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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 considered for injectable GLP-1 receptor agonist therapy or currently on insulin therapy

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ABSTRACT

Injectable therapies such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and insulin are high-efficacy options for people with type 2 diabetes (T2D) who require treatment intensification. In addition to high glycemic efficacy, GLP-1RAs offer weight loss benefits, and some agents have been shown to reduce cardiovascular risk. This article summarizes data from two clinical studies with the first oral GLP-1RA, oral semaglutide, in situations where injectable therapy is often considered, and provides guidance on use in primary care. PIONEER 4 compared oral semaglutide 14 mg with an injectable GLP-1RA, liraglutide 1.8 mg, or placebo in patients uncontrolled on oral glucose-lowering therapies. PIONEER 8 compared oral semaglutide with placebo in patients with T2D already on insulin therapy. Treatment with oral semaglutide gave similar reductions in glycated hemoglobin (HbA_{1c}) compared with liraglutide at 26 weeks, and significantly greater reductions at 52 weeks. Changes in body weight with oral semaglutide were significantly greater compared with liraglutide after 26 and 52 weeks. Adding oral semaglutide 7 or 14 mg to insulin resulted in significant reductions in HbA_{1c} and body weight at both 26 and 52 weeks compared with placebo, and facilitated a decrease in total daily insulin dosage. Oral semaglutide was associated with low proportions of patients experiencing severe or blood-glucose-confirmed symptomatic hypoglycemia when added to oral glucose-lowering therapies, and did not increase the incidence of such events when added to insulin. The tolerability profile of oral semaglutide was consistent with that seen for injectable GLP-1RAs, with gastrointestinal side effects seen most frequently; most were transient and tended to occur during dose escalation. For patients requiring treatment intensification after oral therapy or as add-on to insulin, oral semaglutide provides effective glucose lowering and body weight loss, with low risk of hypoglycemia, thus broadening the range of therapeutic options for treatment of T2D in primary care.

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Oral semaglutide; type 2 diabetes; injectable therapy; treatment escalation; comparative studies; insulin; glucagon-like peptide-1 receptor agonist

Article overview and relevance to clinical practice

- Type 2 diabetes (T2D) is a progressive disease, and most patients require treatment escalation to achieve and maintain glycemic control, which can include treatment with a high efficacy injectable therapy such as a glucagon-like peptide-1 receptor agonist (GLP-1RA) or insulin.
- In general, GLP-1RA therapy is characterized by high glycemic efficacy, achievement of glycemic targets, and weight loss, with some agents demonstrating cardiovascular (CV) benefits in individuals at high CV risk.
- One example of such an agent in this class is once-weekly subcutaneous semaglutide, which is associated with a high degree of glycemic efficacy (mean HbA_{1c} reduction ~1.1–1.8%), weight loss (~3.5–6.5 kg), and CV risk reduction.
- Semaglutide has also been developed as an oral formulation, which was approved by the US Food and Drug Administration (FDA) in September 2019 for the treatment of T2D, and offers the option of GLP-1RA therapy without the need for injections.
- In this article, we assess the suitability of once-daily oral semaglutide in clinical situations where injectable therapy is often considered, summarizing the clinical evidence for oral semaglutide:
  - compared with a subcutaneous injectable GLP-1RA as second- or third-line therapy;
  - in people who are already receiving insulin therapy and require treatment intensification.
  - We also provide guidance on the incorporation of oral semaglutide into clinical practice in primary care for the treatment of patients in these settings.

1. Injectable therapies for the treatment of type 2 diabetes

The latest Standards of Medical Care in Diabetes from the American Diabetes Association (ADA) and the Consensus Statement from the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) include two classes of injectable therapy in the treatment algorithm: insulin and glucagon-like peptide-1 receptor agonists (GLP-1RAs) [1,2]. These injectable therapies

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are traditionally considered to be high glycemic efficacy therapies amongst the treatment choices currently available for people with type 2 diabetes (T2D) [1,2].

Treatment selection for people with T2D should consider several factors in addition to efficacy and tolerability, including the risk of hypoglycemia, effects on body weight, cost, patient preference, and comorbidities [1]. Table 1 summarizes important considerations for the use of injectable therapies for T2D. Insulin has traditionally been used when disease progression means that oral glucose-lowering therapies alone are no longer able to maintain glycemic control [1,12]. However, insulin use has a greater risk of causing hypoglycemia and weight gain compared with other therapies [12–15].

The ADA recommends considering subcutaneous GLP-1RAs in several settings, including as the first injectable therapy (prior to insulin) in most patients and as add-on therapy in patients already receiving basal insulin who require treatment intensification [1]. In the most recent update to the Standards of Medical Care, based on the results of cardiovascular (CV) outcomes trials, GLP-1RAs (or oral sodium-glucose co-transporter-2 [SGLT2] inhibitors) with proven CV benefit are the preferred second-line treatment option for high-risk patients, regardless of glycated hemoglobin (HbA_{1c}) [1,16]. In addition to having high glycemic efficacy, GLP-1RAs have a lower risk of hypoglycemia compared with insulin and are associated with weight loss instead of weight gain [1,14]. Therefore, GLP-1RAs are also prioritized in the clinical recommendations when weight gain should be minimized or when weight loss is desirable [1].

Since the approval of the first GLP-1RA by the US Food and Drug Administration (FDA) in 2005, the class has expanded and there are currently six subcutaneous GLP-1RAs available in the USA (exenatide, exenatide extended-release [ER], liraglutide, lixisenatide, dulaglutide, and semaglutide). A detailed review of clinical experience with GLP-1RAs is provided in the first article of this supplement [11].

1.1. Subcutaneous semaglutide: efficacy outcomes of the SUSTAIN program and development of oral semaglutide

Semaglutide is a GLP-1RA that has high (94%) homology with human GLP-1 but has structural modifications to increase binding to serum albumin and delay degradation in the plasma, giving a long elimination half-life suitable for once-weekly administration by subcutaneous injection [3,18,19]. The clinical effects of subcutaneous semaglutide were investigated in the SUSTAIN program, which encompassed the full spectrum of diabetes care, including early therapy (SUSTAIN 1), and comparisons with other GLP-1RA therapies (exenatide ER [SUSTAIN 3], dulaglutide [SUSTAIN 7]), and with insulin therapy (SUSTAIN 4) [20–24]. A summary of selected efficacy outcomes from the SUSTAIN program is shown in Table 2. Subcutaneous semaglutide demonstrated superior and sustained reductions in HbA_{1c} versus all comparators, including other injectable therapies, and the 1 mg dose appears to have the greatest weight loss efficacy within the GLP-1RA class [22,25,26]. In addition, subcutaneous semaglutide was found to significantly reduce the risk of major adverse CV events in patients with T2D at high CV risk in the SUSTAIN 6 study [6], and is now approved by the FDA for reducing the risk of such events in patients with T2D and established CV disease [3].

An oral formulation of semaglutide was approved in the USA in September 2019 for the treatment of T2D [27], providing an alternative to subcutaneous injections of GLP-1RAs. The oral semaglutide tablet is co-formulated with the absorption enhancer, sodium N-8-[2-hydroxybenzoyl] amino) caprylate (SNAC) [28]. A phase 2 dose-finding study of double-blind once-daily oral semaglutide versus once-daily placebo or open-label once-

Table 1. Summary of key clinical considerations for injectable therapies for T2D [1,2].

Clinical consideration	GLP-1RAs	Insulins
Effect on HbA_{1c} levels	↓↓	↓↓
Effect on body weight	↓	↑
Hypoglycemia risk	Neutral	↑
Cardiovascular effects	Benefit in patients with, or at high risk of ASCVD (select GLP-1RAs*) Neutral for heart failure	Neutral for ASCVD and heart failure
Renal effects	Beneficial effect on diabetic kidney disease seen with select agents† No renal dose adjustments or limitations with dulaglutide, liraglutide, oral semaglutide or subcutaneous semaglutide; specific considerations for other GLP-1RAs‡ Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions	Neutral effect on diabetic kidney disease Lower insulin dose required with impaired renal function; dose should be adjusted based on clinical response
Other considerations	Gastrointestinal side effects common (nausea, vomiting and diarrhea) Injection site reactions (with subcutaneous GLP-1RAs) Boxed warning of thyroid C-cell tumors in rodents with exenatide ER, dulaglutide, liraglutide, subcutaneous semaglutide and oral semaglutide; human relevance has not been determined. These agents are contraindicated in patients with a personal or family history of MTC or MEN 2	Injection site reactions

*Dulaglutide, liraglutide and once-weekly subcutaneous semaglutide have a label indication for reducing CVD events [3–5]; †improvements in renal outcomes versus placebo have been reported for dulaglutide, liraglutide and once-weekly subcutaneous semaglutide in cardiovascular outcomes trials [6–8]; ‡exenatide is not recommended in patients with eGFR <30 mL/min/1.73 m^2 or ESRD [9]; exenatide ER is not recommended in patients with eGFR <45 mL/min/1.73 m^2 or ESRD [10]; lixisenatide is not recommended in patients with ESRD [11].

ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; ER, extended-release; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; MEN 2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; T2D, type 2 diabetes.

Table 2. Summary of selected efficacy outcomes from SUSTAIN 1–7 studies with subcutaneous semaglutide [22].

Endpoint	SUSTAIN 1 Monotherapy (30 weeks)			SUSTAIN 2 versus sitagliptin (56 weeks)			SUSTAIN 3 versus exenatide ER (56 weeks)		SUSTAIN 4 versus IGlar (30 weeks)			SUSTAIN 5 Add-on to basal insulin (30 weeks)			SUSTAIN 6 versus placebo (CVOT) (104 weeks)				SUSTAIN 7 versus dulaglutide (40 weeks)			
	Sema 0.5 mg	Sema 1.0 mg	Pbo	Sema 0.5 mg	Sema 1.0 mg	Sita 100 mg	Sema 1.0 mg	Exe 2.0 mg	Sema 0.5 mg	Sema 1.0 mg	IGlar	Sema 0.5 mg	Sema 1.0 mg	Pbo	Sema 0.5 mg	Sema 1.0 mg	Pbo 0.5 mg	Pbo 1.0 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
HbA_{1c} change from baseline (%)	−1.5*	−1.6*	<−0.1	−1.3*	−1.6*	−0.5	−1.5*	−0.9	−1.2*	−1.6*	−0.8	−1.4*	−1.8*	−0.1	−1.1*	−1.4*	−0.4	−0.4	−1.5*	−1.1	−1.8*	−1.4
Body weight change from baseline (kg)	−3.7*	−4.5*	−1.0	−4.3*	−6.1*	−1.9	−5.6*	−1.9	−3.5*	−5.2*	1.2	−3.7*	−6.4*	−1.4	−3.6*	−4.9*	−0.7	−0.5	−4.6*	−2.3	−6.5*	−3.0
Composite endpoint† (% of patients)	66	65	19	63	74	27	56	28	47	64	16	54	67	7	NR	NR	NR	NR	64	44	74	58

Studies shaded blue evaluated once-weekly subcutaneous semaglutide vs other injectable therapies or as add-on to basal insulin. Efficacy analyses for SUSTAIN 1–5 and 7 were based on all randomized and exposed patients using on-treatment data collected prior to onset of rescue medication.
*$p < 0.05$ versus (dose-matched) comparator (SUSTAIN 7: semaglutide 0.5 mg versus dulaglutide 0.75 mg and semaglutide 1.0 mg versus dulaglutide 1.5 mg); †percentage of patients achieving the outcome of HbA_{1c} <7.0% (<53 mmol/mol), no weight gain and no severe or blood glucose-confirmed hypoglycemia.
CVOT, cardiovascular outcomes trial; Dula, dulaglutide; ER, extended-release; Exe, exenatide extended-release; HbA_{1c}, glycated hemoglobin; IGlar, insulin glargine; NR, not reported; Pbo, placebo; Sema, semaglutide; Sita, sitagliptin.

weekly subcutaneous semaglutide confirmed that oral semaglutide resulted in better glycemic control than placebo over 26 weeks [29]. This study established that effective GLP-1RA therapy could be administered orally and supported the rationale for the comprehensive phase 3a PIONEER clinical trial program, which evaluated the efficacy and safety of oral semaglutide. Individual studies in this program compared oral semaglutide with placebo, oral glucose-lowering therapies, or injectable GLP-1RAs in various populations along the spectrum of care, including in those with T2D uncontrolled by diet and exercise alone, on one or more oral glucose-lowering therapies, or in those treated with insulin [17]. In addition, a CV outcomes trial (PIONEER 6) established the CV safety of oral semaglutide [30,31]. Oral semaglutide can be considered for use either early or late in the T2D treatment continuum. In this review, we consider the clinical evidence for its use in settings in which an injectable GLP-1RA or insulin would traditionally have been recommended, and discuss how best to integrate oral semaglutide into clinical practice in this setting. We summarize the clinical evidence for oral semaglutide from two studies within the PIONEER program: when compared with a subcutaneous GLP-1RA, liraglutide, as second- or third-line therapy (after metformin) in PIONEER 4 [32]; and in people with T2D who are already receiving insulin therapy and require treatment intensification in PIONEER 8 [33].

2. Clinical evidence for oral semaglutide versus injectable GLP-1RA and as add-on to insulin

2.1. Study designs

Both PIONEER 4 (NCT02863419) and PIONEER 8 (NCT03021187) were 52-week studies. PIONEER 4 was a randomized, double-blind, double-dummy study and PIONEER 8 was a randomized, double-blind, placebo-controlled study (Table 3). PIONEER 4 compared oral semaglutide 14 mg versus liraglutide 1.8 mg or placebo (2:2:1 randomization ratio) [32]. In PIONEER 8, patients were randomized to receive one of three different doses of oral semaglutide (3, 7, or 14 mg) or placebo as add-on to insulin therapy (1:1:1:1 ratio) [33]. In this review, we focus on results for the recommended maintenance doses of oral semaglutide (i.e. 7 and 14 mg [27]).

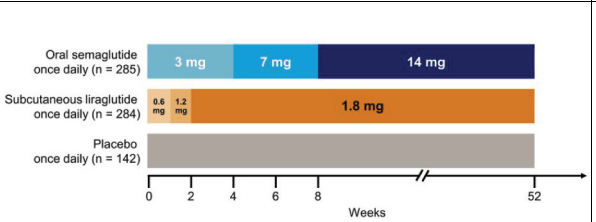
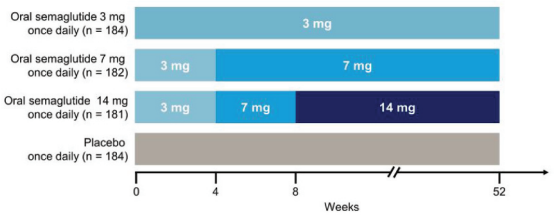
In the phase 2 dose-finding study, it was noted that initiating oral semaglutide at a low dose, followed by gradual dose escalation, helped to minimize gastrointestinal adverse events (AEs) [29]. Therefore, a fixed dose-escalation schedule was used in all PIONEER trials, including PIONEER 4 and PIONEER 8. Oral semaglutide was initiated at 3 mg once daily and the dose increased every 4 weeks to the randomized once-daily maintenance dose (7 or 14 mg) as appropriate. In PIONEER 4, patients randomized to liraglutide started treatment with a dose of 0.6 mg once daily with an increase to 1.2 mg once daily after 1 week and to the 1.8 mg once-daily dose after 2 weeks [32].

2.1.1. Endpoints

Both studies included identical primary and confirmatory secondary endpoints: change in HbA_{1c} from baseline to week 26 and change in body weight from baseline to week 26, respectively (Table 3) [32,33]. Secondary endpoints in both studies encompassed:

- Standard assessments of glycemic control and body weight;
- Composite endpoints combining glycemic control, body weight changes and hypoglycemia incidence;
- Patient-reported outcomes (PROs):
  - Diabetes Treatment Satisfaction Questionnaire (DTSQ) only in PIONEER 4
  - DTSQ, the 36-item Short-Form Health Survey version 2 [SF-36], and Impact of Weight on Quality of Life-Lite questionnaire Clinical Trial Version (IWQOL-Lite-CT) in PIONEER 8.

Table 3. Overview of the design of the PIONEER 4 and PIONEER 8 trials [32,33].

Trial design characteristic	PIONEER 4	PIONEER 8
Patient population	711 adults with T2D uncontrolled with metformin ± an SGLT2 inhibitor	731 adults with T2D uncontrolled with insulin ± metformin
Treatment arms and duration of therapy		
Background therapy	• All patients: metformin ≥1500 mg (or maximum tolerated) • Optional: SGLT2 inhibitor, received by: ○ 74 patients (26%) in the oral semaglutide 14 mg arm ○ 73 patients (26%) in the liraglutide 1.8 mg arm ○ 36 patients (25%) in the placebo arm	• All patients: insulin ≥10 U/day as basal, basal-bolus or premixed insulin formulations, received by (at screening): ○ basal insulin: 306 patients (42%) ○ basal-bolus insulin: 284 patients (39%) ○ premixed insulin: 129 (18%) • Optional: metformin ≥1500 mg (or maximum tolerated) • Background insulin doses were adjusted during the study as follows: ○ randomization to week 8: 20% reduction in total daily dose recommended ○ week 8–26: insulin doses adjusted at investigator's discretion, but not exceeding pre-randomization dosage ○ week 26–52: insulin dose adjusted at investigator's discretion, without limits
Primary endpoint	Change in HbA_{1c} from baseline to 26 weeks	
Confirmatory secondary endpoint	Change in body weight from baseline to 26 weeks	

HbA_{1c}, glycated hemoglobin; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.

In addition, PIONEER 8 investigated changes in the total daily insulin dosage between treatment arms [33]. Both studies included standard assessments of safety and tolerability, as well as analyses of the number of severe (based on ADA classification) or blood-glucose confirmed (<56 mg/dL [<3.1 mmol/L]) symptomatic hypoglycemic episodes [32,33].

2.2. Study results

Efficacy data presented in this article are based on the treatment policy estimand, which evaluated the treatment effect for all randomized patients regardless of trial product discontinuation or use of rescue medication. Further information on the estimand concept can be found in article 2 of this supplement [34] and in a review by Aroda and colleagues [35].

2.2.1. Patient demographics

In total, 711 patients were randomized in PIONEER 4, and 731 in PIONEER 8 (Table 3) [32,33]. Patients in PIONEER 4 were, on average, slightly younger than those in PIONEER 8 (mean age: 56 versus 61 years), while both studies included a roughly 50:50 split of male and female patients. In PIONEER 4, most patients were white (73%), 13% were Asian, and 4% were black or African American, whereas PIONEER 8 included a lower proportion of white patients (51%) and a higher proportion of Asian patients (36%), with 7% black or African American [32,33].

In both studies, mean HbA_{1c} at baseline was ~8%, although the mean duration of diabetes was notably shorter in PIONEER 4 (7.6 years) relative to PIONEER 8 (15.0 years), reflecting the more advanced stage of patients on insulin within the T2D treatment intensification pathway in PIONEER 8. Patients in PIONEER 4 and PIONEER 8 had a mean body weight at baseline of 94.0 kg (body mass index [BMI]: 33.0 kg/m^2) and 85.9 kg (BMI: 31.0 kg/m^2), respectively [32,33]. In PIONEER 8, the mean total daily insulin dosage at baseline for the enrolled population was 58 U/day. Basal insulin only was received by 42% of patients, basal-bolus by 39%, and premixed insulin by 18% [33].

2.2.2. Glycemic control

Mean changes from baseline in HbA_{1c} after 26 and 52 weeks are shown in Table 4. In PIONEER 4, after 26 weeks, oral semaglutide was found to provide statistically superior reductions in HbA_{1c} to placebo (1.2% versus 0.2%, respectively; $p < 0.0001$) and was non-inferior to liraglutide (1.2% versus 1.1%, respectively; $p < 0.0001$ for non-inferiority) [32]. After 52 weeks, significantly greater reductions in HbA_{1c} were reported with oral semaglutide compared with both comparators (1.2% versus 0.2% with placebo [$p < 0.0001$] and 0.9% with liraglutide [$p < 0.001$]]) [32]. In PIONEER 8, the oral semaglutide 7 and 14 mg doses both provided statistically significant HbA_{1c} reductions ($p < 0.0001$ for both) compared with placebo at both time points in patients receiving insulin ± metformin (0.9%, 1.3%, and 0.1%, respectively, after 26 weeks, and 0.8%, 1.2%, and 0.2% after 52 weeks) [33].

In PIONEER 4, more patients receiving oral semaglutide 14 mg achieved an HbA_{1c} target of <7.0% (<53 mmol/mol) compared with placebo after both 26 weeks (67.6% versus 14.2% for oral semaglutide and placebo, respectively; p value for the estimated odds ratio [EOR] < 0.0001) and 52 weeks (60.7% versus 15.0%, respectively; p value for the EOR < 0.0001) (Table 4) [27]. The proportion of patients achieving this target was also numerically greater with oral semaglutide 14 mg compared with liraglutide 1.8 mg (67.6% versus 61.8% of patients at 26 weeks and 60.7% versus 55.0% at 52 weeks) but the EOR did not achieve statistical significance [32]. Similarly in PIONEER 8, oral semaglutide 7 or 14 mg increased the proportion of patients achieving HbA_{1c} <7.0% versus placebo when added to insulin ± metformin at

Table 4. Overview of the efficacy outcomes of the PIONEER 4 and PIONEER 8 trials [32,33].

	PIONEER 4 (add-on to metformin ± an SGLT2 inhibitor)			PIONEER 8 (add-on to insulin ± metformin)		
	Oral semaglutide 14 mg (n = 285)	Liraglutide 1.8 mg (n = 284)	Placebo (n = 142)	Oral semaglutide 7 mg (n = 182)	Oral semaglutide 14 mg (n = 181)	Placebo (n = 184)
Mean change in HbA_{1c} from baseline, %						
Week 26	−1.2*	−1.1	−0.2	−0.9*	−1.3*	−0.1
Week 52	−1.2*†	−0.9	−0.2	−0.8*	−1.2*	−0.2
Mean change in body weight from baseline, kg						
Week 26	−4.4*†	−3.1	−0.5	−2.4*	−3.7*	−0.4
Week 52	−4.3*†	−3.0	−1.0	−2.0*	−3.7*	0.5
HbA_{1c} <7.0% (<53 mmol/mol), % of patients						
Week 26	67.6*	61.8	14.2	42.5*	58.4*	6.8
Week 52	60.7*	55.0	15.0	39.6*	54.2*	9.3
Body weight reduction ≥5%, % of patients						
Week 26	43.5*†	27.7	7.5	30.5*	38.7*	2.8
Week 52	44.7*†	24.5	12.0	28.1*	39.4*	5.2
HbA_{1c} <7.0% (<53 mmol/mol) without weight gain, and without severe‡ or blood glucose-confirmed symptomatic hypoglycemia, % of patients						
Week 26	60.8*	53.5	11.2	27.0*	43.9*	2.3
Week 52	56.4*	48.3	11.3	25.4*	36.3*	4.7

Data are for the treatment policy estimand, including all patients regardless of premature discontinuation of trial product or use of rescue medication. PIONEER 8 includes results for the recommended maintenance doses of oral semaglutide 7 and 14 mg only.

*$p < 0.05$ versus placebo for the estimated treatment differences (continuous endpoints) or estimated odds ratio (binary endpoints); †$p < 0.05$ versus liraglutide for the estimated treatment differences (continuous endpoints) or estimated odds ratio (binary endpoints); ‡severe hypoglycemia was defined according to the ADA classification (requires assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions). Blood glucose confirmation of symptomatic hypoglycemia was based on a blood glucose value <56 mg/dL (<3.1 mmol/L) with symptoms consistent with hypoglycemia.

ADA, American Diabetes Association; HbA_{1c}, glycated hemoglobin; SGLT2, sodium-glucose co-transporter-2.

26 weeks (target achieved by 42.5%, 58.4%, and 6.8% of patients, respectively; p value for the EOR < 0.0001 for both doses) and 52 weeks (target achieved by 39.6%, 54.2%, and 9.3% of patients, respectively; p value for the EOR < 0.0001 for both doses) (Table 4) [34].

Key clinical take-home points: efficacy

PIONEER 4

- Glycemic efficacy of oral semaglutide was similar to injectable GLP-1RA therapy (liraglutide) at 26 weeks (HbA_{1c} reductions from baseline of 1.2% vs 1.1%, respectively), with significantly greater efficacy after 52 weeks (HbA_{1c} reductions of 1.2% vs 0.9%, respectively).
- Reductions from baseline in body weight with oral semaglutide were significantly greater than liraglutide after 26 (4.4 kg vs 3.1 kg, respectively) and 52 weeks (4.3 kg vs 3.0 kg, respectively).

PIONEER 8

- When added to insulin, oral semaglutide 7 and 14 mg provided mean HbA_{1c} reductions from baseline of 0.9% and 1.3% compared with 0.1% for placebo after 26 weeks, and 0.8% and 1.2% compared with 0.2% for placebo after 52 weeks
- Moreover, oral semaglutide 7 and 14 mg provided mean body weight reductions from baseline of 2.4 kg and 3.7 kg compared with 0.4 kg for placebo after 26 weeks, and reductions of 2.0 kg and 3.7 kg compared with an increase of 0.5 kg with placebo after 52 weeks.
- Total daily insulin dosage was significantly reduced when oral semaglutide was added to insulin (mean change from baseline in total daily insulin dosage was 6U and 7U with oral semaglutide 7 and 14 mg at 52 weeks, compared with an increase of 10 U with placebo).

2.2.3. Body weight

In both PIONEER 4 and PIONEER 8, the reductions in body weight with oral semaglutide were statistically significantly greater than those seen in the comparator arms after both 26 and 52 weeks [32,33]. In PIONEER 4, after 26 weeks, oral semaglutide reduced body weight by 4.4 kg, compared with 3.1 kg with liraglutide ($p < 0.001$) and 0.5 kg with placebo ($p < 0.0001$); reductions of similar magnitude were still present after 52 weeks (respective values of 4.3 kg, 3.0 kg, and 1.0 kg; $p < 0.01$ versus liraglutide; $p < 0.0001$ versus placebo) [32]. Oral semaglutide 14 mg increased the proportion of patients achieving a body weight reduction of ≥5% versus liraglutide 1.8 mg and placebo after both 26 weeks (43.5%, 27.7%, and 7.5% of patients, respectively; p value for the EOR < 0.001 versus liraglutide and < 0.0001 versus placebo) and 52 weeks (44.7%, 24.5%, and 12.0%, respectively; p value for the EOR < 0.0001 versus both comparators) [32]. After 26 weeks in PIONEER 8, changes from baseline in body weight were –-2.4 kg, −3.7 kg and −0.4 kg with oral semaglutide 7 and 14 mg, and placebo, respectively ($p \leq 0.0001$ for oral semaglutide groups versus placebo), and again were largely maintained after 52 weeks (respective values of −2.0 kg, −3.7 kg, and +0.5 kg; $p < 0.0001$ for both doses versus placebo) [33]. In PIONEER 8, the proportion of patients achieving body weight reduction of ≥5% was greater for oral semaglutide 7 and 14 mg than placebo when added to insulin ± metformin at 26 weeks (30.5%, 38.7%, and 2.8%, respectively; p value for the EOR < 0.0001 for both doses) and 52 weeks (28.1%, 39.4%, and 5.2%, respectively; p value for the EOR < 0.0001 for both doses) [33].

2.2.4. Composite endpoints

In PIONEER 4, the proportions of patients achieving the composite endpoint of HbA_{1c} <7.0% without weight gain and without severe or blood glucose-confirmed symptomatic hypoglycemia were greater with oral semaglutide versus placebo after both 26 weeks (60.8% versus 11.2%; p value for the EOR < 0.0001) and 52 weeks (56.4% versus 11.3%; p value for the EOR < 0.0001), and similar for oral semaglutide and liraglutide (53.5% of liraglutide patients at 26 weeks and 48.3% at 52 weeks; no significant difference in EOR versus oral semaglutide) (Table 4) [32]. In PIONEER 8, the proportion of patients achieving this endpoint was greater with oral semaglutide 7 and 14 mg versus placebo when added to insulin ± metformin (27.0%, 43.9%, and 2.3%, respectively, after 26 weeks, and 25.4%, 36.3%, and 4.7%, respectively, after 52 weeks; all p values for the EOR < 0.0001) [28].

2.2.5. Patient-reported outcomes

Treatment satisfaction is an important PRO that assesses both a patient's expectations and their actual experience of treatment. In PIONEER 4 treatment satisfaction, assessed through changes from baseline in DTSQ scores, was significantly improved with oral semaglutide compared with placebo, and was similar to liraglutide, after both 26 and 52 weeks [32]. It should be noted that PIONEER 4 included a double-blind, double-dummy design, whereby patients received both a tablet and an injection, regardless of which treatment arm they were randomized to. As such, the treatment satisfaction scores in this study do not capture the potential differences in satisfaction that may be derived from the differing routes of administration of oral semaglutide and liraglutide. In PIONEER 8, oral semaglutide 7 and 14 mg significantly improved DTSQ total treatment satisfaction scores from baseline relative to placebo after both 26 and 52 weeks [33].

Changes in quality of life from baseline were assessed in PIONEER 8 using the SF-36 Health Survey version 2. Scores across the majority of components were similar with oral semaglutide and placebo when added to insulin ± metformin. Significant improvements were seen in the following components: mental health with oral semaglutide 14 mg versus placebo after 26 weeks, and general health with oral semaglutide 7 and 14 mg versus placebo after 52 weeks [33]. The impact of weight on the patient's quality of life was determined using changes from baseline in IWQOL-Lite-CT total scores, which were found to be significantly improved after 26 and 52 weeks with oral semaglutide 14 mg compared with placebo when added to insulin ± metformin, but were not significantly different for 7 mg [33].

2.2.6. Insulin use

In PIONEER 8, background insulin doses were adjusted during the study as described in Table 3. At randomization, a 20% reduction in total daily insulin dosage was recommended. During weeks 8–26, insulin could be increased back up to the pre-randomization dose as indicated, and freely titrated at the investigator's discretion thereafter. The total daily insulin dosage was significantly reduced from baseline with oral semaglutide 7 and 14 mg compared with placebo at both 26 and 52 weeks [33]. At 52 weeks, the total daily insulin dosage was reduced by a mean of 6 U and 7 U with oral semaglutide 7 and 14 mg, respectively, compared with an increase of 10 U with placebo ($p < 0.0001$ for both doses).

2.2.7. Safety and tolerability

2.2.7.1 Adverse events. The AE profile for oral semaglutide in the two PIONEER trials was consistent with the AE profile seen with the GLP-1RA class [36–38]. In both PIONEER 4 and 8, the most frequently reported AEs with oral semaglutide were gastrointestinal in nature, most commonly nausea or diarrhea (Table 5) [32,33]. Nausea and diarrhea were reported in similar proportions of patients randomized to oral semaglutide 14 mg and the comparator GLP-1RA liraglutide 1.8 mg in PIONEER 4 (nausea: 20% versus 18% of patients, respectively; diarrhea: 15% versus 11% of patients respectively) [32].

In both studies, episodes of nausea were mild-to-moderate in severity and typically transient [32,33]. The proportion of patients reporting nausea in oral semaglutide groups peaked shortly after the completion of the 8-week dose-escalation phase [32,33]. In PIONEER 4, the peak occurrence of nausea was sooner after treatment initiation with liraglutide (after approximately 2 weeks) compared with oral semaglutide (after approximately 8 weeks), which the authors suggested may relate to the 2-week dose titration schedule with liraglutide compared with the longer titration period for oral semaglutide [32] – this result may have implications for counseling patients regarding the timing of potential gastrointestinal AEs with oral semaglutide. For the context of clinical practice, it should be recognized that reports of nausea in these studies were not solely confined to the initial weeks of treatment, and nausea was reported in small numbers of patients randomized to both oral semaglutide and liraglutide over the course of 52 weeks [32,33].

The proportion of patients discontinuing treatment due to AEs was higher with oral semaglutide than placebo in both studies, with gastrointestinal AEs the most common reason for cessation of treatment [32,33]. When compared with the subcutaneous GLP-1RA in PIONEER 4, the proportion of patients discontinuing treatment due to AEs was 11% with oral semaglutide 14 mg versus 9% with liraglutide 1.8 mg, and was 4% in the placebo group [32]. In PIONEER 8, discontinuation due to AEs occurred in 9% and 13% of patients with oral semaglutide 7 and 14 mg, respectively, compared with 3% with placebo [33]. In both studies, the proportions of patients reporting serious AEs were similar in the oral semaglutide and placebo groups [32,33].

Table 5. Overview of key on-treatment adverse events from the PIONEER 4 and PIONEER 8 trials [32,33].

	PIONEER 4 (add-on to metformin ± an SGLT2 inhibitor)			PIONEER 8 (add-on to insulin ± metformin)		
Number of patients (%)	Oral semaglutide 14 mg (n = 285)	Liraglutide 1.8 mg (n = 284)	Placebo (n = 142)	Oral semaglutide 7 mg (n = 181)	Oral semaglutide 14 mg (n = 181)	Placebo (n = 184)
≥1 AE	229 (80)	211 (74)	95 (67)	142 (78)	151 (83)	139 (76)
Serious AEs	31 (11)	22 (8)	15 (11)	19 (10)	12 (7)	17 (9)
AEs leading to premature trial product discontinuation	31 (11)	26 (9)	5 (4)	16 (9)	24 (13)	5 (3)
Deaths*	3 (1)	4 (1)	1 (1)	0	3 (2)	0
Most common AEs (occurring in ≥10% of patients in any treatment group in either study)						
Nausea	56 (20)	51 (18)	5 (4)	30 (17)	42 (23)	13 (7)
Diarrhea	43 (15)	31 (11)	11 (8)	22 (12)	27 (15)	11 (6)
Nasopharyngitis	41 (14)	37 (13)	15 (11)	21 (12)	18 (10)	27 (15)
Decreased appetite	16 (6)	20 (7)	0	18 (10)	23 (13)	2 (1)
Severe or blood glucose-confirmed symptomatic hypoglycemic episodes[†]	2 (1)	7 (2)	3 (2)	47 (26)	48 (27)	54 (29)
Severe or blood glucose-confirmed symptomatic hypoglycemic episodes[†] by background insulin regimen						
Basal insulin	-	-	-	12 (16)	10 (13)	16 (20)
Basal-bolus insulin	-	-	-	29 (40)	31 (44)	27 (38)
Premixed insulin	-	-	-	6 (19)	7 (20)	11 (34)
AEs of special interest (in-trial events)						
Diabetic retinopathy	8 (3)	3 (1)	2 (1)	8 (4)	9 (5)	8 (4)
Acute pancreatitis[‡]	0	1 (0.4)	1 (1)	0	0	0
Cardiovascular events[‡]	4 (1)	3 (1)	2 (1)	5 (3)	5 (3)	5 (3)
Malignant neoplasm[‡#]	3 (1)	3 (1)	0	2 (1)	2 (1)	0
Papillary malignant thyroid neoplasm[‡]	1 (0.4)	1 (0.4)	0	NR	NR	NR

PIONEER 8 includes results for the recommended maintenance doses of oral semaglutide 7 and 14 mg only.

*All deaths in PIONEER 4 were judged as not treatment-related by the investigator. EAC-reported cause of death was malignancy (n = 3), acute myocardial infarction (n = 1), sudden cardiac death (n = 1), cardiovascular procedure (n = 1), non-prescription drug reaction or overdose (n = 1), and undetermined (n = 1). In PIONEER 8, of the 3 deaths reported, none reported severe or blood glucose-confirmed symptomatic hypoglycemic episodes during the study; EAC-reported cause of death was infection (n = 1) and undetermined as medical records were unavailable (n = 2); [†]severe hypoglycemia was defined according to the ADA classification (requires assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions). Blood glucose confirmation of symptomatic hypoglycemia was based on a blood glucose value <56 mg/dL (<3.1 mmol/L) with symptoms consistent with hypoglycemia; [‡]External Event Adjudication Committee-confirmed event; [#]excludes malignant thyroid neoplasms.

ADA, American Diabetes Association; AE, adverse event; EAC, Event Adjudication Committee; NR, not reported; SGLT2, sodium-glucose co-transporter-2.

2.2.7.2. Hypoglycemia. As would be anticipated given the inherently low propensity for GLP-1RAs to induce hypoglycemia, both oral semaglutide and liraglutide were associated with very low proportions of patients experiencing severe or blood glucose-confirmed symptomatic hypoglycemic episodes in the PIONEER 4 study (1% and 2% of patients, respectively, compared with 2% in the placebo group) (Table 5) [32]. The number of such events was higher in PIONEER 8, which was expected given that patients were receiving background insulin, but the addition of oral semaglutide to insulin did not increase the proportion of patients with hypoglycemia compared with placebo [33]. The proportions of patients experiencing such hypoglycemic episodes were 26%, 27%, and 29% in the oral semaglutide 7 and 14 mg groups, and the placebo group, respectively (Table 5). Most occurred in patients receiving basal-bolus background insulin therapy (Table 5). Few patients experienced severe episodes of hypoglycemia (n = 1 in the placebo and oral semaglutide 7 mg groups; n = 2 in the oral semaglutide 14 mg group).

Key clinical take-home points: safety and tolerability

PIONEER 4

- Safety and tolerability were generally consistent between oral semaglutide and the injectable GLP-1RA, liraglutide.
- Consistent with the GLP-1RA class, mild-to-moderate gastrointestinal AEs were the predominant form of AE reported.
- The most common AE reported was nausea, which was typically transient in nature.

PIONEER 8

- There was no increase in the risk of hypoglycemia when oral semaglutide was added to insulin ± metformin.
- Dose reduction of insulin/insulin secretagogues may reduce the risk of hypoglycemia when initiating a GLP-1RA such as oral semaglutide.

2.2.7.3. Adverse events of special interest. PIONEER 4 and 8, along with other studies in the PIONEER clinical trial program, examined the occurrence of various AEs of special interest following treatment with oral semaglutide [32,33].

2.2.7.3.1. Malignant neoplasms. Prescribing information for oral semaglutide and some other GLP-1RAs contains warnings about the potential risk of thyroid C-cell tumors based on observations in rodent studies, including medullary thyroid carcinoma (MTC), and these products are contraindicated in patients with a personal or family history of MTC or a history of multiple endocrine neoplasia syndrome type 2 [13,22,34–36]. In both PIONEER 4 and 8, reports of malignant neoplasms were very low (≤1.1% of patients per group in oral semaglutide 7 or 14 mg groups) (Table 5), and no cases of MTC were reported in either trial [32,33]. For a more in-depth discussion of this topic, see article 5 of this supplement [39].

2.2.7.3.2. Diabetic retinopathy. Rapid reductions in HbA_{1c} have previously been reported to be associated with worsening of pre-existing diabetic retinopathy [40]. For oral semaglutide and some other GLP-1RAs, the prescribing information contains warnings about diabetic retinopathy complications and the need for monitoring for progression of diabetic retinopathy in patients with a history of this condition [3,4,27]. In PIONEER 4 and 8, diabetic retinopathy-related AEs occurred in few patients, with similar incidence across treatment groups (Table 5) [32,33]. Most events in PIONEER 8 were identified during routine examination (40 of 49 events) and did not require treatment (41 of 49 events) [33]. Patients with proliferative retinopathy or maculopathy requiring acute treatment were excluded from these studies [32,33].

2.2.7.3.3. Acute pancreatitis. Following post-approval marketing surveillance and reports in clinical trials of GLP-1RAs, the prescribing information for oral semaglutide and other agents in this class contains warnings regarding the risk of pancreatitis [3–5,9–11,27]. The incidence of acute pancreatitis was very low across PIONEER 4 and 8 and was not identified in any patients receiving oral semaglutide (Table 5) [32,33]. It should be noted that both studies excluded patients with a history of acute or chronic pancreatitis, and more generally the prescribing information for oral semaglutide and other GLP-1RAs highlights the lack of (or at best limited) evidence in patients with a history of pancreatitis [3–5,9–11,27]. Consequently, other glucose-lowering therapies should be considered instead of GLP-1RAs in patients with a history of pancreatitis [3,4,9–11,27].

2.2.7.3.4. Cardiovascular events. Incidences of CV events in PIONEER 4 and 8 were low and similar across treatment groups (Table 5) [32,33]. A dedicated evaluation of CV outcomes with oral semaglutide was performed in the PIONEER 6 study [30], which is discussed in article 4 of this supplement [31].

3. Clinical implications of oral semaglutide as an alternative to injectable GLP-1RA therapy

As the first oral GLP-1RA, oral semaglutide expands treatment options and choices for patients requiring treatment intensification, with clinical data showing effective glucose lowering and body weight loss, without increasing the risk of hypoglycemia. The PIONEER program included patient populations and treatment regimens that are relevant for large sections of the T2D treatment continuum seen in clinical practice. By enrolling people with T2D and inadequate glycemic control while receiving metformin with or without an SGLT2 inhibitor, PIONEER 4 demonstrated the efficacy and safety of adding oral semaglutide to these commonly used agents [32]. PIONEER 8 enrolled a population of patients receiving a variety of insulin regimens at baseline, with or without metformin, and included a period during which background insulin dose could be adjusted at the investigator's discretion, mirroring clinical practice [33]. However, these studies were both 52-week clinical trials, and longer-term, real-world data from use in clinical

practice will be important for enhancing understanding of the clinical profile of oral semaglutide in these settings.

PIONEER 4 showed that, in people with T2D uncontrolled on oral glucose-lowering therapies, oral semaglutide 14 mg provides similar reductions in HbA_{1c} to the injectable GLP-1RA liraglutide after 26 weeks' treatment, and significantly greater reductions after one year. Body weight reductions were significantly greater with oral semaglutide versus liraglutide at both time points. This study represents a comparison of the maximum approved doses of oral semaglutide [27] and of liraglutide [5], thereby providing a robust evaluation of the efficacy that can be expected from these agents in this patient population. Previous head-to-head studies have demonstrated differences between specific GLP-1RAs in efficacy, with subcutaneous semaglutide providing greater reductions in both HbA_{1c} and body weight than dulaglutide and exenatide ER [20,23].

Key clinical take-home points

- For patients requiring treatment intensification after oral therapy or as add-on to insulin therapy, oral semaglutide offers an oral GLP-1RA option
  - with significant improvements in HbA_{1c} and body weight in patients with T2D;
  - with a low risk of hypoglycemia;
  - without the requirement for injections.
- Improvements in HbA_{1c} and body weight have been demonstrated with oral semaglutide compared with the injectable GLP-1RA, liraglutide.
- Adding oral semaglutide to insulin provides reductions in HbA_{1c} and body weight, without increasing the risk of hypoglycemia, while also allowing reductions in total daily insulin dosage.
- In patients already taking insulin, sulfonylureas or other insulin secretagogues, the risk of hypoglycemia may be lowered by reducing the dose of these concomitant medications when initiating a GLP-1RA such as oral semaglutide.
- Consistent with other agents in the GLP-1RA class
  - Gastrointestinal disorders, namely mild-to-moderate and transient nausea, were the most frequent AEs;
    - Patients should be advised that these AEs tend to occur during treatment initiation and informed of strategies to relieve them (e.g. ,gradual dose escalation, stop eating when feeling full, avoid high-fat foods, etc.);
  - Treatment should be discontinued if pancreatitis is suspected and not reinitiated if clinically confirmed;
  - Individuals with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy during treatment with oral semaglutide, in line with standard practice for all patients with diabetic retinopathy;
  - Patients should be advised to read the medication guide and counseled on relevant warnings and precautions (see the prescribing information and article 5 in this supplement for further information on counseling).

As PIONEER 4 is the only phase 3 head-to-head study to date to compare oral semaglutide with a subcutaneous GLP-1RA in an international population, clinical trial comparisons with other GLP-1RAs beyond liraglutide are lacking. However, a recently published systematic review and network meta-analysis provides some insight (accepting the inherent challenges of network meta-analyses, such as the potential for heterogeneity, inconsistency, and bias to influence the results [41]) [42]. This analysis reported that when added to 1–2 oral glucose-lowering therapies, oral semaglutide 14 mg provided HbA_{1c} reductions that were significantly or numerically greater than all comparator GLP-1RAs studied (statistically significantly greater than once-weekly dulaglutide 0.75 mg or exenatide 2 mg, twice-daily exenatide 5 or 10 µg, and once-daily liraglutide 1.2 mg or lixisenatide 20 µg; numerically, but not statistically, greater than once-weekly subcutaneous semaglutide 0.5 mg or dulaglutide 1.5 mg, and once-daily liraglutide 1.8 mg), with the exception of subcutaneous semaglutide 1 mg once weekly, for which numerically greater reductions were seen [42].

PIONEER 8 demonstrates that oral semaglutide can be added to insulin, resulting in improved glycemic control and weight loss, without an increased risk of hypoglycemia, as well as allowing a reduction in insulin dosage [33]. Indeed, similar proportions of patients experienced hypoglycemic episodes with addition of oral semaglutide or placebo.

When oral semaglutide is used with insulin, the prescribing information states that consideration should be given to lowering the dose of insulin to reduce the risk of hypoglycemia [27]. In PIONEER 8, when oral semaglutide or placebo were added to basal, basal-bolus, or premixed insulin therapy, a 20% dose reduction in total daily insulin dosage was recommended at randomization and maintained to at least 8 weeks. After 8 weeks, insulin dose could be adjusted up to the pre-randomization dose, and after 26 weeks could be freely adjusted at the discretion of the investigators. Even after this period of free adjustment, the dose of background insulin was below baseline in patients receiving oral semaglutide but was greater than baseline in patients receiving placebo. Despite greater use of insulin in the placebo group, there was little improvement in glycemic control over the course of the trial in the placebo group, whereas glycemic control was significantly improved in the group adding oral semaglutide to insulin, highlighting the challenges and limitations of insulin therapy even in a clinical trial setting [33].

When initiating treatment with oral semaglutide, the expectations of patients should be taken into account, and patients should be educated on several important aspects of treatment. Because of its formulation, the presence of food and fluid in the stomach impairs absorption of oral semaglutide [28,43,44]. Consequently, the medication guide recommends that oral semaglutide is taken whole in the fasting state (e.g., upon waking), with a sip of water (up to 4 fl oz/120 mL), and at least 30 minutes before the first food, beverage, or other oral medications of the day [27]. Gastrointestinal AEs, while common with GLP-1RAs, do not affect the majority of patients with oral semaglutide [27]. Moreover, they tend to occur during dose escalation [27]

and are usually mild-to-moderate in severity [32,45–47]. Patients should be counseled that they may experience a sense of fullness, satiety, or even nausea, and if they experience nausea, that this typically dissipates [32,33].

Consistent with other GLP-1RAs [30], clinicians should continue to be aware of the warnings and precautions with regard to MTC, acute pancreatitis, and diabetic retinopathy complications [27]. Overall, the results of PIONEER 4 and PIONEER 8 do not indicate an increased risk of these AEs with oral semaglutide treatment. However, these are comparatively short-term (1 year) studies with population sizes selected primarily for comparing glycemic control between treatment groups, rather than for assessing the incidence of these AEs. The wider clinical trial program for oral semaglutide, as discussed elsewhere in this supplement and summarized in Brunton et al. [39], provides further insight into the incidence of these events.

Many patients with T2D receiving existing glucose-lowering therapies or on insulin therapy may require treatment intensification through the addition of a GLP-1RA to help manage their glucose levels. The availability of oral semaglutide therefore provides clinicians and patients with an additional option to help achieve glycemic targets and improve patient outcomes. From a practical perspective, the route of administration of oral semaglutide may be preferred by some patients, and may help overcome injection barriers and avoid the additional staff and training requirements for injectable therapies [48–50].

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