Editorial

Oral Semaglutide : Revolutionizing Diabetes Care with a Patient-Friendly GLP-1 Receptor Agonist

The journey of oral semaglutide represents a significant milestone in diabetes therapeutics. Traditionally, GLP-1 receptor agonists, used for their potent glucose-lowering effects and cardiovascular benefits, have been administered via subcutaneous injections. This method of administration often posed barriers to adherence and patient acceptance due to needle phobia and the inconvenience of injections.

Oral Semaglutide, marketed under the brand name Rybelsus, was developed to overcome these barriers. It is the first oral GLP-1 receptor agonist approved for the treatment of Type 2 Diabetes Mellitus (T2DM). The approval came after extensive clinical trials under the PIONEER program, which assessed its efficacy, safety, and tolerability compared to other antidiabetic agents. The development of oral semaglutide leveraged advances in pharmaceutical technology, specifically the use of an absorption enhancer, Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate (SNAC), which facilitates the absorption of semaglutide in the stomach. This innovation addressed the challenge of delivering a peptide drug, which typically degrades in the gastrointestinal tract, through an oral route.

Mechanism of Action :

Semaglutide is a GLP-1 receptor agonist that mimics the incretin hormone GLP-1. It enhances glucose-dependent insulin secretion and inhibits glucagon release, which helps in lowering blood glucose levels. Additionally, it slows gastric emptying and promotes satiety, contributing to weight loss.

The mechanism of action of semaglutide includes —

(1) Stimulation of Insulin Secretion : In response to food intake, semaglutide enhances the secretion of insulin from pancreatic beta cells in a glucose-dependent manner, reducing the risk of hypoglycemia.

(2) Inhibition of Glucagon Release : It suppresses the release of glucagon from alpha cells in the pancreas, decreasing hepatic glucose production.

(3) Gastric Emptying Delay : By slowing gastric emptying, semaglutide helps in reducing postprandial glucose spikes.

(4) Promoting Satiety : It acts on the brain to promote a feeling of fullness, thereby aiding in weight reduction.

Oral semaglutide, using the SNAC technology, is absorbed in the stomach. The SNAC component creates a local high pH environment which protects semaglutide from degradation and enhances its permeability across the gastric epithelium. Once absorbed, it follows the same metabolic pathway as injectable semaglutide, exerting its therapeutic effects systemically.

Advantages of Oral Administration over Injectable Forms :

The oral formulation of semaglutide offers several advantages over its injectable counterparts, which can lead to improved patient adherence and outcomes:

(1) Enhanced Patient Adherence : The oral administration route is generally preferred by patients over injections. This preference can significantly improve adherence to therapy, particularly in those with a fear of needles or an aversion to injections.

(2) Convenience : Oral semaglutide can be easily incorporated into daily routines without the need for special training on injection techniques, storage requirements for injectable formulations, or the discomfort associated with injections.

(3) Early Initiation of Therapy : The convenience and acceptability of an oral GLP-1 receptor agonist can facilitate earlier initiation of therapy in the course of T2DM management. This can be crucial in achieving early glycemic control and reducing the risk of diabetes-related complications.

(4) Reduction of Injection-Related Issues : The oral route eliminates complications related to injections, such as injection site reactions, which can include pain, bruising, and infection .

These advantages make oral semaglutide a promising option for many patients with T2DM, particularly those who are averse to injections. It expands the therapeutic options available and aligns with patient preferences, potentially leading to better adherence and improved clinical outcomes.

Oral semaglutide represents a paradigm shift in the management of T2DM, providing the benefits of GLP-1 receptor agonist therapy in a patient-friendly oral formulation. Its development is a testament to the advances in pharmaceutical technology and a significant step forward in diabetes care.

Clinical Efficacy :

Overview of Pivotal Clinical Trials (PIONEER Programme)

The clinical efficacy of oral semaglutide has been extensively evaluated through the PIONEER program, a series of phase 3 clinical trials designed to assess its safety and effectiveness in managing Type 2 Diabetes Mellitus (T2DM). The PIONEER program includes 10 pivotal trials, each addressing different aspects of oral semaglutide therapy, including its comparison with other antidiabetic agents, its effects in various patient populations, and its cardiovascular outcomes.

(1) Impact on Glycemic Control (HbA1c Reduction)

The primary endpoint in the majority of the PIONEER trials was the reduction in HbA1c levels. Oral semaglutide consistently demonstrated superior glycemic control compared to placebo and other active comparators.

In the PIONEER 1 trial, which evaluated oral semaglutide as monotherapy, patients treated with oral semaglutide 14 mg once daily achieved a mean reduction in HbA1c of 1.5% from baseline, compared to 0.1% with placebo (P<0.001). Similarly, in the PIONEER 2 trial, oral semaglutide 14 mg once daily reduced HbA1c by 1.3% compared to a 0.9% reduction with empagliflozin (P<0.001). The PIONEER 3 trial compared oral semaglutide with sitagliptin, showing a significant reduction in HbA1c of 1.0% versus 0.3% with sitagliptin (P<0.001).

The results of these trials underscore the potent glucose-lowering effect of oral semaglutide, making it a valuable option for achieving glycemic targets in patients with T2DM.

(2) Weight Loss Benefits

In addition to its effects on glycemic control, oral semaglutide has shown significant benefits in weight reduction, an important consideration for many patients with T2DM. The weight loss effects were consistently observed across the PIONEER trials.

In PIONEER 1, patients treated with oral semaglutide 14 mg once daily experienced an average weight loss of 4.2 kg, compared to 1.2 kg with placebo (P<0.001) . In PIONEER 2, the mean weight reduction was 4.7 kg with oral semaglutide 14 mg once daily, versus 3.1 kg with empagliflozin (P<0.001). PIONEER 4, which compared oral semaglutide with subcutaneous liraglutide, reported a weight loss of 4.3 kg for oral semaglutide 14 mg daily, compared to 3.0 kg for liraglutide (P<0.001) .

These findings highlight the dual benefits of oral semaglutide in managing both blood glucose levels and body weight, offering a comprehensive therapeutic advantage for patients with T2DM. Table 1 summarises the key results of PIONEER trials.

Safety and Tolerability :

(A)Common Adverse Events (Gastrointestinal Issues) —

The safety and tolerability profile of oral semaglutide is generally consistent with other GLP-1 receptor agonists, with gastrointestinal adverse events being the most commonly reported. In clinical trials, nausea, vomiting, and diarrhea were frequently observed, particularly during the initial weeks of treatment as the body adjusts to the medication.

(1) Nausea : Nausea was the most frequently reported adverse event, affecting a significant portion

Table1 — *Overview of PIONEER Trials for Oral Semaglutide*

PIONEER Trial	Comparison	Duration (weeks)	Primary Outcome	Mean HbA1c Reduction(%)	Weight Loss (kg)	Reference
PIONEER 1	Placebo	26	HbA1c Reduction	1.5	4.2	Aroda VR, *et al.* Diabetes Care 2019; 42:1724-32.
PIONEER 2	Empagliflozin	52	HbA1c Reduction	1.3	4.7	Rodbard HW, *et al.* Diabetes Care. 2019; 42(12):2272-81.
PIONEER 3	Sitagliptin	78	HbA1c Reduction	1.0	2.6	Rosenstock J, *et al.* JAMA. 2019;321:1466-80.
PIONEER 4	Liraglutide	52	HbA1c Reduction	1.2	4.3	Pratley R, *et al.* Lancet. 2019;394:39-50.
PIONEER 5	Placebo	26	HbA1c Reduction	1.0	2.3	Mosenzon O, *et al.* Lancet Diabetes Endocrinol. 2019;7:515-27.
PIONEER 6	Placebo	104	Cardiovascular Outcomes	N/A	N/A	Husain M, *et al.* N Engl J Med. 2019;381:841-851.
PIONEER 7	Sitagliptin	52	HbA1c Reduction	1.3	2.9	Pieber TR, *et al.* Lancet Diabetes Endocrinol. 2019;7:528-39.
PIONEER 8	Placebo	52	HbA1c Reduction	0.9	2.0	Zinman B, *et al.* Diabetes Care. 2019;42:2262-71.
PIONEER 9	Liraglutide	26	HbA1c Reduction	1.6	3.8	Yamada Y, *et al.* J Diabetes Investig. 2019;10:30.
PIONEER 10	Dulaglutide	52	HbA1c Reduction	1.4	3.0	Yabe D, *et al.* J Diabetes Investig. 2019;10:30.

of patients. In the PIONEER 1 trial, 20% of patients treated with oral semaglutide 14 mg experienced nausea, compared to 3% in the placebo group. Similarly, in the PIONEER 2 trial, nausea was reported in 16% of patients receiving oral semaglutide 14 mg compared to 5% of those on empagliflozin.

(2) Vomiting : Vomiting was less common than nausea but still reported at a higher incidence than with placebo or some other comparators. In PIONEER 4, 8% of patients on oral semaglutide 14 mg experienced vomiting, compared to 2% in the placebo group and 4% in the liraglutide group.

(3) Diarrhea : Diarrhea was another common gastrointestinal side effect. In the PIONEER 3 trial, 9% of patients on oral semaglutide 14 mg reported diarrhea, versus 4% in the sitagliptin group.

These gastrointestinal side effects were generally mild to moderate in severity and tended to diminish over time. A gradual dose-escalation strategy can help mitigate these adverse events.

(B) Comparison with Other GLP-1 Receptor Agonists —

When compared with other GLP-1 receptor agonists, oral semaglutide shows a similar safety profile, but with some variations in the incidence of gastrointestinal adverse events.

(A) Liraglutide : In the PIONEER 4 trial, oral semaglutide 14 mg had a comparable incidence of nausea and vomiting to liraglutide 1.8 mg, with nausea reported in 20% of patients on oral semaglutide versus 19% on liraglutide . Vomiting was reported in 8% of patients on oral semaglutide compared to 6% on liraglutide.

(2) Dulaglutide : The PIONEER 10 trial compared oral semaglutide with dulaglutide and found similar rates of gastrointestinal adverse events. Nausea was reported in 15% of patients on oral semaglutide 14 mg and 12% of those on dulaglutide 1.5 mg.

(3) Exenatide and Other GLP-1 Agonists : Similar rates of gastrointestinal side effects have been reported with other GLP-1 receptor agonists like exenatide. However, the oral administration of semaglutide offers a more convenient option, which may enhance patient adherence despite the comparable side effect profile.

Overall, the incidence and severity of gastrointestinal adverse events with oral semaglutide are consistent with those observed with subcutaneous GLP-1 receptor agonists. The key to managing these side effects lies in patient education and gradual dose titration.

(C) Long-Term Safety Data —

Long-term safety data for oral semaglutide have been evaluated primarily through the PIONEER 6 trial, a cardiovascular outcomes trial that provided insights into the extended safety profile of this medication.

(1) Cardiovascular Safety : The PIONEER 6 trial demonstrated that oral semaglutide does not increase the risk of Major Adverse Cardiovascular Events (MACE) compared to placebo. The trial included patients at high cardiovascular risk and found a non-significant reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (Hazard Ratio [HR] 0.79; 95% CI 0.57-1.11).

(2) Mortality : All-cause mortality was lower in the oral semaglutide group compared to placebo, with an odds ratio (OR) of 0.58 (95% CI 0.37-0.92). Cardiovascular mortality was also reduced (OR 0.55, 95% CI 0.31-0.98).

(3) Diabetic Retinopathy : Concerns about diabetic retinopathy have been raised with GLP-1 receptor agonists. However, the PIONEER trials indicated no significant increase in the incidence of diabetic retinopathy with oral semaglutide compared to placebo or active comparators. Further studies are needed to fully understand the long-term impact on diabetic retinopathy, particularly in patients with preexisting retinopathy.

(4) Pancreatitis and Other Serious Adverse Events : The incidence of acute pancreatitis was low and not significantly different between oral semaglutide and comparators in the PIONEER trials. Similarly, there was no increased risk of severe hypoglycemia or other serious adverse events attributable to oral semaglutide .

In summary, oral semaglutide has a safety profile comparable to other GLP-1 receptor agonists, with the most common adverse events being gastrointestinal in nature. Long-term data from the PIONEER program support its cardiovascular safety and overall tolerability, making it a viable option for the management of T2DM.

Cardiovascular Outcomes :

(A) Cardiovascular Safety and Benefits

Oral semaglutide, like other GLP-1 receptor agonists, has shown promising cardiovascular safety and benefits, particularly in reducing Major Adverse Cardiovascular Events (MACE). The PIONEER 6 trial, a dedicated cardiovascular outcomes trial, provided substantial evidence supporting the cardiovascular safety of oral semaglutide. This trial included patients with Type 2 Diabetes Mellitus (T2DM) who were at high cardiovascular risk and aimed to demonstrate that oral semaglutide does not increase the risk of cardiovascular events compared to placebo.

(B) PIONEER 6 Trial Results

The PIONEER 6 trial was a randomized, double-blind, placebo-controlled trial designed to evaluate the cardiovascular safety of oral semaglutide in patients with T2DM. The primary endpoint was the first occurrence of a Major Adverse Cardiovascular Event (MACE), which included cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Trial Design and Population : The trial enrolled 3,183 patients with T2DM and high cardiovascular risk.

Participants were randomly assigned to receive oral semaglutide or placebo in addition to standard care.

Primary Endpoint : The primary composite endpoint (MACE) occurred in 3.8% of patients in the oral semaglutide group compared to 4.8% in the placebo group (Hazard Ratio [HR], 0.79; 95% CI, 0.57 to 1.11).

Although the trial was not powered for superiority, the results suggested a numerical reduction in MACE with oral semaglutide.

Secondary Endpoints : Cardiovascular death occurred in 0.9% of patients in the oral semaglutide group compared to 1.9% in the placebo group (HR, 0.55; 95% CI, 0.31 to 0.98).

Nonfatal myocardial infarction occurred in 2.3% of patients in both groups (HR, 1.18; 95% CI, 0.73 to 1.90).

Nonfatal stroke occurred in 0.8% of patients in the oral semaglutide group compared to 1.0% in the placebo group (HR, 0.74; 95% CI, 0.35 to 1.57).

All-Cause Mortality : All-cause mortality was lower in the oral semaglutide group compared to the placebo group (HR, 0.58; 95% CI, 0.37 to 0.92).

Implications for Patients with High Cardiovascular Risk.

The results from the PIONEER 6 trial have significant implications for the management of patients with T2DM who are at high cardiovascular risk.

(C) Cardiovascular Safety

The trial confirmed that oral semaglutide does not increase the risk of major adverse cardiovascular events, thus supporting its cardiovascular safety profile.

This finding is consistent with the cardiovascular benefits observed with other GLP-1 receptor agonists, such as liraglutide and injectable semaglutide.

Potential Cardiovascular Benefits : While the trial was not powered to demonstrate superiority, the numerical reduction in cardiovascular events suggests potential cardiovascular benefits of oral semaglutide.

The significant reduction in cardiovascular death and all-cause mortality provides further support for the use of oral semaglutide in patients at high cardiovascular risk .

Clinical Implications : The cardiovascular safety profile of oral semaglutide makes it a viable option for T2DM patients, especially those with established cardiovascular disease or at high cardiovascular risk.

The convenience of oral administration may improve adherence to GLP-1 receptor agonist therapy, potentially leading to better cardiovascular outcomes in the long term.

Comparative Effectiveness :

The PIONEER trials provide extensive data on the comparative effectiveness of oral semaglutide against other antidiabetic agents, including SGLT-2 inhibitors, DPP-4 inhibitors, and other GLP-1 receptor agonists. These head-to-head comparisons as shown in Table 2 highlight the advantages of oral semaglutide in terms of glycemic control, weight loss, and adverse event profiles.

Advantages Over SGLT-2 Inhibitors, DPP-4 Inhibitors, and Other GLP-1 Receptor Agonists—

(1) Advantages Over SGLT-2 Inhibitors (eg, Empagliflozin)

- **Glycemic Control :** In the PIONEER 2 trial, oral semaglutide demonstrated a greater reduction in

Table 2 — *Head-to-Head Comparisons with Other Antidiabetic Agents*

PIONEER Trial	Comparison Agent	Mean HbA1c Reduction (%)	Weight Loss (kg)	Gastrointestinal Adverse Events (%)	Reference
PIONEER 2	Empagliflozin	1.3	4.7	16	Rodbard HW, *et al.* Diabetes Care. 2019;42(12):2272-2281.
PIONEER 3	Sitagliptin	1.0	2.6	9	Rosenstock J, *et al.* JAMA. 2019;321:1466-1480.
PIONEER 4	Liraglutide	1.2	4.3	20	Pratley R, *et al.* Lancet. 2019;394:39-50.
PIONEER 7	Sitagliptin	1.3	2.9	11	Pieber TR, *et al.* Lancet Diabetes Endocrinol. 2019;7:528-539.

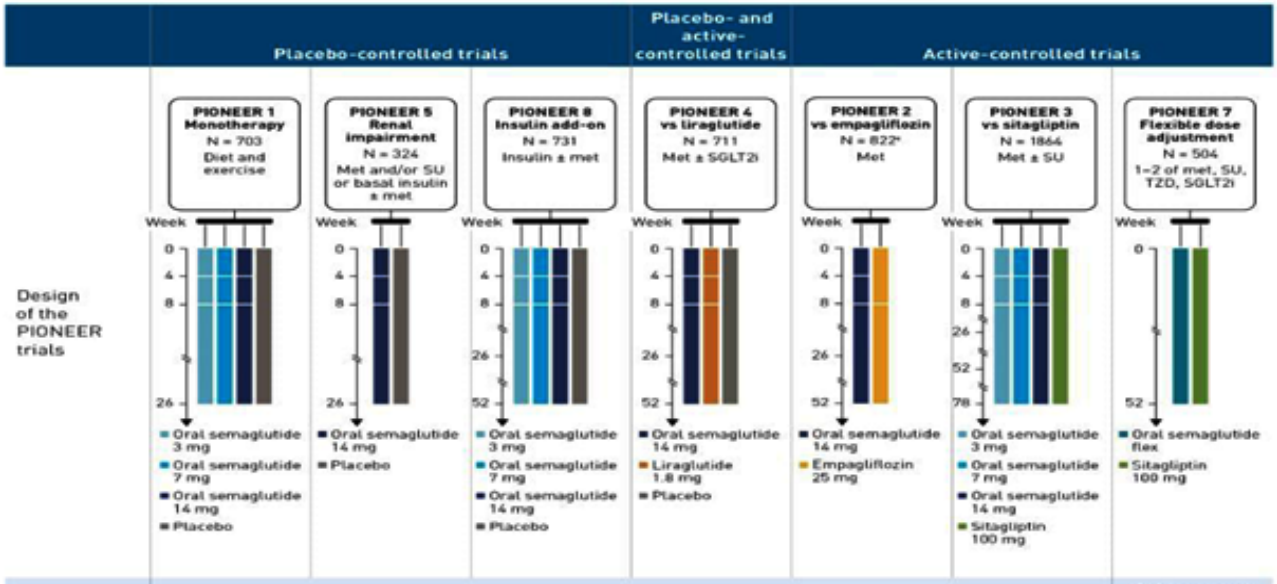
HbA1c compared to empagliflozin (1.3% *versus* 0.9%).

- **Weight Loss :** Patients on oral semaglutide experienced more significant weight loss than those on empagliflozin (4.7 kg *versus* 3.1 kg) .
- **Adverse Events :** While gastrointestinal adverse events were more frequent with semaglutide, the overall tolerability was similar when considering the benefits of weight loss and glycemic control.

(2) Advantages Over DPP-4 Inhibitors (eg, Sitagliptin)

- **Glycemic Control :** In both PIONEER 3 and PIONEER 7 trials, oral semaglutide showed superior HbA1c reductions compared to sitagliptin (1.0% *versus* 0.3% and 1.3% *versus* 0.8%, respectively).
- **Weight Loss** : Oral semaglutide led to greater weight loss compared to sitagliptin (2.6 kg *versus* 1.1 kg in PIONEER 3 and 2.9 kg *versus* 0.6 kg in PIONEER 7).

FIGURE 1. Overview of the Design and Baseline Patient Characteristics From the Global PIONEER Trials[15-21,AA]



Primary end point	Change in A1C from baseline to week 26						Achievement of A1C < 7.0% (53 mmol/mol) at week 52
Confirmatory secondary end point	Change in body weight from baseline to week 26						Change in body weight from baseline to week 52
Baseline characteristics, mean (with SD where published)							
Age, years	55 (11)	70 (8)	61 (10)	56 (10)	58 (10)	58	57 (9.9)
A1C, %	8.0 (0.7)	8.0 (0.7)	8.2 (0.7)	8.0 (0.7)	8.1 (0.9)	8.3	8.3 (0.6)
A1C, mmol/mol	63 (8)	64 (8)	66	64 (8)	65 (1.0)	67	67 (6.4)
Duration of diabetes, years	3.5 (4.9)	14.0 (8.0)	15.0 (8.1)	7.6 (5.5)	7.5 (6.1)	8.6	8.8 (6.2)
Body weight, kg	88.1 (22.1)	90.8 (17.6)	85.9 (21.8)	94.0 (21.0)	91.6 (20.3)	91.2	88.6 (19.8)

A1C, glycated hemoglobin; met, metformin; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.
*All 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).
†Text in italics indicates permitted background medication for patients included in the trials.
‡One patient was enrolled at 2 sites, so analyses were based on 821 patients.

- **Adverse Events :** Gastrointestinal events were more common with semaglutide, but its benefits in weight reduction and glycemic control outweigh these side effects for many patients.

(3) Advantages Over Other GLP-1 Receptor Agonists (eg, Liraglutide)

- **Glycemic Control :** In the PIONEER 4 trial, oral semaglutide provided similar HbA1c reductions compared to liraglutide (1.2% *versus* 1.1%).
- **Weight Loss :** Oral semaglutide showed comparable weight loss benefits to liraglutide (4.3 kg *versus* 3.8 kg) .
- **Adverse Events :** The incidence of gastrointestinal side effects was similar, with nausea being the most common. However, the oral route of administration may improve adherence compared to the injectable form of liraglutide.

Patient Adherence and Quality of Life :

Impact of Oral Formulation on Patient Adherence

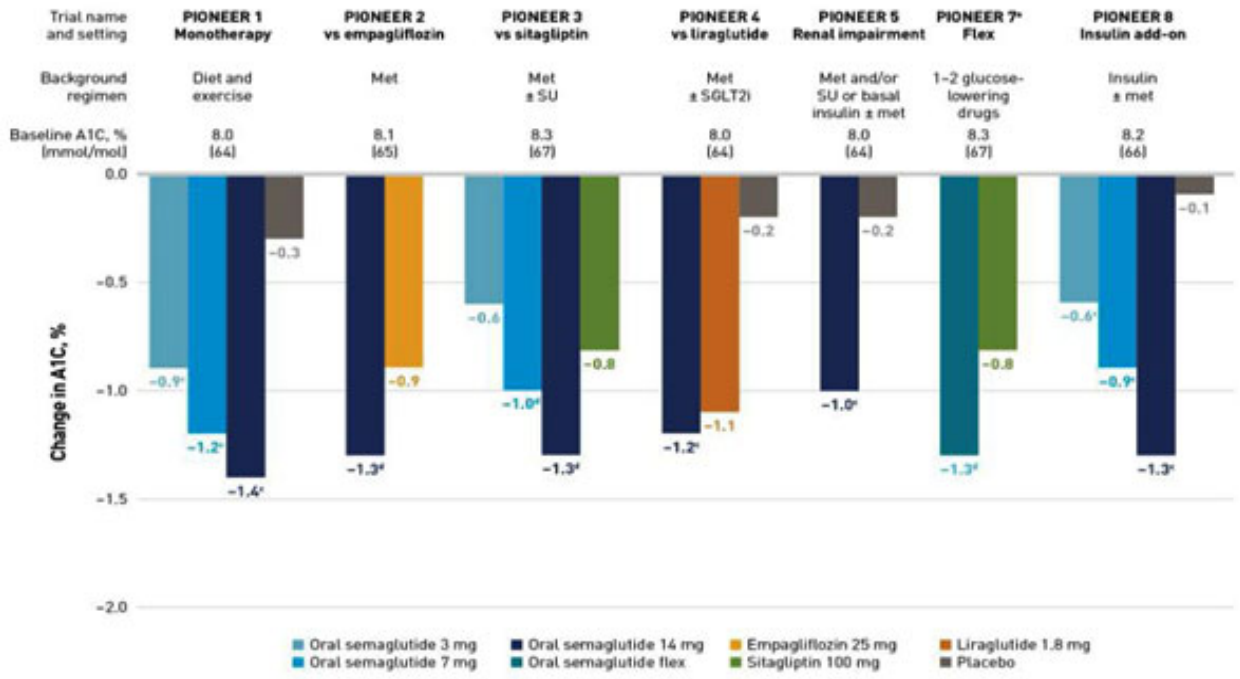
One of the significant advantages of oral semaglutide over injectable formulations of GLP-1 receptor agonists is its potential to improve patient adherence. Medication adherence is a critical factor in the management of chronic conditions such as Type 2 Diabetes Mellitus (T2DM). Non-adherence to prescribed medication regimens can lead to suboptimal glycemic control, increased risk of complications, and higher healthcare costs.

Convenience and Ease of Use : Oral semaglutide offers a convenient alternative to injections, which can be a barrier to adherence for many patients. The ease of swallowing a pill compared to administering an injection can significantly improve the willingness of patients to initiate and continue therapy.

Reduced Injection-Related Anxiety : Needle phobia and discomfort associated with injections can deter patients from adhering to injectable therapies. Oral semaglutide eliminates the need for needles, reducing the anxiety and discomfort that some patients experience with injectable GLP-1 receptor agonists.

Simplified Treatment Regimen : The oral formulation allows for a simplified treatment regimen, which can enhance adherence. Patients can integrate oral semaglutide into their daily routine without the need for special storage or administration techniques associated with injectable medications.

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.
[A]The primary end point of PIONEER 7 was achievement of an A1C level <7.0% (53 mmol/mol) at week 52.
[B]Data 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.

Patient Preferences and Satisfaction :

The preference for oral medication over injections is well-documented in the literature. Patient satisfaction is influenced by multiple factors, including the route of administration, frequency of dosing, and perceived efficacy and safety of the medication.

(1) Preference for Oral Medication: Surveys and studies have shown that patients with T2DM generally prefer oral medications over injectable therapies. This preference is driven by the desire for convenience, ease of use, and avoidance of pain or discomfort associated with injections.

In a survey conducted among patients with T2DM, a significant proportion indicated a preference for oral semaglutide over injectable GLP-1 receptor agonists, highlighting the importance of patient-centric treatment options.

(2) Satisfaction with Treatment : Treatment satisfaction encompasses several dimensions, including efficacy, side effects, and ease of use. Patients treated with oral semaglutide have reported high levels of satisfaction due to its effective glycemic control and weight loss benefits, combined with the convenience of oral administration.

In clinical trials, patient-reported outcomes have indicated greater satisfaction with oral semaglutide compared to other treatments, underscoring the positive impact on patient experiences.

Quality of Life Improvement :

Managing T2DM effectively involves not only controlling blood glucose levels but also enhancing the overall quality of life for patients. Quality of life improvements are a critical aspect of comprehensive diabetes care.

(1) Improved Glycemic Control : Effective glycemic control with oral semaglutide leads to a reduction in diabetes-related symptoms and complications, contributing to a better quality of life. Patients achieving target HbA1c levels often experience fewer symptoms of hyperglycemia and hypoglycemia.

(2) Weight Loss Benefits : Weight loss is a significant benefit of GLP-1 receptor agonists, including oral semaglutide. Weight reduction can lead to improvements in physical health, mobility, and self-esteem, which are important components of quality of life.

Patients who experience weight loss with oral semaglutide often report enhanced physical functioning and reduced limitations in daily activities, contributing to overall well-being.

(3) Reduced Cardiovascular Risk : Oral semaglutide has been shown to have cardiovascular benefits, reducing the risk of major adverse cardiovascular events. Improved cardiovascular health directly correlates with better quality of life, as it reduces the burden of cardiovascular disease and associated complications.

(4) Mental Health and Emotional Well-Being: The anxiety and stress associated with managing a chronic condition like T2DM can impact mental health. By providing a convenient and effective treatment option, oral semaglutide can reduce the mental burden of diabetes management, leading to improvements in emotional well-being.

Patient-reported outcomes have shown that those using oral semaglutide experience less diabetes-related distress and a more positive outlook on their health and treatment regimen.

Administration and Practical Considerations :

Dosing Regimen and Administration Guidelines : Oral semaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus (T2DM). The recommended dosing regimen and administration guidelines are critical for ensuring the medication's efficacy and minimizing adverse effects.

The initial dosing schedule begins with 3 mg once daily for 30 days to allow the body to adjust and to minimize gastrointestinal side effects. After 30 days, the dose should be increased to 7 mg once daily. If further glycemic control is required, the dose can be increased to 14 mg once daily after an additional 30 days. Dosing schedule and administration instructions are described in Table 3.

Challenges and Solutions for Effective Absorption :

Effective absorption of oral semaglutide is essential to achieve its therapeutic benefits. Several factors can influence its absorption, and practical solutions can help mitigate these challenges :

(1) Gastric Emptying : Oral semaglutide delays gastric emptying, which can impact the absorption of other oral medications. Patients should closely follow administration instructions to mitigate this effect.

(2) Timing with Other Medications : To avoid interactions, patients should take oral semaglutide at least 30 minutes before any other oral medications. This helps ensure that the semaglutide is absorbed effectively before other drugs are introduced into the digestive system .

(3) Hydration : Taking semaglutide with more than 4 ounces of water or any other beverage can reduce its absorption. Patients should be instructed to take it with only a small amount of plain water.

Table 3 — *Dosing Schedule and Administration Instructions*

Dosage Form	Dosing Schedule	Administration Instructions	Dose Increase Instructions	Special Instructions
3 mg	Once daily for 30 days	Take at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water.	After 30 days on the 3 mg dose, increase the dose to 7 mg once daily.	Swallow tablets whole. Do not cut, crush, or chew tablets.
7 mg	Once daily	Take at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water.	If additional glycemic control is needed after at least 30 days on the 7 mg dose, increase the dose to 14 mg once daily.	Swallow tablets whole. Do not cut, crush, or chew tablets.
14 mg	Once daily	Take at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water.	N/A	Swallow tablets whole. Do not cut, crush, or chew tablets.

Patient Education and Support :

Patient education and support are crucial for optimizing the benefits of oral semaglutide and ensuring adherence to the treatment regimen :

(A) Understanding the Regimen : Patients should be thoroughly informed about the dosing schedule, the importance of taking the medication on an empty stomach, and the required waiting period before eating or taking other medications. This information helps patients understand the necessity of strict adherence to the administration guidelines.

(B) Managing Side Effects : Common side effects, such as nausea and vomiting, should be discussed with patients. They should be provided with strategies to manage these effects and encouraged to contact their healthcare provider if they experience severe or persistent symptoms. Starting with a lower dose and gradually increasing can help manage these side effects effectively.

(C) Support Resources : Providing patients with access to support resources, such as educational materials and patient support programs, can help them better understand their treatment and manage their condition effectively. Resources should include contact information for healthcare providers and patient hotlines.

Economic Considerations :

(A) Cost-Effectiveness Analysis

The cost-effectiveness of oral semaglutide has been evaluated in various studies, highlighting its economic value compared to other antidiabetic treatments. Table 4 summarizes key findings from the relevant studies.

(1) Guzauskas, *et al* (2021):

- Population: United States
- Cost per QALY: $117,500
- Comparators: Sitagliptin, Empagliflozin, Liraglutide
- Conclusion: Oral semaglutide is cost-effective compared to several other treatments. However, the cost per QALY is higher compared to Empagliflozin.

(2) Feng, *et al* (2023):

- Population: China
- Cost per QALY: $39,853.22
- Comparators: Placebo, Injectable GLP-1 RAs
- Conclusion: Oral semaglutide is cost-effective compared to placebo and several injectable GLP-1 RAs at a reduced price. The study emphasizes the need for further price reductions to enhance cost-effectiveness.

(B) Impact on Healthcare Costs

Oral semaglutide's impact on healthcare costs is significant due to its ability to improve glycemic control and reduce diabetes-related complications, which can lead to substantial long-term savings:

(1) Reduction in Complications

Oral semaglutide has demonstrated efficacy in reducing major adverse cardiovascular events (MACE) and improving overall glycemic control. This reduction in complications can decrease the need for hospitalizations and other costly medical interventions.

(2) Hospitalization and Treatment Costs :

Improved glycemic control and weight management can lead to lower healthcare costs by reducing the incidence of diabetes-related

Table 4 — *A Few Cost Effectiveness Analysis Studies*

Study	Population	Cost per QALY	Comparators	Conclusion
Guzauskas, *et al.* 2021	US	$117,500	Sitagliptin, Empagliflozin, Liraglutide	Cost-effective compared to several other treatments, but higher than Empagliflozin
Feng, *et al.* 2023	China	$39,853.22	Placebo, Injectable GLP-1 RAs	Cost-effective compared to placebo and several injectable GLP-1 RAs at a reduced price

complications. Effective management with oral semaglutide may translate to fewer emergency visits and hospital admissions .

(C) Insurance and Reimbursement Issues

Ensuring access to oral semaglutide involves navigating insurance coverage and reimbursement policies:

(1) Coverage Variability : Insurance coverage for new medications like oral semaglutide can vary widely. Inclusion in formularies and understanding patient coverage options are critical for ensuring access.

(2) Prior Authorization : Many insurance plans may require prior authorization for oral semaglutide, necessitating detailed documentation from healthcare providers to justify its use based on medical necessity and patient benefit.

(3) Patient Assistance Programs : Pharmaceutical companies often provide patient assistance programs to help those who cannot afford their medications. Information on these programs should be made readily available to patients and healthcare providers to ensure access to treatment .

Future Directions and Research :

Ongoing and Future Clinical Trials

Research into oral semaglutide continues to expand, focusing on its long-term efficacy, safety, and potential new applications. Several ongoing and future clinical trials aim to address these areas:

(1) Long-Term Efficacy and Safety : Studies are underway to assess the long-term efficacy and safety of oral semaglutide beyond the typical trial durations. These studies aim to provide more comprehensive data on the sustainability of glycemic control and weight loss, as well as the long-term impact on cardiovascular health and other diabetes-related complications.

(2) New Indications : Researchers are exploring the potential use of oral semaglutide for other conditions beyond type 2 diabetes. This includes investigating its effects on prediabetes, obesity, and even Non-alcoholic Steatohepatitis (NASH), given its impact on weight loss and metabolic parameters.

(3) Comparative Effectiveness : Future trials are planned to compare oral semaglutide directly with other emerging diabetes treatments, including newer GLP-1 receptor agonists, dual agonists, and SGLT-2 inhibitors, to further establish its place in therapy.

Potential New Indications and Formulations :

(1) Indications : Beyond type 2 diabetes, there is interest in evaluating oral semaglutide for weight

Summary of Other Main Efficacy Outcomes in the PIONEER Program[15-21,A,b]

Placebo-controlled trials

Trial name and setting	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		3	7	14	
Estimated mean reduction from baseline at 26 weeks													
Body weight, kg	-1.5	-2.3	-3.7[c]	-1.4	-4.4[c,d]	-3.1	-0.5	-3.4[c]	-0.9	-1.4[c]	-2.4[c]	-3.7[c]	-0.4
Observed proportion of patients achieving thresholds at 26 weeks													
A1C level <7%	55[c]	69[c]	77[c]	31	68[c]	62	14	58[c]	23	28[c]	43[c]	58[c]	7
Weight loss ≥5%	20	27[c]	41[c]	15	44[c,d]	28	8	36[c]	10	13[c]	31[c]	39[c]	3

Active-controlled trials

Trial name and setting	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	100	14	1.8		14	100
Estimated mean reduction from baseline at 26 weeks (except 52 weeks in PIONEER 7)[b]											
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]	-0.7
Observed proportion of patients achieving thresholds at 26 weeks (except 52 weeks in PIONEER 7)[b]											
A1C level <7%	67[d]	40	27	42[d]	55[d]	32	68[c]	62	14	58[d]	25
Weight loss ≥5%	41	36	13	19[d]	30[d]	10	44[c,d]	28	8	27[d]	12

A1C, glycated hemoglobin.
[a]The primary end point of PIONEER 7 was achievement of an A1C level <7.0% (53 mmol/mol) at week 52.
[b]Data in this table 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.

management in patients without diabetes, given its significant impact on weight reduction. Studies are also looking at its potential in reducing cardiovascular events in high-risk populations without diabetes.

(2) Formulations : Future research may lead to new formulations of oral semaglutide that improve its bioavailability and patient compliance. This could include different dosing strategies, combination therapies with other antidiabetic agents, or formulations that reduce gastrointestinal side effects.

Research on Long-Term Effects and Real-World Data :

Long-Term Effects :

(1) Long-term studies are critical to understanding the effects of chronic use of oral semaglutide, particularly regarding its impact on diabetic retinopathy, renal function, and cardiovascular health over several years.

(2) Real-World Data: Real-world evidence is being gathered to complement clinical trial data, providing insights into the medication's performance in routine clinical practice. This includes data on adherence, effectiveness in diverse populations, and long-term safety.

Conclusion :

Oral semaglutide represents a significant advancement in the management of type 2 diabetes, offering an effective oral alternative to injectable GLP-1 receptor agonists. Key findings from the literature highlight its efficacy in reducing HbA1c, promoting weight loss, and providing cardiovascular benefits. The medication's safety profile is consistent with that of other GLP-1 receptor agonists, with gastrointestinal issues being the most common adverse events.

Clinical Implications for Healthcare Providers: For healthcare providers, oral semaglutide offers a valuable option for patients who prefer oral medications over injections, potentially improving adherence and outcomes. It is important to educate patients on the correct administration to ensure maximum absorption and efficacy. Monitoring for side effects and adjusting doses as needed will help manage adverse reactions and optimize therapy.

Future Outlook for Oral Semaglutide in Diabetes Management : The future of oral semaglutide in diabetes management is promising, with ongoing research likely to expand its indications and improve formulations. As more data become available from long-term studies and real-world evidence, the role of oral semaglutide will be further clarified, potentially leading to broader use in diabetes care and other metabolic conditions.

Further Readings

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