

Efficacy of Oral Semaglutide: Overview of the PIONEER Clinical Trial Program and Implications for Managed Care

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Current Use of Glucagon-like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a well-established treatment for type 2 diabetes (T2D), offering effective glycemic control, weight loss, and a low risk of hypoglycemia.¹ Both the American Diabetes Association (ADA) Standards of Medical Care in Diabetes and the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) consensus statement recommend a GLP-1RA or a sodium–glucose cotransporter 2 inhibitor (SGLT2i) over alternative options such as a dipeptidyl peptidase-4 inhibitor (DPP-4i), a thiazolidinedione (TZD), or a sulfonylurea (SU) for the second-line treatment of patients with inadequate glycemic control on metformin, with the AAACE/ACE consensus statement indicating preference for a GLP-1RA over an SGLT2i.^{2,3} In addition, the AAACE/ACE consensus statement advocates a GLP-1RA or an SGLT2i as the preferred first-line treatment option for patients with, or at high risk of, atherosclerotic cardiovascular disease (CVD), chronic kidney disease, or heart failure.³

Over the last 10 to 15 years, GLP-1RAs have become well established as an efficacious treatment option for patients with T2D, and provide both effective glycemic control and weight loss, but also have a well-characterized safety profile. Until September 2019, GLP-1RAs were only available for administration by subcutaneous injection twice daily (exenatide⁴), once daily (lixisenatide⁵ and liraglutide⁶), or once weekly (semaglutide,⁷ dulaglutide,⁸ and exenatide extended-release⁹). However, in US analyses of claims data, only 5.4% of adult patients with T2D without CVD, and 4.1% with T2D and established CVD, were prescribed a GLP-1RA.¹⁰ The authors suggested a possible reason was that some patients experienced challenges in attaining newer classes of antidiabetic therapies, for example, due to medication cost and high-deductible health care plans. The low rates of GLP-1RA utilization may also be in part because, until recently, all GLP-1RAs were administered by subcutaneous injection, a route that may be less preferable to some patients compared with oral administration.^{2,11} As such, an oral GLP-1RA could potentially aid initiation of this class of drug earlier in the diabetes treatment trajectory.

ABSTRACT

The first tablet formulation of a glucagon-like peptide-1 receptor agonist (GLP-1RA), oral semaglutide, was approved in September 2019 for the treatment of adults with type 2 diabetes (T2D). This article reviews data from the PIONEER phase 3a clinical trial program, which assessed the efficacy and safety of oral semaglutide in more than 9500 patients at different stages on the disease trajectory (mean diabetes duration, 3.5–15 years) and on a range of background treatment regimens (monotherapy, added to 1 or 2 oral glucose-lowering agents, or added to insulin). The studies compared oral semaglutide (doses of 3 mg, 7 mg, or 14 mg) with placebo, and selected commonly used glucose-lowering agents (empagliflozin 25 mg, sitagliptin 100 mg, or liraglutide 1.8 mg). Across the studies, oral semaglutide provided greater glycated hemoglobin (A1C) reductions than placebo, empagliflozin, or sitagliptin at 26 weeks, and similar A1C reductions as liraglutide. The proportion of patients achieving the A1C level recommended by the American Diabetes Association of less than 7.0% (53 mmol/mol) was greater with oral semaglutide (7 mg, 42%–69%; 14 mg, 55%–77%) than placebo (7%–31%) and active comparators (25%–62%), with durable target achievement. Oral semaglutide was associated with similar reductions in body weight as empagliflozin and greater reductions than placebo, sitagliptin, or liraglutide. Oral semaglutide was also efficacious in patients with T2D and moderate renal impairment. These findings indicate that oral semaglutide presents a valuable option for treating patients with T2D in a managed care setting, with the potential to expand the number of patients benefiting from GLP-1RAs.

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For author information and disclosures, see end of text.

KEY TAKEAWAY POINTS

- The first oral glucagon-like peptide-1 receptor agonist (GLP-1RA), oral semaglutide, was approved by the FDA for the treatment of adults with type 2 diabetes (T2D) in September 2019, and has since received approval in the European Union, United Kingdom, and Japan.
- This article reviews results from the PIONEER clinical trials that established the efficacy of oral semaglutide compared with selected commonly used glucose-lowering agents.
- Across the spectrum of patients with T2D, oral semaglutide 14 mg demonstrated similar glycated hemoglobin (A1C) reductions to the injectable GLP-1RA liraglutide (1.8 mg), and greater A1C reductions than the sodium-glucose cotransporter 2 inhibitor empagliflozin (25 mg).
 - Oral semaglutide 7 mg and 14 mg demonstrated greater A1C reductions than the dipeptidyl-peptidase-4 inhibitor sitagliptin (100 mg) at 26 weeks.
- The proportion of patients achieving the recommended A1C target by the American Diabetes Association of a level less than 7.0% (53 mmol/mol) was consistently greater with oral semaglutide (7 mg, 42%-69%; 14 mg, 55%-77%) than with placebo (7%-31%) and active comparators (25%-62%) at week 26, and target achievement was sustained until the end of the trials (up to 78 weeks for oral semaglutide 7 mg and 14 mg in PIONEER 3 [$P = .01$ and $P < .001$, respectively]).
- Oral semaglutide was associated with a similar reduction in body weight to empagliflozin, and a greater reduction than sitagliptin or liraglutide, at week 26.
- The availability of oral semaglutide, an efficacious and potentially convenient therapy, provides an additional valuable option for patients in a managed care setting, and may increase the number of patients who receive timely and effective T2D management.

Oral semaglutide, the first GLP-1RA developed as a tablet, was approved by the FDA in September 2019 to improve glycemic control in adults with T2D,¹² and has since received approval in the European Union, United Kingdom, and Japan.^{13,14} This article describes the PIONEER phase 3a clinical trial program, which generated data on oral semaglutide in over 9500 patients with T2D in a range of clinical settings, with a focus on the efficacy results and their implications for managed care specialists.

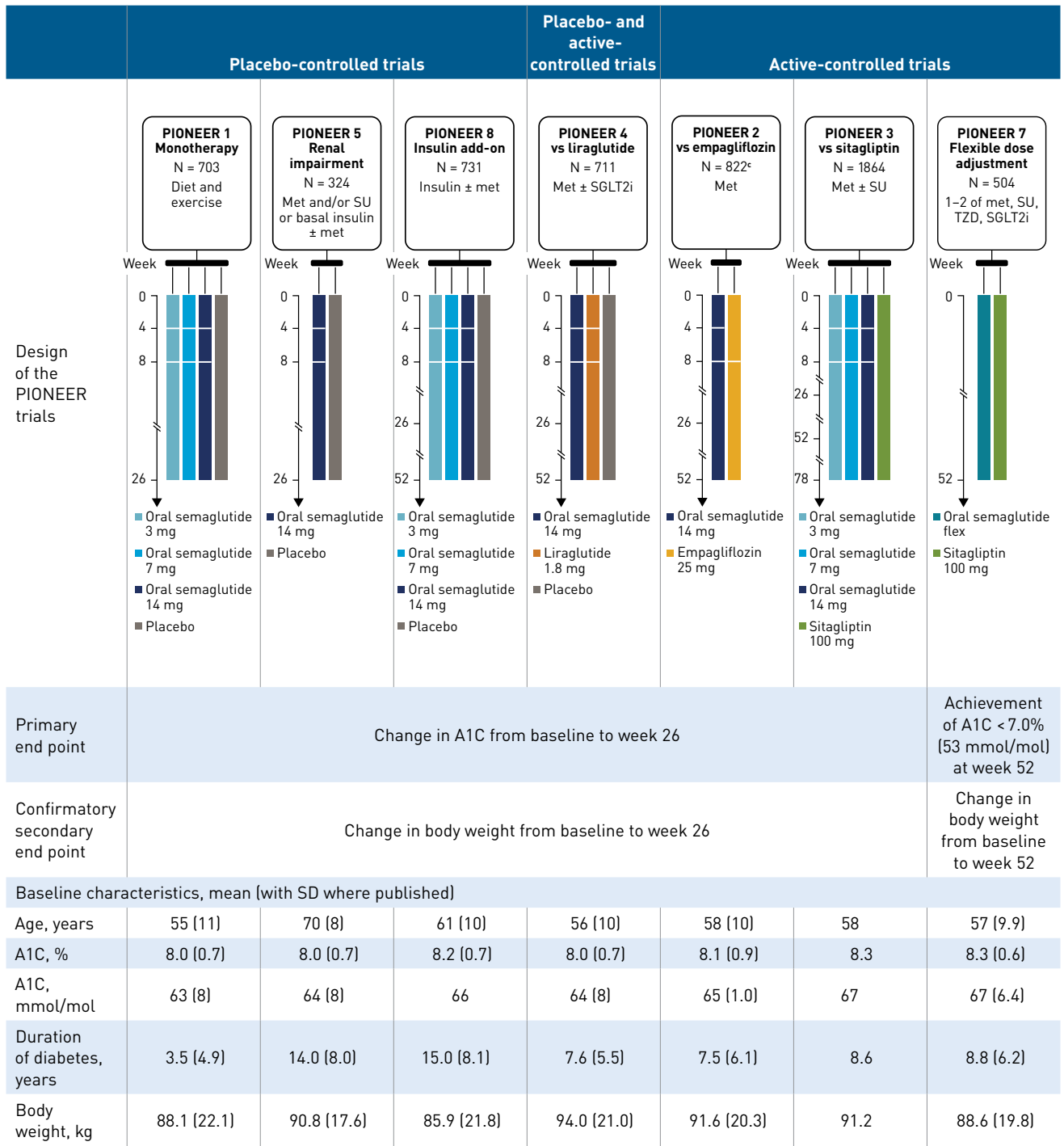
Overview of the PIONEER Clinical Trial Program

The comprehensive global PIONEER program included patients who were representative of those typically encountered in clinical practice (Figure 1).¹⁵⁻²¹ Common inclusion criteria for the PIONEER trials were at least 18 years old, a diagnosis of T2D at least 90 days prior to screening, and inadequate glycemic control, with an A1C level within the range of 7.0% to 9.5% (53-80 mmol/mol),¹⁵⁻¹⁸ 7.0% to 10.5% (53-91 mmol/mol),^{19,20} or 7.5% to 9.5% (58-80 mmol/mol),²¹ depending on the trial. The various trials assessed the effects of oral semaglutide 3, 7, and 14 mg in patients across the wide spectrum of the T2D disease course. Oral semaglutide was initiated at a dose of 3 mg for all patients, before escalating to 7 mg after 4 weeks, and then to 14 mg after a further 4 weeks depending on the treatment arm.¹⁵⁻²⁰ PIONEER 7 was an exception: patients were initiated at a 3-mg dose and after 8-week intervals the dose could then be increased or decreased, as described earlier.²¹ Patients with early T2D (mean diabetes duration, 3.5 years) managed on diet and exercise only were studied in PIONEER 1.¹⁵ Effects in patients with more established T2D (mean diabetes duration, 7.4 years) already receiving 1 or 2 oral glucose-lowering agents were studied in: PIONEER 2 (metformin only); PIONEER 3 (metformin \pm SU); PIONEER 4 (metformin \pm SGLT2i); and PIONEER 7 (1 or 2 oral agents including metformin, SU, TZD, or SGLT2i).^{16,19-21} Patients with advanced disease (mean diabetes duration, 15.0 years) taking insulin (basal, basal-bolus, or premixed; with or without metformin) who required additional treatment were studied in PIONEER 8.¹⁸ Further studies were conducted in the settings of renal impairment (PIONEER 5),¹⁷ and CVD (PIONEER 6).²²

Four trials compared oral semaglutide with commonly used glucose-lowering agents from drug classes recommended for patients who require further treatment intensification, namely, the SGLT2i, empagliflozin (PIONEER 2), the DPP-4i, sitagliptin (PIONEER 3 and 7), and the once-daily injectable GLP-1RA, liraglutide (PIONEER 4).^{16,19-21}

The PIONEER 7 trial assessed the efficacy and safety of oral semaglutide, administered according to an individualized and flexible dose-adjustment approach, compared with a fixed dose of sitagliptin (100 mg) for 52 weeks.²¹ Rather than the fixed-dose schedule used in the other PIONEER trials (after initial dose escalation), flexible dose adjustment was utilized, designed to mimic the individualized approach used in clinical practice, whereby

FIGURE 1. Overview of the Design and Baseline Patient Characteristics From the Global PIONEER Trials^{15-21,a,b}



A1C, glycated hemoglobin; met, metformin; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

^aAll trials shown here included a 2-week screening period and 5-week follow-up period (for those not continuing into the extension phase in PIONEER 7).

^bText in italics indicates permitted background medication for patients included in the trials.

^cOne patient was enrolled at 2 sites, so analyses were based on 821 patients.

the dose was increased or decreased depending on the patient's glycemic response and gastrointestinal tolerability.

Oral semaglutide was also evaluated in specific patient populations. Renal function is a consideration when choosing an additional glucose-lowering treatment. For example, renal excretion of DPP-4is (except linagliptin) necessitates dose adjustment in patients with renal dysfunction.³ In a pharmacokinetic study of oral semaglutide in patients with renal impairment, including end-stage renal disease, no clinically relevant change in semaglutide exposure was observed; therefore, no dose adjustment is recommended.^{12,23} The PIONEER 5 trial was conducted to explore the efficacy and safety of oral semaglutide 14 mg versus placebo in patients with T2D and moderate renal impairment (estimated glomerular filtration rate [eGFR], 30–59 mL/min/1.73 m²).¹⁷ In this trial, 60% of patients had an eGFR of 45 to less than 60 mL/min/1.73 m² and 40% had an eGFR of 30 to less than 45 mL/min/1.73 m²,¹⁷ whereas mean eGFR was at least 95 mL/min/1.73 m² in the PIONEER 1 to 4 and 7 trials,^{15,16,19–21} and 92 mL/min/1.73 m² in PIONEER 8.¹⁸ Atherosclerotic CVD (coronary heart disease, cerebrovascular disease, or peripheral arterial disease) is the leading cause of morbidity and death in patients with T2D, resulting in an annual cardiovascular (CV)-related expenditure of \$37.3 billion associated with diabetes.²⁴ The CV outcomes trial, PIONEER 6, assessed the effects of oral semaglutide versus placebo in patients with T2D at high risk of CV events,²² and is discussed in a separate article.²⁵

Oral semaglutide was initiated at a dose of 3 mg for all patients, before escalating to 7 mg after 4 weeks, and then to 14 mg after a further 4 weeks depending on the treatment arm.^{15–20} PIONEER 7 was an exception: patients were initiated at a 3-mg dose and after 8-week intervals the dose could then be increased or decreased, as described earlier.²¹ Patients were instructed to take oral semaglutide once daily in the morning on an empty stomach, with no more than 4 fl oz (120 mL) water, and to wait 30 minutes before consuming any food, further fluids, or any other oral medication.^{15–21} This is because a shorter delay may decrease semaglutide absorption.¹²

The primary and confirmatory secondary end points in most PIONEER trials were change from baseline in A1C level and body weight, respectively, at week 26 (Figure 1^{15–21}). An exception was PIONEER 7, in which the primary end point was the proportion of patients achieving the ADA-recommended target of an A1C level less than 7.0% (53 mmol/mol) at week 52.²¹ A1C and body weight outcomes were not evaluated for statistical difference to placebo in PIONEER 6,²² so results are not discussed herein.

How Does the Phase 3a Program of Oral Semaglutide Compare With That of Injectible Semaglutide?

Injectable once-weekly semaglutide was first approved by the FDA in 2017 to improve glycemic control in T2D,⁷ based on results from the SUSTAIN phase 3a clinical trial program. The global phase 3a

program for injectable semaglutide was conducted in 7215 participants across 6 trials: SUSTAIN 1, 4, and 5 for 30 weeks; SUSTAIN 2 and 3 for 56 weeks; and SUSTAIN 6 for 104 weeks.^{26–31} Following completion of the SUSTAIN 1 through SUSTAIN 6 trials, results from 4 phase 3b trials with injectable semaglutide (N=2868; SUSTAIN 7–10) were published.^{32–35}

Across the 6 SUSTAIN phase 3a trials, 2 doses of injectable semaglutide were evaluated (0.5 mg and 1.0 mg), except in SUSTAIN 3, where only semaglutide 1.0 mg was evaluated.^{26–31} Once-weekly injectable semaglutide was compared with placebo (SUSTAIN 1, 5, and 6) and the active comparators, sitagliptin (SUSTAIN 2), exenatide extended-release (SUSTAIN 3), and insulin glargine (SUSTAIN 4).

Similar to the PIONEER trials, the primary and confirmatory secondary end points of SUSTAIN 1 through SUSTAIN 5 were change from baseline in A1C level and body weight, respectively; unlike in PIONEER, the main efficacy outcomes were evaluated at the end of treatment (30 or 56 weeks).^{26–30} As with PIONEER, there was a dedicated CV outcomes trial, SUSTAIN 6, to assess the effects of injectable semaglutide versus placebo, for 104 weeks, in patients with T2D at high risk of CV events.³¹ Although patients with renal impairment were included in this trial, this patient population was not assessed in a separate phase 3 trial of injectable semaglutide.

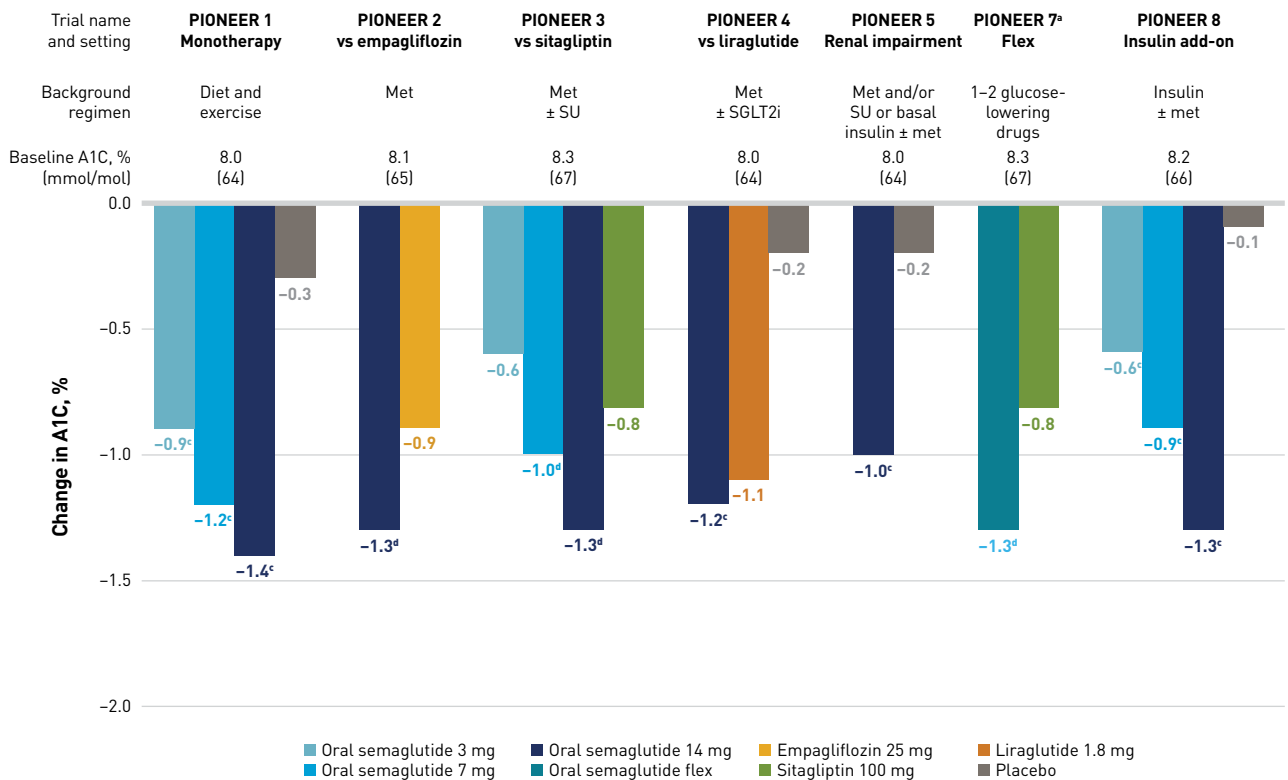
Efficacy and safety results from the phase 3 SUSTAIN program showed that once-weekly injectable semaglutide provided a highly efficacious treatment option for patients with T2D. Patients receiving semaglutide experienced consistently reduced A1C levels, greater body weight loss versus comparators, and benefited from a low risk of hypoglycemia and a similar overall safety profile with the GLP-1RA class.

Efficacy of Oral Semaglutide in the PIONEER Trials

The following key efficacy data are for the treatment policy estimand, which assessed the treatment effect for all patients randomized regardless of treatment discontinuation or use of rescue medication (patients receiving additional glucose-lowering medication initiated during the trial), and reflects the intention-to-treat principle.^{15–21} In the placebo-controlled PIONEER 1 and PIONEER 8 studies, oral semaglutide 3 mg showed superior reductions in A1C levels (–0.6% to –0.9%) and body weight (–1.4 kg to –1.5 kg), and a significantly greater proportion of patients achieved an A1C level less than 7.0% versus placebo ($P < .0001$).^{15,18} However, the 3-mg dose is intended for treatment initiation only, and the remainder of this section will focus on semaglutide 7 mg and 14 mg, which will be predominately utilized in clinical practice as the indicated doses used to maintain glycemic control.¹²

Glycemic Control

Results for A1C reductions from baseline in placebo- and active-controlled trials are shown in [Figure 2](#).^{15–21} In the PIONEER 1 trial,

FIGURE 2. Reduction in A1C Levels With Oral Semaglutide and Comparators at the Primary Analysis Time Point (26 Weeks, Except for PIONEER 7^{a,b})¹⁵⁻²¹

A1C, glycated hemoglobin; met, metformin; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea.

^aThe primary end point of PIONEER 7 was achievement of an A1C level <7.0% (53 mmol/mol) at week 52.

^bData in the figure are for the treatment policy estimand (regardless of study drug discontinuation or rescue medication).

^c $P < .05$ for the estimated treatment difference with oral semaglutide vs placebo.

^d $P < .05$ for the estimated treatment difference with oral semaglutide vs active comparator.

once-daily oral semaglutide monotherapy at 7 mg and 14 mg demonstrated superior improvements in A1C versus placebo at 26 weeks in patients with T2D insufficiently controlled with diet and exercise (estimated treatment difference [ETD]: -0.9% [7 mg], -1.1% [14 mg]; $P < .001$ for both).¹⁵ Similar findings were reported in PIONEER 4.¹⁶ In patients with uncontrolled T2D taking metformin with or without an SGLT2i, oral semaglutide 14 mg was superior to placebo in decreasing A1C levels at 26 weeks (ETD, -1.1%; $P < .0001$).¹⁶ In this trial, comparisons were also made to the injectable GLP-1RA, liraglutide. A1C reductions were similar with oral semaglutide 14 mg and injectable liraglutide 1.8 mg at 26 weeks (ETD, -0.1%; $P = .0645$).

In PIONEER 2, oral semaglutide 14 mg was superior to empagliflozin 25 mg at reducing A1C levels at 26 weeks (ETD, -0.4%; $P < .0001$) when used as second-line treatment in patients with uncontrolled T2D taking metformin.¹⁹ Oral semaglutide 7 mg and 14 mg also provided superior improvements in A1C levels versus

sitagliptin 100 mg at 26 weeks in PIONEER 3 (ETD, -0.3% [7 mg], -0.5% [14 mg]; $P < .001$ for both), which included patients with uncontrolled T2D on metformin with or without an SU.²⁰ The glucose-lowering effect of oral semaglutide was sustained with the 14-mg dose, and at 78 weeks, the ETDs for change from baseline in A1C level were -0.1% and -0.4% for oral semaglutide 7 mg and 14 mg, respectively, versus sitagliptin 100 mg ($P = .06$ [7 mg]; $P < .001$ [14 mg]).²⁰

When flexible dose adjustment was assessed in PIONEER 7, the supportive secondary efficacy end point, change from baseline in A1C level, showed that oral semaglutide resulted in greater reductions than sitagliptin 100 mg at 52 weeks (ETD, -0.5%; $P < .0001$). Of those patients receiving treatment at week 52, 30% and 59% were on the 7-mg and 14-mg doses, respectively.²¹

In PIONEER 8, which included patients with a more advanced stage of T2D who were receiving insulin (basal, basal-bolus, or premixed), oral semaglutide 7 mg and 14 mg reduced A1C level

TABLE. Summary of Other Main Efficacy Outcomes in the PIONEER Program^{15-21,ab}

Trial name and setting	Placebo-controlled trials										
	PIONEER 1 Monotherapy		PIONEER 4 vs placebo and liraglutide		PIONEER 5 Renal impairment		PIONEER 8 Insulin add-on				
Comparators	Oral semaglutide	Placebo	Oral semaglutide	Liraglutide	Placebo	Oral semaglutide	Placebo	Oral semaglutide	Placebo		
Dose, mg	3	7	14	14	1.8	14	14	14	3	7	14
Estimated mean reduction from baseline at 26 weeks	-1.5	-2.3	-3.7 ^c	-1.4	-3.1	-0.5	-3.4 ^c	-0.9	-1.4 ^c	-2.4 ^c	-3.7 ^c
Body weight, kg				-4.4 ^{c,d}							
Observed proportion of patients achieving thresholds at 26 weeks											
A1C level < 7%	55 ^c	69 ^c	77 ^c	31	62	14	58 ^c	23	28 ^c	43 ^c	58 ^c
Weight loss ≥ 5%	20	27 ^c	41 ^c	15	28	8	36 ^c	10	13 ^c	31 ^c	39 ^c

Trial name and setting	Active-controlled trials									
	PIONEER 2 vs empagliflozin		PIONEER 3 vs sitagliptin		PIONEER 4 vs placebo and liraglutide		PIONEER 7 ^a Flexible dose vs sitagliptin			
Comparators	Oral semaglutide	Empagliflozin	Oral semaglutide	Sitagliptin	Oral semaglutide	Liraglutide	Placebo	Oral semaglutide	Sitagliptin	
Dose, mg	14	25	3	7	14	14	100	14	100	
Estimated mean reduction from baseline at 26 weeks (except 52 weeks in PIONEER 7) ^a										
Body weight, kg	-3.8	-3.7	-1.2 ^d	-2.2 ^d	-3.1 ^d	-0.6	-4.4 ^{c,d}	-3.1	-0.5	-2.6 ^d
Observed proportion of patients achieving thresholds at 26 weeks (except 52 weeks in PIONEER 7) ^a										
A1C level < 7%	67 ^d	40	27	42 ^d	55 ^d	32	68 ^c	62	14	58 ^d
Weight loss ≥ 5%	41	36	13	19 ^d	30 ^d	10	44 ^{c,d}	28	8	27 ^d

A1C, glycosylated hemoglobin.

^aThe primary end point of PIONEER 7 was achievement of an A1C level < 7.0% (53 mmol/mol) at week 52.

^bData in this table are for the treatment policy estimand (regardless of study drug discontinuation or rescue medication).

^cP < .05 for the estimated treatment difference with oral semaglutide vs placebo.

^dP < .05 for the estimated treatment difference with oral semaglutide vs active comparator.

significantly more than placebo at week 26 (ETD, -0.9% [7 mg], -1.2% [14 mg]; $P < .0001$ for both), an effect that was sustained to week 52.¹⁸ At baseline, the overall mean total daily insulin dosage was 58 U/day. An insulin dose reduction of 20% was recommended when initiating oral semaglutide (unless clinically inappropriate), and the majority of patients (75.3%) achieved an insulin dose reduction of 15% to 25% during the 8-week study drug initiation period (8.4% had an insulin dose reduction $<15\%$ and 3.4% had a $>25\%$ reduction). Between weeks 8 and 26, insulin dose could be altered without exceeding the prerandomization dose, and was freely adjustable thereafter. By week 52, the total daily insulin was significantly reduced from baseline with oral semaglutide 7 mg and 14 mg by a mean of 6 units and 7 units, respectively, compared with an increase of 10 units with placebo ($P < .0001$ for both).¹⁸

PIONEER 5 included patients with moderate renal impairment on a range of different background medications, including insulin, and had an older study population compared with other trials (Figure 1¹⁵⁻²¹).¹⁷ Oral semaglutide 14 mg was significantly more effective than placebo in reducing A1C levels at week 26 (ETD, -0.8% ; $P < .0001$). The overall safety profile, including renal safety, was consistent with other GLP-1RAs, as discussed in the article on the safety of oral semaglutide.²⁵

Across the PIONEER studies, the proportion of patients achieving the ADA-recommended target of an A1C level less than 7.0% (53 mmol/mol) was consistently greater with oral semaglutide 7 mg (42%–69%) and 14 mg (55%–77%) than with placebo (7%–31%), and with active comparators, liraglutide 1.8 mg (62%), empagliflozin 25 mg (40%), and sitagliptin 100 mg (32%) (Table).¹⁵⁻²¹ This advantage was generally maintained or improved at the end of the trial (52 or 78 weeks).¹⁵⁻²¹ In PIONEER 7, where target achievement at week 52 was the primary end point, the proportion of patients with an A1C level less than 7.0% (53 mmol/mol) was more than twice as high with flexibly dosed oral semaglutide than with sitagliptin (58% vs 25%, respectively).²¹ This was despite 4 times as many patients in the sitagliptin group receiving rescue medication versus oral semaglutide (15.9% vs 3.2%, respectively) up to week 52.

Using data from the SUSTAIN and PIONEER trials, population pharmacokinetic and exposure–response analyses were used to investigate if the oral route of administration impacted the efficacy and tolerability of semaglutide when compared with injectable administration.³⁶ Although there was more variability in plasma concentrations for oral semaglutide than for the injectable formulation, there was overlap of the exposure ranges between the oral semaglutide 7 mg and 14 mg doses and the injectable semaglutide 0.5 mg and 1.0 mg doses. In addition, the results showed that the exposure–response relationships for efficacy and tolerability were similar, regardless of whether semaglutide was administered via injection or tablet.

Body Weight Reductions

Oral semaglutide was effective in reducing body weight across the continuum of T2D and with different background glucose-lowering medications (Table).¹⁵⁻²¹ Oral semaglutide 7 mg and 14 mg given as monotherapy reduced body weight versus placebo at 26 weeks in patients with early T2D managed with diet and exercise (ETD, -0.9 kg [7 mg] to -2.3 kg [14 mg]), with reductions reaching significance for the 14-mg dose ($P < .001$).¹⁵ Against the GLP-1RA, liraglutide 1.8 mg, oral semaglutide 14 mg provided a greater body weight reduction at week 26 (ETD, -1.2 kg; $P = .0003$), and this reduction was sustained to 52 weeks (ETD, -1.3 kg; $P = .0019$).¹⁶

In patients receiving background metformin in PIONEER 2, oral semaglutide 14 mg reduced body weight by 3.8 kg at 26 weeks, similar to the 3.7-kg reduction seen with empagliflozin 25 mg.¹⁹ Compared with sitagliptin 100 mg, oral semaglutide was associated with significantly greater reductions in body weight with the 7-mg and 14-mg doses at week 26 in PIONEER 3 (ETD, -1.6 kg [7 mg], -2.5 kg [14 mg]; $P < .001$ for both),²⁰ and when flexibly dosed for 52 weeks in PIONEER 7 (ETD, -1.9 kg; $P < .0001$).²¹

In patients with more advanced T2D receiving background insulin in PIONEER 8, patients receiving oral semaglutide 7 mg and 14 mg experienced significant reductions in body weight versus placebo at 26 weeks (ETD, -2.0 kg; $P = .0001$ [7 mg]; ETD, -3.3 kg; $P < .0001$ [14 mg]).¹⁸ In light of this, the authors suggested that oral semaglutide may help overcome some of the adverse effects associated with insulin use, such as weight gain, which may contribute to therapeutic inertia in the initiation or intensification of an insulin regimen.¹⁸ Oral semaglutide 14 mg also significantly reduced body weight versus placebo in patients with moderate renal impairment at 26 weeks (ETD, -2.5 kg; $P < .0001$).¹⁷

The proportion of patients achieving a weight loss of at least 5% was greater with oral semaglutide 7 mg (19%–27%) and 14 mg (30%–44%) versus placebo (3%–15%), and was greater with oral semaglutide 14 mg than the active comparators liraglutide 1.8 mg (28%), empagliflozin 25 mg (36%), and sitagliptin 100 mg (10%) (Table).¹⁵⁻²¹

Implications for Managed Care

Effective glycemic control has been associated with improved diabetes-related outcomes and reduced risk or delay of debilitating and costly complications.^{37,38} Studies have also shown improved glycemic control to be associated with lower health care costs. A collaborative endocrinologist-pharmacist diabetes intense medical management approach demonstrated greater A1C reductions versus usual primary care physician management (-2.4% vs -0.8% at 6 months; $P < .001$). Using data from April 2009 to November 2013, the estimated mean 3-year cost difference per patient due to improved A1C levels, from a health system perspective, was \$8793 with diabetes intense medical management versus \$3506 with a primary care physician.³⁷ In addition, a separate study determined

that decreases in A1C levels versus no change were associated with 24% (\$2503) and 17% (\$1690) lower average annual health care costs during the first and second year follow-ups, respectively.³⁸

The PIONEER program established oral semaglutide as providing effective glycemic control across a range of different patient populations receiving different background medications at different stages of the disease trajectory. With oral semaglutide 14 mg, the magnitude of A1C reductions (1.0%-1.3%) and the proportion of patients achieving an A1C level less than 7% (55%-77%) were similar to injectable liraglutide, and higher than empagliflozin and sitagliptin at 26 weeks.^{16,19-21} Furthermore, data indicate that the glucose-lowering effect of oral semaglutide was sustained up to 52 weeks (PIONEER 2, 3, and 7),^{16,19,21} and 78 weeks (PIONEER 3).²⁰ Considering these results, oral semaglutide offers an efficacious treatment option, with comparable outcomes to injectable GLP-1RAs, that can be taken in tablet form. Thus, oral semaglutide enables potentially greater accessibility to a larger number of patients across the diabetes treatment continuum. An evaluation of the cost per patient achieving treatment targets with oral semaglutide was conducted across the active comparator PIONEER trials.³⁹ Oral semaglutide was consistently associated with a lower annual cost of control versus active comparators (liraglutide 1.8 mg, empagliflozin 25 mg, and sitagliptin 100 mg) when analyzing 4 different end points (A1C level \leq 6.5%: \$6996-\$15,036 lower cost; A1C level $<$ 7%: \$346-\$4497 lower cost; \geq 1.0%-point A1C reduction and weight loss \geq 3.0%: \$525-\$32,277 lower cost; and A1C level $<$ 7.0% without hypoglycemia and without weight gain: \$1255-\$7510 lower cost).³⁹

Some treatments for T2D are associated with weight gain (eg, TZDs, insulin, and SUs) or are weight neutral (eg, DPP-4is), whereas GLP-1RAs and SGLT2is are associated with weight loss.^{2,3} In the PIONEER trials, oral semaglutide 14 mg was associated with greater weight loss than sitagliptin and liraglutide, and equivalent weight loss to empagliflozin at week 26, with reductions up to 4.4 kg, depending on the study.^{16,19-21} Therefore, oral semaglutide can offer multidimensional benefits to patients, such as aiding weight loss while still providing effective glycemic control. The ADA glycemic treatment guidelines recommend a preference for therapies offering weight loss, such as GLP-1RAs,² and weight loss in patients with T2D could also decrease their risk of developing comorbidities, such as CVD, and reduce the annual associated cost implications.²³

Given the prominent position of GLP-1RAs in the treatment of T2D according to US recommendations, the availability of oral semaglutide may open up the GLP-1RA class for patients and prescribers with a preference for oral versus injectable therapy, and may lead to their earlier use in the diabetes treatment trajectory. ■

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