. Monitoring is thus recommended in patients with a history of diabetic retinopathy who are treated with oral semaglutide [18]. Indeed, monitoring is recommended for

Table 2. Selected safety data for PIONEER trials 1, 2, 3, and 7.

					GI AEs				Hypoglycemia	
Trial (N randomized)	Treatment arm	AEs, n(%)	SAEs,n (%)	AEs leading to premature trial productdiscontinuation, n (%)	Nausea, n(%)	Vomiting, n(%)	Diarrhea, n(%)	GI AEs leading to premature trial productdiscontinuation, n (%)	Severe or BG-confirmed symptomatichypoglycemic events,*[†‡] n (%)	Severe hypoglycemic episodes,*[†]n (%)
PIONEER 1(N = 703) [20]	Oral semaglutide 3 mg(n = 175)	101 (58)	5 (3)	4 (2)	14 (8)	5 (3)	15 (9)	3 (2)	5 (3)	0
	Oral semaglutide 7 mg(n = 175)	93 (53)	3 (2)	7 (4)	9 (5)	8 (5)	9 (5)	4 (2)	2 (1)	1 (1)
	Oral semaglutide 14 mg(n = 175)	99 (57)	2 (1)	13 (7)	28 (16)	12 (7)	9 (5)	9 (5)	1 (1)	0
	Placebo(n = 178)	99 (56)	8 (4)	4 (2)	10 (6)	4 (2)	4 (2)	1 (1)	1 (1)	0
PIONEER 2(N = 822)[#] [21]	Oral semaglutide 14 mg(n = 410)	289 (70)	27 (7)	44 (11)	81 (20)	30 (7)	38 (9)	33 (8)	7 (2)	1 (<1)
	Empagliflozin 25 mg(n = 409)	283 (70)	37 (9)	18 (4)	10 (2)	7 (2)	13 (3)	3 (1)	8 (2)	1 (<1)
PIONEER 3(N = 1,864) [23]	Oral semaglutide 3 mg(n = 466)	370 (80)	64 (14)	26 (6)	34 (7)	13 (3)	45 (10)	11 (2)	23 (5)	0
	Oral semaglutide 7 mg(n = 464)	363 (78)	47 (10)	27 (6)	62 (13)	28 (6)	53 (11)	16 (3)	24 (5)	0
	Oral semaglutide 14 mg(n = 465)	370 (80)	44 (9)	54 (12)	70 (15)	42 (9)	57 (12)	32 (7)	36 (8)	1 (<1)
	Sitagliptin 100 mg(n = 466)	388 (83)	58 (12)	24 (5)	32 (7)	19 (4)	37 (8)	12 (3)	39 (8)	4 (1)
PIONEER 7(N = 504) [22]	Oral semaglutide (flexible 3, 7, or 14 mg)(n = 253)	197 (78)	24 (9)	22 (9)	53 (21)	14 (6)	22 (9)	14 (6)	14 (6)	0
	Sitagliptin 100 mg(n = 250)	172 (69)	24 (10)	8 (3)	6 (2)	2 (1)	8 (3)	2 (1)	14 (6)	0

*Hypoglycemic episodes were reported on a separate form to AEs; [†]requiring assistance of another person to actively administer carbohydrate or glucagon, or take other corrective actions; [‡]based on a BG value (<56 mg/dL) with symptoms consistent with hypoglycemia; [#]data from one patient was excluded due to duplication (already enrolled in the trial at another site).
AE, adverse event; BG, blood glucose; GI, gastrointestinal; SAE, serious adverse event.

Table 3. AEs related to diabetic retinopathy for PIONEER trials 1, 2, 3, and 7.

Trial (N randomized)	Treatment arm	Patients experiencing AEs related to diabetic retinopathy, n (%)
PIONEER 1 (N = 703) [20]	Oral semaglutide 3 mg (n = 175)	1 (1)
	Oral semaglutide 7 mg (n = 175)	6 (3)
	Oral semaglutide 14 mg (n = 175)	2 (1)
	Placebo (n = 178)	3 (2)
PIONEER 2 (N = 822) [21]	Oral semaglutide 14 mg (n = 410)	14 (3)
	Empagliflozin 25 mg (n = 409)	5 (1)
PIONEER 3 (N = 1,864) [23]	Oral semaglutide 3 mg (n = 466)	31 (7)
	Oral semaglutide 7 mg (n = 464)	28 (6)
	Oral semaglutide 14 mg (n = 465)	26 (6)
	Sitagliptin 100 mg (n = 466)	36 (8)
PIONEER 7 (N = 504) [22]	Oral semaglutide (flexible 3, 7, or 14 mg) (n = 253)	6 (2)
	Sitagliptin 100 mg (n = 250)	6 (2)

AE, adverse event.

all people with diabetic retinopathy [36]. As noted, patients with diabetic retinopathy were included in studies of the PIONEER trial program. However, patients with proliferative retinopathy or maculopathy requiring acute treatment were excluded.

Across the four PIONEER studies described in this review, diabetic retinopathy-related AEs were infrequent and generally occurred with a similar incidence between oral semaglutide and comparators (Table 3). In PIONEER 3 and 7, some diabetic retinopathy-related AEs were identified by routine eye examination as part of the trial protocol, and were mostly of mild or moderate severity, and did not require treatment [22,23].

The incidence of various other AEs of special interest was investigated within these studies, including acute kidney injury, cardiovascular events, hospitalization for heart failure, malignant neoplasms, thyroid-related events, and lactic acidosis [20–23]. Across the trials, the incidence of such events was low, with no significant imbalances reported between treatment groups [20–23].

Key clinical take-home points: safety and tolerability

- Across the PIONEER 1, 2, 3, and 7 trials, the safety and tolerability of oral semaglutide were consistent with the known profile of the GLP-1RA class.
- Oral semaglutide 7 and 14 mg were generally associated with more gastrointestinal AEs than sitagliptin, empagliflozin, or placebo.
- Gastrointestinal AEs generally occurred early in treatment, abated over time, and were mostly mild-to-moderate in severity (resulting discontinuation rates were 2–8% across the oral semaglutide 7 and 14 mg groups).
- In patients taking sulfonylureas or insulin, consider lowering the dose of these agents to reduce the risk of hypoglycemia when adding oral semaglutide.

3. Implications for use of oral semaglutide by primary care clinicians

GLP-1RAs as a class have a well-established efficacy and safety profile and are increasingly used in the treatment of individuals with T2D because of their good glycemic efficacy, ability to reduce body weight, and low incidence of hypoglycemia [3,4]. The availability of oral semaglutide now provides an additional treatment choice for patients with T2D who may benefit from a GLP-1RA therapy. The PIONEER 2, 3, and 7 trial results [21–23] indicate that oral semaglutide can be an effective choice as second-line therapy (and beyond) when additional antihyperglycemic therapy is needed to achieve glycemic targets recommended by treatment guidelines and algorithms [3,4]. These randomized trials were conducted in controlled environments, over periods of up to 78 weeks [20–23]. As with any new therapy, data from observational research and pharmacovigilance efforts in clinical practice are required to provide further insight into the long-term, real-world efficacy and safety of oral semaglutide.

As part of adopting an individualized patient-centered approach to T2D management, clinicians and patients must decide together which treatment regimens are likely to provide the greatest benefit, least risk, and most acceptability. Oral semaglutide may improve patient and clinician willingness to initiate treatment with a GLP-1RA. While some patients may still prefer a once-weekly injectable formulation to a daily tablet that has detailed administration instructions, PRO data from PIONEER 7 suggest that the administration requirements for flexibly dosed oral semaglutide did not adversely impact patient-reported treatment convenience or satisfaction compared with the oral DPP-4 inhibitor, sitagliptin [22,29].

Medication adherence is a key factor influencing treatment success. Potential differences in clinical outcomes between randomized controlled studies and real-world studies have been reported, and these differences can in part be attributed to poor medication adherence [37,38]. HbA_{1c} reductions in real-world studies were similar between GLP-1RAs (–0.52%) and DPP-4 inhibitors (–0.51%), whereas GLP-1RAs were more effective than DPP-4 inhibitors in randomized clinical trials (–1.30 versus –0.68) [37]. Poor medication adherence was identified as the key factor in the difference between clinical and real-world studies, accounting for ~75% of the gap [37,38]. Given that oral medications are generally associated with better adherence than injectable therapies [39], oral semaglutide may help to bridge this adherence gap and allow patients to gain the full benefit of the greater potency of GLP-1RA therapy compared with DPP-4 inhibitors. This is particularly important because poor adherence can increase the risk of long-term complications and mortality, as well as more frequent hospitalizations and higher healthcare costs [38]. As with other GLP-1RAs, gastrointestinal AEs may

influence patient adherence with oral semaglutide, and patients should be counseled on the nature of these events and how best to manage them, as discussed in detail in the final article in this supplement [40].

Key clinical take-home points

- Oral semaglutide can be considered a suitable option for people with T2D requiring treatment escalation after metformin (or one or more antihyperglycemic therapies).
- Patients should be advised to take oral semaglutide with no more than 4 fluid ounces of plain water only, at least 30 minutes before the first food, beverage, or any other oral medications of the day.
- Patients should start treatment with oral semaglutide at the 3 mg dose for 30 days before escalating to 7 mg, and if needed after a further 30 days, to 14 mg.
- Although these dosing conditions may appear somewhat more detailed than those of other oral antihyperglycemic agents, patient-reported treatment convenience or satisfaction was similar for oral semaglutide and sitagliptin.

Acknowledgments

Under the direction of the authors, medical writing and editorial support were provided by Nicola Beadle of Axis, a division of Spirit Medical Communications Group Ltd. (funded by Novo Nordisk Inc.). The authors were involved with drafting the outline and critically editing all drafts during the development of the article, and all authors provided their final approval for submission.

Declaration of interest

F.L. serves on a speakers' bureau for Janssen Pharmaceuticals.

L.B. has received: consultant fees from AstraZeneca, Gilead Sciences Inc., Janssen Pharmaceuticals, Merck, Novo Nordisk, and Sanofi; speaker honoraria from Janssen Pharmaceuticals, Novo Nordisk, and Sanofi; and research grant support from Novo Nordisk and Sanofi.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This article was supported by Novo Nordisk Inc.; the company was provided with the opportunity to perform a medical accuracy review.

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