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REVIEW

Oral Semaglutide: A Review of the First Oral Glucagon-Like Peptide 1 Receptor Agonist

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Abstract

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are highly effective at lowering hemoglobin A1c (HbA1c) and facilitating weight loss. Four agents in the GLP-1 RA class, albiglutide, liraglutide, dulaglutide, and semaglutide, also have cardioprotective effects. However, subcutaneous administration of these agents remains a major reason for their underutilization. A new coformulation of semaglutide with sodium N-[8-(2-hydroxybenzoyl) amino caprylate (SNAC) is the first oral GLP-1 RA reviewed by the U.S. Food and Drug Administration (FDA). The SNAC technology prevents destruction of semaglutide in the stomach and facilitates transcellular absorption through the gastric membrane enabling semaglutide to reach systemic circulation intact. The oral formulation of semaglutide was studied in the PIONEER trials, demonstrating similar efficacy to the presently available GLP-1 RAs with regard to HbA1c lowering and weight loss. Although the PIONEER 6 trial suggests positive effects on cardiovascular mortality with oral semaglutide, these benefits may not fully be appreciated until the completion of the SOUL trial.

Keywords: Oral GLP-1 receptor agonists, SNAC technology, PIONEER trials, Semaglutide.

Introduction

As of 2017, more than 30 million Americans are living with diabetes and the prevalence is expected to increase to 60.6 million by 2060.[1,2] Type 2 diabetes mellitus (T2DM) accounts for 90%–95% of these diagnoses. Improved understanding of the pathophysiology of T2DM has led to the development of new drugs targeting these disease pathways.

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are synthetically modified peptides similar to endogenous GLP-1. These agents target the incretin system, which is often defective in patients with T2DM.[3–5] In 2005, the first GLP-1 RA, exenatide, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of T2DM. Since then, six additional GLP-1 RAs entered the market, including four once-weekly subcutaneous products (albiglutide, dulaglutide, exenatide extended release and semaglutide).

Not only do GLP-1 RAs provide significant reductions in hemoglobin A1c (HbA1c) and body weight with little risk of hypoglycemia, several have also been shown to improve cardiovascular outcomes, especially in patients with established atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD). Emerging data with these agents also suggest improvements in renal outcomes.[6] Given these benefits, the American Diabetes Association (ADA) 2019 Standards of Medical Care in Diabetes prefer GLP-1 RAs as a second-line option after metformin therapy in patients with ASCVD or CKD. In addition, GLP-RAs are now preferred before initiating basal insulin therapy in patients with an HbA1c below 11%.[6]

Despite the many benefits of GLP-1 RAs, subcutaneous administration remains a barrier to initiating therapy. Past attempts to develop oral peptide formulations failed due to poor absorption and degradation in the stomach. However, a new coformulation of semaglutide and sodium N-[8-(2-hydroxybenzoyl) amino]caprylate (SNAC) may overcome these barriers. The purpose of this review is to describe the mechanism of SNAC and to examine the present data regarding the first oral GLP-1 RA, semaglutide, to determine its potential therapeutic role.

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Structure

The structure of semaglutide is similar to native human GLP-1, a 30 amino acid peptide with the exception of three structural modifications.[7,8] The amino acid substitution from alanine to alpha-aminoisobutyric acid at position 8 makes semaglutide resistant to systemic degradation by dipeptidyl peptidase-IV (DPP-IV). The second change is the addition of an 18-length carbon chain and spacer to lysine at position 26, which increases albumin binding.[7] Since albumin has a half-life of several weeks, increasing the binding affinity to albumin increases the half-life of semaglutide by preventing renal elimination.[7] The third change is an amino acid substitution at position 34 from lysine to arginine, which is thought to enhance the stability of semaglutide by limiting acylation options for the remaining lysine in the molecule.[7] Together, these structural changes provide a potent and long-acting GLP-1 analog.

Absorption Enhancing Mechanism of SNAC Technology

Historically, oral delivery of peptide-based drugs was limited by several properties leading to poor bioavailability.[8] Peptides are large in size and hydrophilic.[9] These molecules, particularly macromolecules with a molecular weight above 1000 Da, do not diffuse across the phospholipid bilayer of the intestinal membranes via passive diffusion or carrier-mediated transcellular transport. These factors increase the time spent in the gastrointestinal (GI) tract, leaving peptides susceptible to pH and enzymatic degradation in the stomach and intestines.[9] To overcome these challenges, semaglutide is noncovalently associated with SNAC as an oral absorption enhancer to prevent enzyme degradation and facilitate absorption.[8,10]

The effects of SNAC on semaglutide absorption are complex (Fig. 1). Coformulation with SNAC addresses the main problem with oral peptide administration, presystemic enzymatic degradation.[8] By exerting buffering action in the stomach, SNAC decreases the efficacy of digestive enzymes.[8] Pepsin, the primary digestive enzyme, has optimal activity between a pH of 2–4 and its activity decreases with increasing pH. The buffering effect of SNAC is localized near the site of tablet erosion, which protects semaglutide from pepsin degradation.[8]

Preventing breakdown of semaglutide by pepsin only protects the structure of the molecule; however, there is still the potential problem with absorption of a large hydrophilic molecule across the gastric membrane. Surrounding semaglutide with hydrophobic SNAC molecules increases the lipophilicity of semaglutide.[8] Once SNAC is incorporated

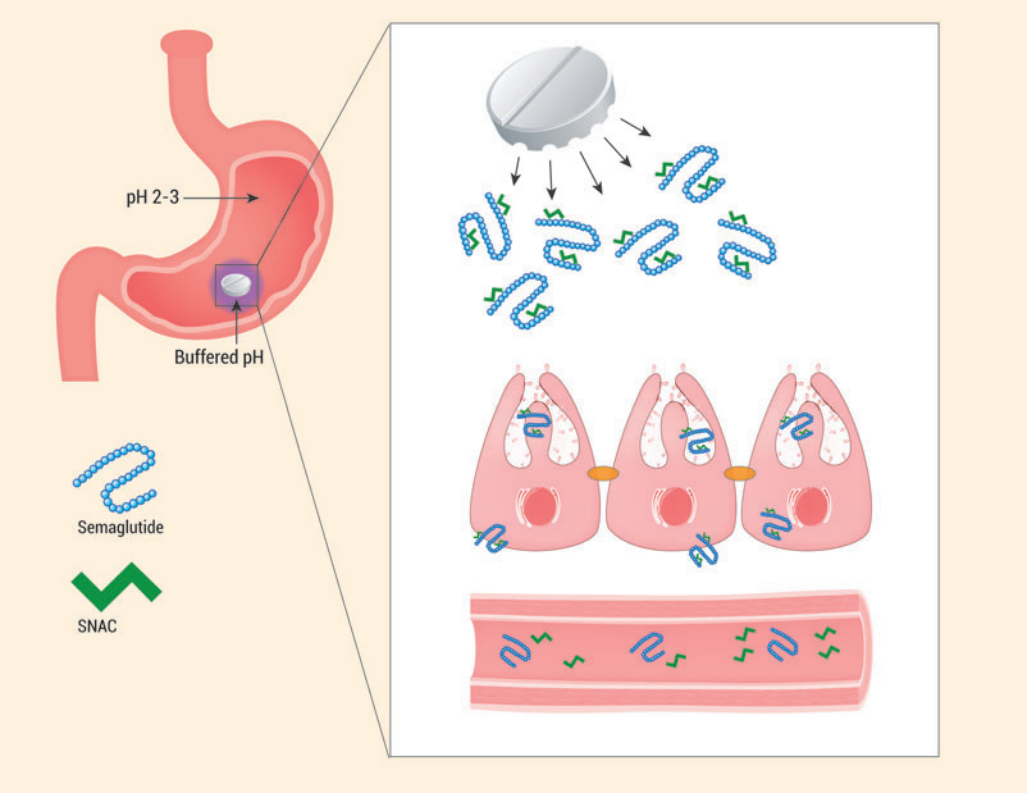

FIG. 1. Absorption mechanics of oral semaglutide coformulated with SNAC. A schematic depicting oral semaglutide coformulated with SNAC in tablet form undergoing dissolution and absorption in the stomach. As the tablet erodes in the stomach, semaglutide and SNAC are released. SNAC exerts a local buffering effect, depicted as the cloudy area around the tablet. The buffering effect protects semaglutide from degradation by the stomach enzyme, pepsin. Without pepsin-induced peptide destruction in the stomach, semaglutide stays weakly and noncovalently associated with SNAC molecules as it travels transcellularly across the gastric membrane. Once SNAC and semaglutide reach systemic circulation, the two molecules disassociate.[8] SNAC, sodium N-[8-(2-hydroxybenzoyl amino]caprylate. Color images are available online.

into the gastric epithelium, it fluidizes the lipid membrane facilitating semaglutide transport and entry into the systemic circulation.[8] When semaglutide and SNAC reach the bloodstream, the two molecules readily dissociate, allowing oral semaglutide to interact with the body in the same manner as subcutaneous semaglutide (Fig. 1).[8]

Pharmacokinetics

Absorption

Most oral medications are absorbed in the intestines; however, semaglutide is completely absorbed in the stomach.[8] The degree of semaglutide absorption is dependent on the quantity of SNAC coformulated with it.[8] Pharmacokinetic studies show 300 mg of SNAC produces the highest semaglutide plasma concentrations.[8] On ingestion in animal studies, the highest concentrations of both semaglutide and SNAC were noted at the site of absorption in the stomach. With increasing distance from the site of absorption, both semaglutide and SNAC concentrations decreased. Only half the concentrations of each are detected at 3 cm from the tablet, while negligible amounts are observed at 6 cm.[8] These results are consistent with the localized buffering effect of SNAC. In addition, these data confirm that complete tablet erosion and absorption occur in the stomach, and reinforce the need to coformulate semaglutide with SNAC instead of simply coadministering each compound.[8]

The bioavailability of oral semaglutide is lower compared with the subcutaneous formulation.[11,12] In addition, interindividual absorption variability may also occur with oral semaglutide.[13] To compensate for these differences, higher doses of oral semaglutide are administered to achieve the same clinical results as the subcutaneous formulation.[11,12] A comparison of pharmacokinetic parameters of both formulations is provided in Table 1.

Because SNAC protects semaglutide from pH-dependent degradation and the consumption of food leads to an increase in gastric pH, the effect of food and water on systemic semaglutide exposure was investigated. Semaglutide absorption was compared in a fed group that ate 30 min before dosing, a fasting group that did not eat until 4 h postdosing, and a reference group that ate 30 min postdosing.[8] The fed group experienced significantly lower systemic semaglutide exposure after the 10th dose, whereas both the fasting and reference groups achieved therapeutic concentrations.[8] Two volumes of water (50 and 120 mL) consumed with semaglutide 10 mg/SNAC 300 mg were also examined.[14] Neither amount of water made significant differences on the pharmacokinetic parameters of oral semaglutide, but it is important to note that most dosing trials typically required consumption of at least 50 mL of water with each study dose.[14] Based on these studies, food intake affects semaglutide pharmacokinetics to a larger extent than water consumption; therefore, patients should be fasting before administration and avoid food at least 30 min postdose for optimal results.[8]

Table 1. Pharmacokinetics of Oral and Subcutaneous Semaglutide[11,12,16]

Parameter	*Oral semaglutide*	*Subcutaneous semaglutide*
AUC (nmol × h/L)	284	3026
Cmax (nM)	15	10
Tmax (h)	1	66
$T_{1/2}$ (h)	152	168

AUC, area under the curve; Cmax, maximum plasma concentration; Tmax, time to reach Cmax; $T_{1/2}$, terminal half-life.

Metabolism and excretion

Semaglutide is primarily metabolized via proteolytic cleavage of the peptide backbone by DPP-IV and neutral endopeptidases and sequential beta-oxidation of the fatty diacid side chain.[15] These degradation products are then excreted in the urine and feces, suggesting potential renal and hepatic involvement.[15,16] However, pharmacokinetic studies show that the addition of 300 mg of SNAC to oral semaglutide displayed similar pharmacokinetic properties to the subcutaneous formulation regardless of the severity of renal or hepatic impairment (Table 1).[11–12,17]

Drug/drug interactions

Because oral semaglutide absorption depends on localized SNAC buffering, coadministration with other agents represents the potential for drug/drug interactions. Omeprazole, lisinopril, warfarin, metformin, digoxin, the combined oral contraceptive ethinyl estradiol/levonorgestrel, rosuvastatin, and furosemide have all been evaluated for drug interactions with semaglutide. None of these agents significantly affected oral semaglutide concentrations.[18–21]

Clinical Trials

Oral semaglutide was studied in 10 phase 3a clinical trials as part of the PIONEER program, which enrolled 8845 people with T2DM. Based on new regulatory guidance, the PIONEER trials performed two analyses on primary and secondary endpoints.[22–27] The primary statistical approach, a treatment policy estimand, evaluated the effect of treatment regardless of discontinuation of treatment or initiation of rescue medication (i.e., intent-to-treat approach). This approach is used to determine how effective the drug will be at a population level, which differs from the secondary statistical approach.

The secondary statistical approach, also referred to as the trial product estimand or on-treatment principle, focuses on an individual level for clinicians and patients. This secondary approach evaluates the treatment effect while on treatment and without the use of rescue medication.[22] This review focuses on the peer-reviewed data for the PIONEER program using the primary statistical approach or the trial policy estimand, since it is the traditional standard for clinical trials.

Published PIONEER Studies

Monotherapy

PIONEER 1 was a phase 3a, double-blinded, randomized controlled trial that evaluated the change in HbA1c at 26 weeks with placebo compared with oral semaglutide at doses of 3 mg, 7 mg, and 14 mg in 703 patients with untreated T2DM. Despite the assigned semaglutide dose in the active arms, all patients were started on 3 mg once daily and titrated

up to the next dose every 4 weeks. The confirmatory secondary efficacy endpoints included change in weight from baseline to week 26.[22]

All three doses of semaglutide were superior to placebo for change in HbA1c at 26 weeks. The changes in HbA1c for the semaglutide arms were –0.9% for 3 mg, –1.2% for 7 mg, –1.4% for 14 mg, and –0.3% for placebo. Unlike HbA1c lowering, changes in body weight were only statistically significant for the 7 and 14 mg doses. The changes in body weight for the semaglutide doses were –1.5 kg for 3 mg, –2.3 kg for 7 mg, –3.7 kg for 14 mg, and –1.4 kg for placebo. Furthermore, all semaglutide doses had a statistically significant greater proportion of patients compared with placebo of achieving an HbA1c of <7% without hypoglycemic episodes and body weight gain, in addition to an HbA1c reduction of ≥1% and a body weight loss of ≥3%.[22]

Semaglutide compared with DPP-IV inhibitors

PIONEER 3, a 78-week, randomized multinational trial that compared the efficacy and safety of oral semaglutide 3, 7, and 14 mg with sitagliptin 100 mg in 1864 people with uncontrolled T2DM on metformin, with or without a sulfonylurea. Patients in the semaglutide arms were started on 3 mg and titrated every 4 weeks until they reached their target dose. The primary endpoint was HbA1c change from baseline to week 26, and the confirmatory secondary outcome was change in body weight from baseline at 26 weeks.[23]

The mean change in HbA1c achieved statistical significance for oral semaglutide doses 7 and 14 mg at week 26. The changes in HbA1c from baseline to 26 weeks for the semaglutide doses were –0.6% for 3 mg, –1% for 7 mg, –1.3% for 14 mg, and –0.8% for sitagliptin. A statistically significant greater proportion of patients also achieved an HbA1c target of <7% at 26 weeks in the oral semaglutide 7 mg (42%) and 14 mg (55%) arms compared with 32% of patients treated with sitagliptin.

Similar to the change in HbA1c, the confirmatory secondary endpoint of change in weight at 26 weeks achieved statistical significance with oral semaglutide 7 and 14 mg doses compared with sitagliptin. The changes in body weight at 26 weeks were –1.2, –2.2, –3.1, and –0.6 kg for semaglutide doses 3, 7, and 14 mg, and sitagliptin, respectively. Overall, compared with sitagliptin, oral semaglutide 7 and 14 mg treatment arms were more likely to achieve two secondary endpoints that summarize results of the trial, including a body weight loss of ≥5% and a target HbA1c <7.0% without hypoglycemia and without weight gain.[23]

Sitagliptin 100 mg was again the comparator agent in PIONEER 7, a 52-week, open-label multinational trial designed to evaluate the efficacy and safety of oral semaglutide in 504 people with uncontrolled T2DM on one to two oral antidiabetic medications. Unlike PIONEER 3 where semaglutide was increased every 4 weeks based on the treatment dose assigned, all patients in the semaglutide arm of PIONEER 7 initially started on 3 mg and underwent dose adjustments based on the patient's HbA1c and GI tolerability. The dosing regimen was referred to as a ''flexible dosing schedule''; however, dose increases were still required to wait a minimum of 8 weeks. The primary outcome of PIONEER 7 was achievement of HbA1c <7% at 52 weeks, and the confirmatory secondary outcome was change in body weight at 52 weeks.[24]

The mean HbA1c for patients at baseline in PIONEER 7 was 8.3%. Both HbA1c reduction and weight loss at 52 weeks were statistically significantly greater in the semaglutide-treated patients (–1.3%; –2.6 kg) compared with the sitagliptin group (–0.8%; –0.7 kg). A greater proportion of patients in the oral semaglutide arm (58% [odds ratio: 4.40, 95% CI: 2 · 89–6 · 70; $P < 0.0001$]) achieved the primary endpoint of HbA1c target <7% compared with 28% of people in the sitagliptin group. It is important to note the final doses at the end of 52 weeks in the oral semaglutide arm as they relate to the trial results. At the end of the trial, 9% of patients were receiving 3 mg, 30% were receiving 7 mg, and 59% were receiving 14 mg of semaglutide in the active arm.[24]

Semaglutide compared with other GLP-1 RAs

PIONEER 4 was a 52-week randomized trial evaluating the efficacy and safety of oral semaglutide 14 mg compared with liraglutide 1.8 mg and placebo in 711 people with uncontrolled T2DM on metformin, with or without an sodium-glucose cotransporter type 2 (SGLT-2) inhibitor. Patients were assigned to semaglutide 14 mg, liraglutide 1.8 mg, or placebo. Those assigned to semaglutide were started on 3 mg and increased every 4 weeks until they reached the maximum tolerated dose or 14 mg. In the liraglutide arm, patients started on 0.6 mg and increased weekly until they reached the maximum tolerated dose or 1.8 mg. The primary endpoint was HbA1c change from baseline to week 26, and the confirmatory secondary outcome was change in body weight from baseline at 26 weeks.[25]

Oral semaglutide was noninferior compared with liraglutide and superior compared with placebo at 26 weeks for the primary endpoint. The changes in HbA1c at 26 weeks among the treatment groups were –1.2%, –1.1%, and –0.2% for semaglutide, liraglutide, and placebo, respectively. However, at 52 weeks, the HbA1c change from baseline was superior for semaglutide (–1.2%) compared with liraglutide (–0.9%). For the changes in body weight at 26 weeks, semaglutide was superior compared with liraglutide and placebo with reductions of 4.4, 3.1, and 0.5 kg, respectively.[25]

Cardiovascular outcomes

PIONEER 6 was a phase 3a, randomized, placebo-controlled cardiovascular outcome trial (CVOT) designed to assess the cardiovascular safety of oral semaglutide 14 mg versus placebo in 3183 patients. Importantly, this trial was not designed to evaluate the superiority of oral semaglutide at reducing cardiovascular events or death. The primary outcome was the time to first major adverse cardiovascular event (MACE), which was defined as the first occurrence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. Patients were eligible if they were ≥50 years with established cardiovascular or kidney disease or ≥60 years with risk factors.

A noninferior 21% relative risk reduction in MACE was observed in the semaglutide arm hazard ratio (HR) 0.79 [95% CI: 0.57–1.11]. Statistically significant reductions in cardiovascular mortality and all-cause mortality were the primary drivers of the primary endpoint. Patients in the semaglutide arm experienced a 51% relative risk reduction in cardiovascular mortality (HR: 0.49; 95% CI: 0.27–0.92) and 49% relative risk reduction in all-cause mortality (HR: 51; 95%

CI: 0.31–0.84). Other secondary endpoints, including nonfatal MI HR 1.18 [95% CI: 0.73–1.9] and nonfatal stroke HR 0.74 [95% CI: 0.35–1.57], did not reach statistical significance.[26]

Chronic kidney disease

PIONEER 5 was a phase 3a, 26-week, randomized multinational trial comparing the efficacy of oral semaglutide 14 mg with placebo in 324 people with uncontrolled T2DM and moderate renal impairment defined as estimated glomerular filtration rate (GFR) of 30–59 mL/min/1.73 m^2. At baseline, patients were on metformin with or without a sulfonylurea or basal insulin. The primary endpoint was HbA1c change from baseline to week 26, and the confirmatory secondary outcome was change in body weight from baseline to 26 weeks.[27]

Oral semaglutide was superior for both HbA1c and weight changes at 26 weeks compared with placebo. The changes in HbA1c and weight at 26 weeks were −1% and −3.4 kg for the semaglutide arm; whereas the changes for the placebo arm were –0.2% and –0.9 kg. A composite outcome of HbA1c <7% without hypoglycemia or weight gain at 26 weeks was also better in the semaglutide arm with 51% of patients attaining it, while only 17% of those given placebo were able to reach it.[27]

Progression of kidney disease and change in blood pressure were also evaluated. No significant changes in renal function based on GFR were observed between groups. However, the geometric mean urine albumin creatinine (baseline UACR/26 week UACR) decreased in the semaglutide arm during the trial, while the placebo group increased. At 26 weeks, the geometric mean UACRs for semaglutide were 0.86 [range: 0.04–56.71] and 1.19 [range: 0.01–79.59] for the placebo arm. The decrease in albuminuria was accompanied by decreases in the systolic and diastolic blood pressures in the semaglutide arm. Systolic and diastolic blood pressure changed by −7 and −2 mm Hg in the semaglutide group, respectively. The placebo group had no change in systolic blood pressure and an increase by 1 mm Hg for diastolic blood pressure.[27]

Unpublished PIONEER Studies

Four trials from the PIONEER program remain unpublished.[28–31] While data are available from the manufacturer, they have not undergone peer review and may change on publication. It is important to note that the manufacturer of oral semaglutide only reports unpublished data using the secondary statistical approach or the trial product estimand; therefore, the following section reports outcome data in this manner. Furthermore, all PIONEER trials, listing the change in HbA1c and weight at 26 weeks, have data available based on the trial product estimand and is the only present way to compare outcomes throughout the PIONEER program. A complete overview of these outcomes is available in Table 2 to fully summarize the results for HbA1c and weight change at 26 weeks.

Table 2. Pioneer Trial Outcomes for Reductions in HbA1c and Weight at 26 Weeks

Trial	*Study design*	*Study duration (weeks)*	*Number of patients*	*Background therapy*	*Treatment arms*	*Change in baseline HbA1c (%)*	*Change in baseline weight (kg)*
PIONEER 1[22]	RCT, DB	26	703	Diet/exercise only	Semaglutide 3 mg	–0.8	–1.7
					Semaglutide 7 mg	–1.3	–2.5
					Semaglutide 14 mg	–1.5	–4.1
					Placebo	–0.1	–1.5
PIONEER 2[28]	RCT, OL	52	816	Metformin	Semaglutide 14 mg	–1.4	–4.2
					Empagliflozin 25 mg	–0.9	–3.8
PIONEER 3[23]	RCT, DB	78	1864	Metformin ± sulfonylurea	Semaglutide 3 mg	–0.5	–1.2
					Semaglutide 7 mg	–1.1	–2.2
					Semaglutide 14 mg	–1.4	–3.3
					Sitagliptin 100 mg	–0.8	–0.7
PIONEER 4[25]	RCT, DB	52	711	Metformin ± SGLT-2 inhibitor	Semaglutide 14 mg	–1.3	–4.7
					Liraglutide 1.8 mg	–1.1	–3.2
					Placebo	–0.1	–0.7
PIONEER 5[27]	RCT, DB	26	324 with moderate renal impairment (GFR 30–59 mL/min/1.73 m^2)	Metformin, sulfonylurea, basal insulin, or combination	Semaglutide 14 mg	–1.1	–3.7
					Placebo	–0.1	–1.1
PIONEER 8[31]	RCT, DB	52	731	Insulin ± metformin	Semaglutide 3 mg	–0.5	–1
					Semaglutide 7 mg	–0.8	–2.9
					Semaglutide 14 mg	–1.2	–4.3
					Placebo	0	0.6
PIONEER 9[29]	RCT, OL	52			Semaglutide 3 mg	–1.1	N/A
					7 mg	–1.5	N/A
					14 mg	–1.7	N/A
					Liraglutide 0.9 mg	–1.4	N/A
					Placebo	–0.1	N/A

Outcomes based on the trial product or secondary analysis estimand.
GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; N/A, data not available.

Semaglutide compared with SGLT-2 inhibitor

PIONEER 2 was a 52-week, randomized, open-label multinational trial that evaluated the efficacy of oral semaglutide 14 mg compared with empagliflozin 25 mg in 816 people with uncontrolled T2DM on metformin. The primary endpoint was HbA1c change from baseline to week 26, and the confirmatory secondary outcome was change in body weight from baseline at 26 weeks. Individuals randomized to oral semaglutide experienced an average HbA1c reduction of 1.4% at 26 weeks (Table 2) and 1.3% at 52 weeks compared with an HbA1c reduction of 0.9% at 26 weeks (Table 2) and 0.8% at 52 weeks with empagliflozin. More patients achieved the HbA1c target of <7% with oral semaglutide 14 mg (72%) compared with empagliflozin 25 mg (47%). The secondary endpoint for weight reduction was similar with oral semaglutide (−4.2 kg) compared with empagliflozin (−3.8 kg) at 26 weeks (Table 2). However, at 52 weeks, the mean weight change continued to increase in the oral semaglutide group and reached superiority over the empagliflozin group. The empagliflozin arm exhibited a sustained 3.8 kg weight reduction at 52 weeks.[28]

Semaglutide compared with GLP-1 RAs

Liraglutide was studied as the comparator agent again in the PIONEER 9 trial. PIONEER 9 was a 52-week, randomized, double-blinded, open-label, phase 3 safety and efficacy trial in Japanese patients with uncontrolled T2DM managed with lifestyle or one antidiabetic drug. It was designed similar to PIONEER 4, but with a lower maximum allowable dose of 0.9 mg for liraglutide. The five treatment arms were oral semaglutide 3, 7, 14 mg, liraglutide 0.9 mg, and placebo.

A statistically significant reduction in HbA1c of 1.7% was observed with oral semaglutide 14 mg compared with 1.4% with liraglutide at 26 weeks (Table 2). However, the 3 and 7 mg doses did not reach superiority compared with the liraglutide arm with HbA1c reductions of 1.1% and 1.5%, respectively (Table 2). Weight reduction at 26 weeks was not reported; however, the 52-week reduction was superior for oral semaglutide 14 mg with a change of −2.8 kg compared with 0.4 kg gain for liraglutide. All semaglutide doses were superior for both HbA1c and weight reductions compared with placebo.[29]

PIONEER 10 was a phase 3a, randomized open-label trial in Japanese patients comparing oral semaglutide 3, 7, and 14 mg with dulaglutide 0.75 mg in people with T2DM inadequately controlled on one oral antidiabetic agent. The primary objective of this study was to compare safety between GLP-1 RAs; however, efficacy data are available for HbA1c and weight changes from baseline to 52 weeks. A statistically significant reduction in HbA1c of 1.8% was observed with oral semaglutide 14 mg compared with 1.3% with dulaglutide at 52 weeks. However, the 3 and 7 mg doses were not statistically superior compared with the dulaglutide arm with HbA1c reductions of 0.7% and 1.4%, respectively. Weight loss from baseline was only statistically superior for the 14 mg dose of semaglutide with a mean weight change of −1.9 kg compared with 1.1 kg gain for dulaglutide 0.75 mg at 52 weeks.[30]

Comparison with insulin therapy

PIONEER 8 was a 52-week, phase 3a, randomized multinational trial comparing oral semaglutide 3, 7, and 14 mg with placebo in 731 people with T2DM on insulin therapy and metformin. No restrictions on the insulin regimen were placed for patients enrolling in PIONEER 8. Insulin dose escalation was not allowed during the first 26 weeks, but adjustments did occur during the final 26 weeks of the 52-week trial.

At 26 weeks, all doses of oral semaglutide were superior to placebo for both HbA1c and weight change from baseline (Table 2). The HbA1c reduction observed among the treatment arms was 0.6% for 3 mg, 1% for 7 mg, and 1.4% for 14 mg of oral semaglutide compared with no change in the placebo arm. Patients treated with 7 and 14 mg of semaglutide also experienced a statistically significant change in the insulin dose of −6 and −7 units, respectively, compared with a 10-unit increase in the placebo arm.[31]

Safety outcomes

The primary adverse effects (AEs) reported in the PIONEER trials were GI related. Nausea tended to be transient, mild, or moderate and occurring during the dose titration phase. The largest discontinuation rates throughout the PIONEER program occurred consistently with the 14 mg dose confirming a dose-related GI effect. Overall, nausea rates occurred in ~15%–20% of patients treated with oral semaglutide; however, this led to only a small increase in discontinuations compared with other active drug arms, including liraglutide.[22–23,25]

To minimize these GI effects, dose escalation of oral semaglutide occurred at 4 weeks or longer intervals. PIONEER 7 also attempted to study a flexible dosing protocol, but GI-related discontinuation rates for oral semaglutide were similar, occurring in 6% of patients in PIONEER 7 and in 6.9% of patients in PIONEER 3.[23–24] No safety signals for other important outcomes, including hypoglycemia, acute kidney injury diabetic retinopathy, or pancreatitis, occurred compared with placebo.[22]

Discussion

Oral semaglutide efficacy and safety outcome data are similar to the subcutaneous formulation of semaglutide and other drugs in the GLP-1 RA class, but without the injection burden to patients. In the PIONEER trials, the maximum HbA1c and weight reduction observed over 26 weeks were 1.7% and 4.7 kg, respectively.[25,29] The degree of response to therapy was dose related. Semaglutide at 3 mg provides a less robust lowering of HbA1c and weight compared with the 14 mg dose. As seen with all GLP-1 RAs, the predominant AEs reported thus far are GI related, primarily mild to moderate nausea; however, only a small proportion of patients in the PIONEER trials required discontinuation indicating that oral semaglutide is well tolerated in most patients.[22–31]

Comparison of oral semaglutide with other GLP-1 RAs

When compared directly with liraglutide and dulaglutide, oral semaglutide was noninferior at lowering HbA1c at 26 weeks, but reached superiority at 52 weeks with the 14 mg dose.[25,30] This likely reflects a slow titration phase causing a delay in reaching its maximum effect. The minor improvement in efficacy with oral semaglutide 14 mg was accompanied by a small increase in GI AEs compared with both GLP-1 RA agents. Weight loss was only superior with the 14 mg dose of oral

semaglutide when compared head to head with liraglutide and dulaglutide. Although not compared directly, subcutaneous semaglutide reported slightly better maximum reductions in HbA1c and weight of 1.7% and 6 kg, respectively.[11] Like other drugs in the GLP-1 RA class, initiation of oral semaglutide at a low dose followed by gradual titration will result in the best combination of tolerability and efficacy.

Comparison of oral semaglutide with other oral antihyperglycemic therapies

Head to head trials show superiority with oral semaglutide over sitagliptin 100 mg and empagliflozin 25 mg relating to HbA1c reduction and weight loss. The ADA standards state that agents in the DPP-IV and SGLT-2 inhibitor classes are expected to reduce HbA1c by 0.5%–0.9%, whereas GLP-1 RAs lower HbA1c by 1%–1.5%.[6] With regard to weight, SGLT-2 inhibitors have also shown the propensity to facilitate weight loss in patients with T2DM, but greater effects are associated with subcutaneous semaglutide.[32] Alternatively, DPP-IV inhibitors are considered ''weight neutral'' and were not expected to provide superior results for weight loss compared. Therefore, the PIONEER studies are really confirmatory trials that establish oral semaglutide ability to provide improved metabolic outcomes compared with other common oral antidiabetic agents.[23–24,28]

Cardiovascular outcomes

Initial results from the PIONEER program clearly suggest that oral semaglutide is highly effective at improving glycemic and weight outcomes, but its cardiovascular benefit remains unclear. The PIONEER 6 trial demonstrated impressive reductions in cardiovascular and all-cause mortality, but failed to meet superiority criteria for the primary outcome of MACE.[26] In SUSTAIN-6, subcutaneous semaglutide reported the opposite results of PIONEER 6.[26,33] Subcutaneous semaglutide met its primary endpoint of reduction in MACE, but the secondary outcomes of cardiovascular death and all-cause mortality were noninferior to the standard-of-care arm. To further complicate the findings, the attainment of the primary endpoint in SUSTAIN-6 was largely driven by reduction in MI and nonfatal stroke, whereas PIONEER 6 results trended toward a higher rate of MI and a smaller reduction in nonfatal stroke for the semaglutide arm compared with SUSTAIN-6.[26,33]

The differences in reported outcomes between SUSTAIN-6 and PIONEER 6 are likely explained by the short duration and small event rates to adequately power a CVOT. The number of patients enrolled in SUSTAIN-6 and PIONEER 6 totaled 3297 and 3183, respectively, or in sum 6480. Furthermore, SUSTAIN-6 had a mean duration of 2.1 years, whereas PIONEER 6's median follow-up was merely 1.33 years. In contrast, the LEADER trial enrolled 9340 patients with a median follow-up of 3.8 years.[34] The consequences of these trial designs have led the manufacturer of semaglutide into ongoing discussions with the FDA about a cardiovascular indication based on the pooled outcomes of SUSTAIN-6 and PIONEER 6. Based on the present trial designs of the semaglutide formulations, the suggested cardiovascular benefits should be considered hypothesis generating only at this time.

Depending on the FDA's decision on the pooled data for the semaglutide formulations, the true effect on cardiovascular outcomes may not be determined until the completion of the SOUL trial. The SOUL trial is a large, randomized, double-blinded phase 3 trial designed to specifically evaluate the impact of oral semaglutide on cardiovascular outcomes in patients with ASCVD or CKD.[33] The SOUL study population will triple the size of participants in the PIONEER 6 study, which will ensure an adequate number of events to assess the superiority of the primary outcome. Patients will be followed for 3.5–5 years to assess the time to the first event in the primary composite outcome of MACE, which includes one of the following: cardiovascular death, nonfatal MI, and nonfatal stroke. The SOUL study has started recruiting, but implications from the trial will not be appreciated until several years after its potential approval by the FDA.[35]

Renal outcomes

The role of GLP-1 RA class in diabetic kidney disease continues to evolve with preliminary data from the LEADER and REWIND trials showing encouraging renal outcomes, particularly in the reduction on albuminuria.[34,36] In the REWIND analysis, the reduction of albuminuria was partially attributed to blood pressure improvements. While PIONEER 5 was designed to evaluate safety in patients with CKD and limited by its short duration, the impressive reduction in blood pressure coupled with improvements in albuminuria is consistent with the LEADER and REWIND data.[27,34,36] Even with the preliminary data from PIONEER 5 and other GLP-1 RA trials, more robust studies designed to evaluate CKD outcomes are needed to confirm the positive renal effects of oral semaglutide and to better understand the role of GLP-1 RAs in CKD.

Potential place in therapy

The treatment of T2DM is evolving away from a rigid algorithmic approach and toward individualized treatment selection. Metformin still remains the initial treatment of choice for T2DM due to its efficacy, cost, ease of administration, and safety profile. Furthermore, trials studying the cardiovascular effects of newer agents, including oral semaglutide, are typically prescribed metformin in conjunction with the investigated agent. The treatment for second-line therapy has grown increasingly complex and requires clinicians to holistically evaluate patients.

Cost remains a concern for new agents and represents a barrier to patient access. One Monte Carlo simulation suggested that oral semaglutide is cost effective in most cases at $85,000 per quality-adjust life years.[37] Beyond cost, oral semaglutide's effects on HbA1c (>−1%) and weight (>−3 kg) associated with the 14 mg dose represent an attractive option after metformin in patients with or without cardiovascular disease. This is especially true given the injection barrier has been removed for patients and clinicians.

The role in secondary prevention for semaglutide is more complex and cannot be fully elucidated until the combined analysis of the CVOTs and/or the SOUL trial is complete. Given that the ADA already recommends SGLT-2 inhibitors and GLP-1 RAs for patients with heart failure or ASCVD, no changes would be expected to the recommendations for individualized treatment decisions based on patient comorbidities.[6] However, even with the slightly lower efficacy compared with subcutaneous semaglutide, oral semaglutide may be the preferred GLP-1 RA by some clinicians based on practicality alone. In addition, the ADA recommends GLP-1 RAs for most

patients before insulin therapy and to be continued once insulin is initiated.[6] With the establishment of a new semaglutide formulation, clinicians may have an orally administered GLP-1 RA available to start early after a diabetes diagnosis and continued as cardiovascular disease develops or as the need for insulin is required.

Limitations

While the PIONEER program is complete, the publicly available and peer-reviewed data from these trials are incomplete. At the time of publication of this article, 6 of the 10 PIONEER trials are published, while the remaining trials only have data available from the manufacturer. Furthermore, cost data of the medication are still unknown and may represent a major barrier for its use much like other new agents.

Administration and titration of oral semaglutide will not be simple. Patients will require substantial counseling on food intake or risk inadequate response. Furthermore, dose optimization may be difficult outside of a clinical trial setting. Pending the FDA decision on approved doses and labeling, an initial starting dose may take 2 months and three different strengths (3, 7, and 14 mg) to reach the dose with maximum efficacy as seen in the PIONEER program. This will require substantial clinician time and strong adherence by the patient to efficiently reach a dose of 14 mg. Besides cost, success with dose optimization of oral semaglutide in clinical practice, compared with injectable GLP-1 RAs, may ultimately determine its place of therapy among the GLP-1 RA class.

Conclusion

The coformulation of oral semaglutide with SNAC is the first orally administered GLP-1 RA awaiting FDA approval for the treatment of T2DM. Its new drug application was submitted in March 2019 and filed under a priority review that is estimated to take 6 months. Studies support that the addition of SNAC enables complete gastric absorption of semaglutide, while preventing degradation of the peptide. This formulation alleviates the inconvenience of subcutaneous injection presently required for delivery of the GLP-1 RA class, while providing similar efficacy. Further evaluation of the effects of semaglutide on cardiovascular disease will determine its role in secondary prevention. Overall, preliminary research suggests that oral semaglutide is an efficacious, safe, and a practical treatment option for patients with T2DM.

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