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REVIEW

A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus

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ABSTRACT

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are a well-established class of glucose-lowering drugs. GLP-1 RAs can be classified according to their structure, duration of action and mode of administration. This review describes the basic and clinical pharmacology of orally administered semaglutide. It highlights the PIONEER clinical trial programme results, and reviews the efficacy, safety and tolerability.

Keywords: GLP-1 receptor agonists; GLP-1 RA; Glucagon-like peptide; Orally administered semaglutide; Pioneer trial

Key Summary Points

GLP-1 RAs (glucagon-like peptide 1 receptor agonists) are a preferred class of glucose-lowering drug.

Subcutaneous treatment with GLP-1 RAs is limited by their injectable mode of administration.

Orally administered semaglutide, a recently developed GLP-1 RA formulation, offers good glucose control in a safe and well-tolerated manner.

This review describes the basic and clinical pharmacology of orally administered semaglutide.

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INTRODUCTION

The prevalence of type 2 diabetes is increasing worldwide; 31 and 60 million adults live with type 2 diabetes in USA and Europe, respectively. India has 77 million people with diabetes mellitus (DM); currently India has the second highest number of diabetes cases in the world preceded only by China [1]. Type 2 diabetes mellitus (T2DM) is a complex and progressive disease associated with significant morbidity and mortality; four million deaths worldwide are attributable to diabetes, with half of these in people aged under 60 years. The risk of death among people with diabetes (aged 20–59 years) is at least double that in those without diabetes [2]. A key factor underlying the global rise in diabetes is the increasing prevalence of obesity,

which is a significant risk factor for diabetes. Different terms have been used to describe the association of obesity and diabetes. Metabolic syndrome is considered as a diagnostic entity; the word 'diabesity' highlights the etiologic effect of obesity on type 2 diabetes. A body mass index (BMI) greater than 35 kg/m^2 is associated with an increased risk of diabetes of more than 40-fold in men and more than 70-fold in women. When combined with overweight/obesity, the risks of serious long-term complications and overall mortality associated with diabetes are further increased [3–5].

The pathophysiology of T2D is progressive and involves multiple defects that contribute to chronic hyperglycaemia. At least eight distinct pathophysiological abnormalities, commonly known as the ominous octet, contribute to impaired glucose homeostasis and are present early in the natural history of T2D [6]. A decreased incretin effect also plays an important role in the progressive β-cell failure of T2D. β-cell resistance to glucagon-like peptide 1 (GLP-1) contributes to progressive failure in the function of β-cells [7]. The incretin effect is significantly impaired in people with T2D, greatly reducing the capacity for insulin release in response to food intake [8].

Incretin-based therapies work either by preventing enzymatic degradation of GLP-1, thus maintaining plasma levels of endogenous GLP-1 (dipeptidyl peptidase 4 inhibitors, DPP4is) or by directly activating GLP-1 receptors and mimicking the action of native GLP-1 (glucagon-like peptide-1 receptor agonists, GLP-1 RAs) [9]. GLP-1 RAs are preferred second-line agents in patients with T2DM with established atherosclerotic cardiovascular diseases (ASCVD) in light of their demonstrated ASCVD benefit, high efficacy, low potential for hypoglycaemia and potential for weight loss. More recently, the European Society of Cardiology (ESC) has deemed GLP-1 RAs to be the first-line therapy for cardiovascular risk reduction in patients with T2DM with very high/high risk [10].

Despite the benefits of GLP-1 RAs, subcutaneous administration is still a major barrier in adopting this therapy. Development of a co-formulation of orally administered semaglutide with the absorption enhancer sodium *N*-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC) has overcome the barrier of poor absorption and degradation in the stomach [11]. This review article will discuss the pharmacology of orally administered semaglutide with a focus on role of SNAC in enhancing the absorption of semaglutide, in addition to efficacy and safety from the PIONEER trials to determine its potential therapeutic role. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CLASSIFICATION OF GLP-1 RA

Classification of GLP-1 RAs is based on their basic structure and pharmacokinetic (PK) properties. By altering the amino acid in the peptide chain they resist degradation by the DPP4 enzyme. Another group was synthetically developed by replicating the structure of a naturally occurring protein isolated from saliva of the gila monster, exendin-4 (Ex-4), with substantial homology to native GLP-1. This naturally occurring protein has GLP-1 receptor-activating properties, and it is resistant to degradation by the DPP4 enzyme. Apart from structural classification, they can also be classified on the basis of their duration of action (short-acting and long-acting GLP-1 RAs). Short-acting GLP-1 RAs are resistant to DPP4 owing to their structural modifications, and longer-acting molecules have undergone some structural modifications to enhance their duration of action, e.g. exenatide once weekly, dulaglutide, albiglutide, liraglutide [12]. GLP-1 RAs can also be classified on the basis of structure, duration of action and mode of delivery, as shown in Table 1 [13].

GLP-1 RAs correct six of the eight components of the ominous octet. Direct activation by GLP-1 RAs has been shown widely to increase insulin and decrease glucagon secretion in a glucose-dependent manner, resulting in reduced blood glucose levels combined with low risk of hypoglycaemia. GLP-1 RAs also have a series of beneficial multifactorial effects beyond glycaemic control that include

Table 1 Classification of GLP-1 RAs based on different parameters [13]

Parameter	Classification	Compound
Classification based on duration of action	Short acting (half-life < 12 h)	Exenatide
		Lixisenatide
	Intermediate acting (half-life 12–24 h)	Liraglutide
	Long acting (half-life 24 h to 1 month)	Exenatide LAR
		Albiglutide
		Semaglutide
		Orally administered semaglutide
	Continuous acting (half-life > 1 month)	ITCA 650
Based on structure	Exendin-based therapy	Exenatide
		Exenatide LAR
		Lixisenatide
	Human GLP-1-based therapy	Liraglutide
		Dulaglutide
		Semaglutide
		Orally administered semaglutide
Based on mode of delivery	Subcutaneous injection	Exenatide
		Exenatide LAR
		Albiglutide
		Lixisenatide
		Liraglutide
		Semaglutide
	Subcutaneous implant	ITCA 650
	Oral ingestion	Orally administered semaglutide

reduction of body weight and improvement of cardiovascular (CV) outcomes [14]. The American Diabetes Association (ADA) recommends GLP-1 RAs in patients with clinical characteristics like presence of established ASCVD and cardiac heart failure or chronic kidney diseases [15]. GLP-1 RAs are peptides and include exenatide, liraglutide, dulaglutide, lixisenatide and semaglutide. Oral peptide drug delivery is limited by low permeability of the gastrointestinal tract and rapid enzymatic and pH-induced degradation in the stomach. As a result, GLP-1 RAs require administration by subcutaneous injection on either a daily or weekly basis [11].

SEMAGLUTIDE

Semaglutide was designed as a potent, long-acting GLP-1 analogue that could be administered subcutaneously (s.c.) once weekly, rather than s.c. once daily, to improve convenience and adherence. Semaglutide has 94% sequence homology with native GLP-1 and three key

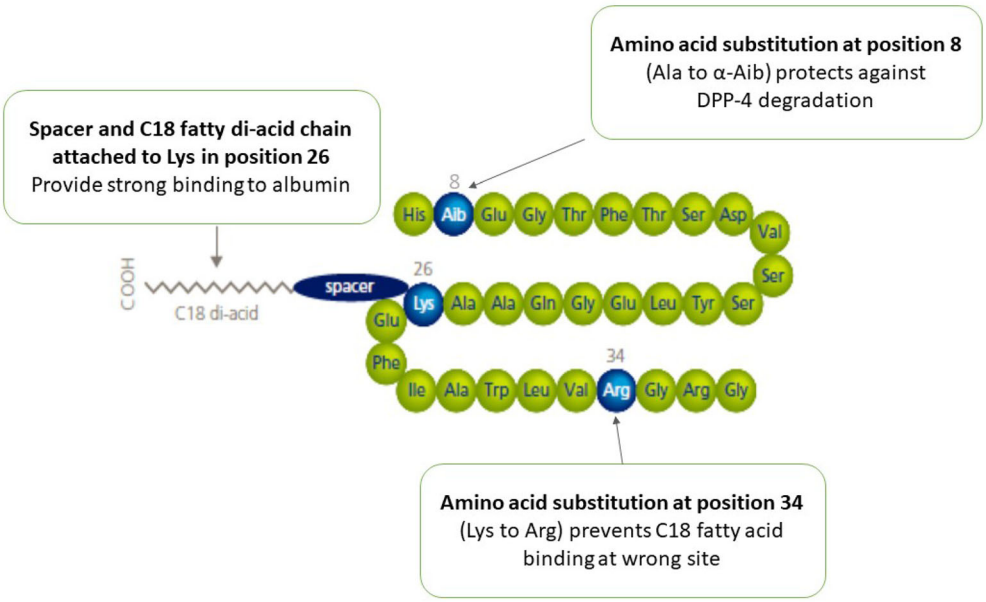

Fig. 1 Structure of semaglutide (subcutaneous formulation)

structural differences that provide extended pharmacokinetics [16] (Fig. 1):

1. Substitution of Ala with Aib at position 8 increases enzymatic (DPP4) stability.
2. Attachment of a linker and C18 di-acid chain at position 26 provides strong binding to albumin.
3. Substitution of Lys with Arg at position 34 prevents C18 fatty acid binding at the wrong site.

Semaglutide subcutaneous formulation proved efficacious across SUSTAIN trials; semaglutide sc 0.5 mg and 1 mg reduced HbA1c levels by 1.8% from baseline and 57–74% of cases experienced a reduction of HbA1c levels to less than 7% with 0.5 mg and 67–79% with 1 mg. It also reduced the body weight by up to 6.5 kg from baseline. In addition, the SUSTAIN 6 trial demonstrated a significant reduction in major CV events with semaglutide versus placebo in patients with T2D at high CV risk. The hazard ratio (HR) for major adverse cardiac events (MACE) was 0.74 (95% CI 0.58, 0.95) in subjects treated with semaglutide versus placebo ($p < 0.001$ for non-inferiority) [17–19].

BARRIERS TO INJECTABLE GLP-1 RA THERAPY

Quite a few barriers have been identified related to injectable GLP-1 RA therapy. Patients' perception of injectable therapy include perceived difficultly to use and fear of injections. This can have effects on the acceptance of therapy or adherence in a patient with type 2 diabetes [20].

To overcome the barriers and to improve the adherence, oral GLP-1 RAs were needed, but oral protein-based drug absorption is limited because of degradation in the stomach due to low pH, proteolytic enzyme activity, and limited permeability across the gastrointestinal (GI) epithelium. The bioavailability of GLP-1 RAs administered orally alone is very low and, in order to avoid degradation, the active molecule has to be protected and delivered through the GI epithelium and into the bloodstream. Co-formulation of GLP-1 RA with an absorption enhancer is necessary to achieve adequate bioavailability after oral administration [11].

ORALLY ADMINISTERED SEMAGLUTIDE

The search for modifications which can enable oral therapy of currently injectable peptides has been ongoing for a long time. Various strategies which were developed include the use of biotin to form biotinylated GLP-1; another method tried was addition of polyethylene glycol (PEG) to form PEGylated GLP-1; the use of nanotechnology to develop non-peptidic receptor agonists was also tried, but the results were not very promising [21].

Orally administered semaglutide is co-formulated with an absorption enhancer, SNAC (Fig. 2), which promotes absorption of semaglutide across gastric mucosa. SNAC has previously been co-formulated with heparin, ibandronate and vitamin B_{12} to increase drug absorption [22–24].

CLINICAL PHARMACOLOGY

Gamma scintigraphy was used in healthy men to study the anatomical site of erosion following absorption of orally administered semaglutide and its erosion kinetics. A randomised, open-label crossover study (Study 3957; NCT01619345) was conducted in 26 healthy men in a fasting state who received a single dose of 10 mg orally administered semaglutide containing a labelled ion exchange resin. Complete tablet erosion occurred in the stomach. Scintigraphic images showed that no erosion had occurred 2 min after dosing, whereas no intact tablet core remained after 140 min. Measurement of semaglutide plasma concentrations confirmed early systemic absorption and an apparently slow elimination phase once present in the systemic circulation (Fig. 3) [25].

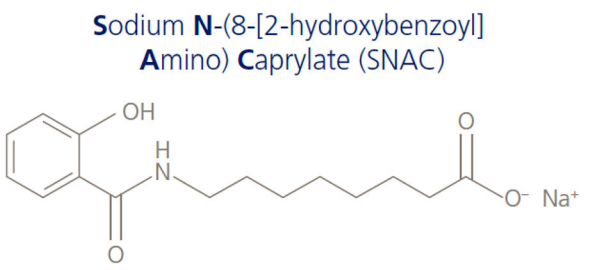

Fig. 2 Structure of SNAC

ROLE OF SNAC IN ABSORPTION OF ORALLY ADMINISTERED SEMAGLUTIDE

A series of in vitro studies were conducted in dogs to investigate the mechanism via which SNAC enhances the absorption of semaglutide. The trans-epithelial transport of semaglutide was examined in cell monolayers of gastric epithelium (NCI-N87) with and without SNAC exposure. The absorption-enhancing action of SNAC on semaglutide was found to require concentrations in the millimolar range, as reflected by a significant increase in the apparent permeability coefficient of semaglutide across gastric epithelial cell monolayers in the presence of 80 mM SNAC. The fold change in the apparent permeability coefficient of semaglutide elicited by SNAC was rapidly reduced following the removal of SNAC (within 60 min), emphasising its relatively short window of action. There was a substantial increase in intracellular uptake of semaglutide by gastric epithelial cells with SNAC exposure compared with control, which was not apparent with EDTA, a modulator of tight junction function; these divergent patterns indicate that SNAC mediates absorption via the transcellular route. The authors concluded that SNAC prevented gastric degradation by neutralizing a low pH microenvironment surrounding the tablet,

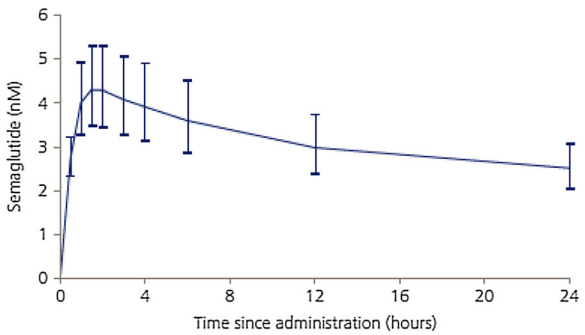

Fig. 3 Estimated mean semaglutide plasma concentration–time profile after a single dose of orally administered semaglutide 10 mg [26]

resulting in an increased concentration-dependent flux of semaglutide across the gastric mucosa [26, 27] (Fig. 4).

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 post dosing, and a reference group that ate 30 min post dosing. The fed group experienced significantly lower systemic semaglutide exposure after the 10th dose, whereas both the fasting and reference groups achieved therapeutic concentrations [26]. Two volumes of water (50 and 120 mL) consumed with semaglutide 10 mg/SNAC 300 mg were also examined. Neither amount of water made significant differences to the PK parameters of orally administered semaglutide. On the basis of these studies, food intake impacts the pharmacokinetics of semaglutide and it is necessary to advise patients to fast before administration of the drug [28]. The PK parameters of orally administered semaglutide and subcutaneously administered semaglutide are listed in Table 2 [29, 30]. Orally administered semaglutide was administered for 10 consecutive days with dose escalation on the 5th day (5 days of 5 mg dosing followed by five days of 10 mg dosing) to avoid gastrointestinal side effects in both normal and renally impaired subjects. After 10 days PK samples were taken for 21 days. C_{max} was 15 nM with a T_{max} of 1 h and a half-life of 1 week [29]. In comparison, subcutaneously administered semaglutide given as a single injection (0.5 mg) has shown a C_{max} of 10 nM with T_{max} of 24 h with a similar 1-week half life [30]. In both studies no difference was seen in normal vs renally impaired subjects.

Semaglutide is primarily metabolized via proteolytic cleavage of the peptide backbone by DPP4 and neutral endopeptidases and sequential beta-oxidation of the fatty di-acid side chain. These degradation products are then excreted in the urine and faeces [29]. There was no apparent effect of renal impairment, hepatic impairment or upper GI disease on the PK and tolerability of orally administered semaglutide, suggesting that dose adjustment is not necessary in these special populations [11, 31–33]. Since orally administered semaglutide absorption depends on localized SNAC buffering, co-administration with other agents has 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

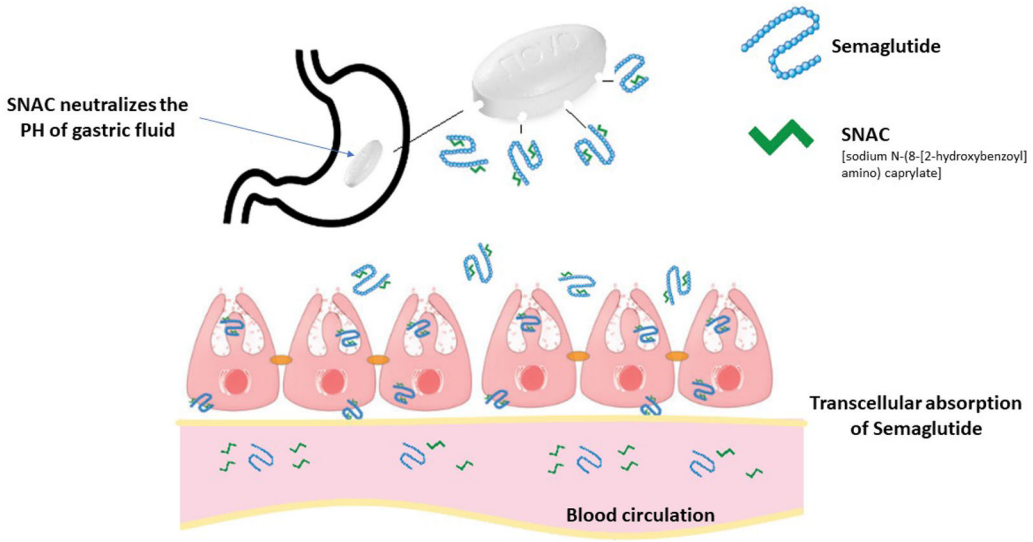

Fig. 4 Mechanism of absorption of semaglutide and SNAC co-formulation tablet

Table 2 Pharmacokinetic parameters of orally administered semaglutide and subcutaneously administered semaglutide [29, 30]

PK parameter	Orally administered semaglutide	Subcutaneously administered semaglutide
AUC (nmol h/L)	284	2600
C_{max} (nM)	15	10
T_{max} (h)	1	24
$T_{1/2}$ (h)	≈ 1 week	≈ 1 week

interactions with semaglutide. None of these agents significantly affected orally administered semaglutide concentrations [34].

ORALLY ADMINISTERED SEMAGLUTIDE CLINICAL DATA: SUMMARY OF PIONEER TRIALS

PIONEER is the phase 3 trial programme of orally administered semaglutide designed to evaluate the risk–benefit profile of orally administered semaglutide. The orally administered semaglutide phase 3a programme evaluated the efficacy, safety and tolerability of once-daily orally administered semaglutide in 9543 randomised subjects with T2D, of whom 5707 were exposed to orally administered semaglutide. In the ten phase 3a trials comprising the programme, relevant contemporary T2D treatment options were used as comparators in head-to-head comparisons. The programme also included a long-term safety trial, trials to evaluate the use of orally administered semaglutide in individuals with moderate renal impairment and as add-on to insulin as well as a cardiovascular outcome trial (CVOT) to evaluate the CV safety profile. Table 3 summarizes the PIONEER trial programmes [35–44].

CARDIOVASCULAR OUTCOMES WITH ORALLY ADMINISTERED SEMAGLUTIDE

PIONEER 6 (NCT02692716) was an event-driven CVOT designed to confirm that treatment with orally administered semaglutide does not result in an unacceptable increase in CV risk compared with placebo. It was a pre-approval cardiac safety assessment trial with a primary objective of non-inferiority to placebo, which was basically done to get early approval as per regulatory guidance. A total of 3183 patients with T2D at high risk of CV events were enrolled; PIONEER 6 achieved its primary endpoint by demonstrating non-inferiority ($p < 0.001$) of MACE (composite of CV death, non-fatal myocardial infarction (MI) and non-fatal stroke) for orally administered semaglutide compared with placebo, both in addition to standard of care. An HR of 0.79 in favour of orally administered semaglutide compared with placebo was observed, but this 21% reduction in MACE did not reach statistical significance ($p = 0.17$ for superiority). Among the individual components of the primary endpoint, there was a reduction in CV death of 51% (HR 0.49; 95% CI 0.27, 0.92) in the orally administered semaglutide group. The HR for non-fatal MI was 1.18 (95% CI 0.73, 1.90) and for non-fatal stroke was 0.74 (95% CI 0.35, 1.57). In addition, a statistically significant reduction in all-cause mortality of 49% (HR 0.51; 95% CI 0.31, 0.84) in favour of orally administered semaglutide was observed. The HR for the expanded MACE outcome was similar to that of the primary outcome (HR 0.82; 95% CI 0.61, 1.10) [40]. In comparison, the subcutaneously administered once-weekly semaglutide CVOT, SUSTAIN 6 has shown superiority over placebo with a significant 26% risk reduction for MACE [19].

The PIONEER 6 trial was aimed at proving CV safety of orally administered semaglutide only. Another trial, SOUL (NCT03914326), has

Table 3 Overview of the PIONEER 1–10 clinical trials on orally administered semaglutide [35–44]

Trial	Comparator	Design	Number of patients	Treatment arm	Key results	Specific comments
PIONEER 1 [35]		26-week, phase 3a, randomised, double-blind, placebo-controlled, parallel-group trial	703	Randomised (1:1:1:1) to once-daily orally administered semaglutide 3 mg, 7 mg, 14 mg or placebo	Significant HbA1c reduction for all doses between 0.6% and 1.1% Significant weight reduction with 14 mg dose (3.4 kg vs 1.8 kg)	Orally administered semaglutide monotherapy demonstrated superior and clinically relevant improvements in HbA1c (all doses) and body weight loss (14 mg dose) versus placebo
PIONEER 2 [36]	Empagliflozin 25 mg	52-week, randomised, open-labelled, active comparator, parallel-group trial	821	Randomised (1:1) orally administered semaglutide 14 mg or empagliflozin 25 mg	Significantly better HbA1c reduction at week 26 (1.9% vs 0.9%) and week 52 (1.3% vs 0.8%). Significant better weight reduction at week 52 (1.3 kg vs 0.9 kg)	Gastrointestinal adverse events were more common with orally administered semaglutide Weight reduction not significant at week 26
PIONEER 3 [37]	Sitagliptin 100 mg	26-week, randomised, double-blind, double-dummy, parallel-group, phase 3a trial	1864	Randomised (1:1:1:1) orally administered semaglutide, 3 mg, 7 mg or 14 mg or sitagliptin, 100 mg	Significantly better reduction in HbA1c and body weight with 7 mg (0.2% HbA1c and − 1.6 kg weight) and 14 mg (0.5% HbA1c and − 2.5 kg weight) semaglutide	Non-inferiority of semaglutide, 3 mg/d, with respect to HbA1c was not demonstrated

Table 3 continued

Trial	Comparator	Design	Number of patients	Treatment arm	Key results	Specific comments
PIONEER 4 [38]	Liraglutide 1.8 mg	52-week, randomised, double-blind, double-dummy, phase 3a trial	711	Randomly assigned (2:2:1) to once-daily orally administered semaglutide (dose escalated to 14 mg), once-daily subcutaneously administered liraglutide (dose escalated to 1.8 mg), or placebo	Semaglutide and liraglutide produced average HbA1c reductions that were similar to each other and significantly better than that of placebo, at 1.2% and 1.1% Semaglutide produced significantly greater weight loss than liraglutide, at an average of 4.4 versus 3.1 kg	Orally administered semaglutide was non-inferior to subcutaneously administered liraglutide and superior to placebo in decreasing HbA1c, and superior in decreasing body weight compared with both liraglutide and placebo
PIONEER 5 [39]		26-week, randomised, double-blind, phase 3a trial aiming to investigate the efficacy and safety of orally administered semaglutide in patients with type 2 diabetes and moderate renal impairment	324, with moderately impaired renal function, estimated glomerular filtration rate of 30–59 mL/min per 1.73 m^2	1:1 randomised to receive orally administered semaglutide (dose escalated to 14 mg once daily) or matching placebo	Orally administered semaglutide (dose escalated to 14 mg/day) was associated with an average 1.0% reduction in HbA1c, versus a 0.2% reduction with placebo Weight reduction of 3.4 kg vs 0.9 kg	Renal function remained unchanged in both groups during the 26 weeks of treatment

Table 3 continued

Trial	Comparator	Design	Number of patients	Treatment arm	Key results	Specific comments
PIONEER 6 [40]		CVOT, event-driven, randomised, double-blind, placebo-controlled trial involving patients at high cardiovascular risk, median time in the trial was 15.9 months	3183	1:1 randomised to once-daily orally administered semaglutide (target dose, 14 mg) or placebo	From baseline to end of study, orally administered semaglutide was associated with a reduction compared with placebo in both HbA1c (− 1.0% versus − 0.3%, respectively) and body weight (− 4.2 kg versus − 0.8 kg, respectively)	Patients with type 2 diabetes and high cardiovascular risk (85% with established disease)
PIONEER 7 [41]	Sitagliptin 100 mg	52-week, multicentre, randomised, open-label, phase 3a trial	504	1:1 randomised orally administered semaglutide with flexible dose adjustments to 3, 7 or 14 mg once daily or sitagliptin 100 mg once daily	Orally administered semaglutide group experienced a statistically significant reduction in HbA1c of 1.3% compared to 0.8% with sitagliptin Significant weight reduction of 2.6 kg vs 0.7 kg with sitagliptin	Compared the flexible dose adjustment of orally administered semaglutide with sitagliptin

Table 3 continued

Trial	Comparator	Design	Number of patients	Treatment arm	Key results	Specific comments
PIONEER 8 [42]		52-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial	731	Patients with T2DM on a stable regimen of basal, basal-bolus (in any combination) or premixed insulin (including combinations of soluble insulin) randomised 1:1:1:1 to either orally administered semaglutide 3 mg, 7 mg, 14 mg or placebo	3, 7 and 14 mg/day doses of orally administered semaglutide achieved average HbA1c reductions of 0.6%, 0.9% and 1.3%, respectively, versus 0.1% for those taking placebo. The corresponding average body weight reductions were 1.4, 2.4 and 3.7 kg versus 0.4 kg	Patients with type 2 diabetes uncontrolled on insulin with or without metformin

Table 3 continued

Trial	Comparator	Design	Number of patients	Treatment arm	Key results	Specific comments
PIONEER 9 [43]	Liraglutide 0.9 mg	52-week, phase 2/3a, randomised, controlled trial	243	Randomly assigned 1:1:1:1:1 to receive double-blind, once-daily treatment with 3 mg, 7 mg or 14 mg orally administered semaglutide or placebo, or open-label treatment with liraglutide 0.9 mg	HbA1c reductions at week 26 (the primary endpoint) ranged from 1.1% to 1.7% (all significant) with 3, 7 and 14 mg/day orally administered semaglutide versus placebo. At the highest dose there was also a significant reduction of 0.3% versus liraglutide 0.9 mg, although this was not sustained at week 52. Weight reduction was − 2.6 kg with orally administered semaglutide 14 mg vs 0.4 kg with 0.9 mg of liraglutide	Trial population: Japanese people with type 2 diabetes taking one antidiabetes medication or treated with diet/exercise only

Table 3 continued

Trial	Comparator	Design	Number of patients	Treatment arm	Key results	Specific comments
PIONEER 10 [44]	Dulaglutide 0.75 mg	52-week, open-label, randomised, active-controlled, phase 3a trial	458	Patients aged 20 years and older with uncontrolled type 2 diabetes were randomly assigned (2:2:2:1) to receive once-daily orally administered semaglutide 3 mg, 7 mg or 14 mg, or once-weekly subcutaneously administered dulaglutide 0.75 mg	The 14 mg dose of semaglutide produced a significant 0.3% HbA1c reduction versus dulaglutide at a dose of 0.75 mg and with estimated treatment difference of − 2.6 kg for orally administered semaglutide 14 mg vs dulaglutide 0.75 mg	Orally administered semaglutide was well tolerated in Japanese patients with type 2 diabetes. Once-daily orally administered semaglutide significantly reduced HbA1c (14 mg dose) and body weight (7 mg and 14 mg doses) versus weekly subcutaneously administered dulaglutide 0.75 mg by week 52

now been initiated to overcome the shortcomings of PIONEER 6 with a primary endpoint focused at proving CV superiority vs placebo.

SAFETY OF ORALLY ADMINISTERED SEMAGLUTIDE

The most common adverse effect observed in all PIONEER studies are gastrointestinal-related, dose-dependent and manifested as nausea, vomiting and diarrhoea. Across the PIONEER trials around 15–23% of patients experienced nausea with orally administered semaglutide 14 mg, and approximately 7–15% of patients on 14 mg orally administered semaglutide discontinued the trial. Approximately 5–7% of patients experienced decrease in appetite, which was consistent across the PIONEER trials [35–44].

When it comes to outcomes and safety measures in different age groups, an exploratory analysis of seven PIONEER trials was done; including PIONEER 1–5, 7 and 8, a total of 5657 patients were included in the analysis. This exploratory analysis evaluated the effect of age at baseline on efficacy (< 45, ≥ 45 to < 65, or ≥ 65 years) and safety (< 65 years and ≥ 65 years). In terms of safety, generally more events and events leading to discontinuation were reported in the patient group aged of 65 years or more. This is in line with what has been seen with other GLP-1 RAs [45].

COST OF ORAL VS INJECTABLE AND OTHER THERAPIES

No new drug adoption is possible without the proper cost-related analysis in relation to already available options. In a cost of control analysis by Hansen et al. for the US market, orally administered semaglutide was found to be cost effective in comparison to dulaglutide, exenatide, liraglutide and lixisenatide. Cost of a 14 mg dose of orally administered semaglutide came out the least at USD 15,430 and USD 17,383 for patients achieving glycaemic targets of $< 7\%$ and $\leq 6.5\%$, respectively [46]. In another cost-effectiveness analysis done for the UK market, orally administered semaglutide 14 mg was found to be cost effective relative to sitagliptin 100 mg and empagliflozin 25 mg and dominant in comparison to liraglutide 1.8 mg daily dose for the treatment of T2DM. The cost-effectiveness ratio per quality-adjusted life year (QUALY) was reported as GBP 11,006 versus empagliflozin and GBP 4930 versus sitagliptin [47].

DOSING AND ADMINISTRATION

Currently orally administered semaglutide is approved by the US Food and Drug Administration (FDA), European Medicines Agency, Health Canada, Australia and Japan as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. It is available as 3, 7 and 14 mg oral tablet formulations.

- Orally administered semaglutide should be taken on an empty stomach.
- Orally administered semaglutide should be swallowed whole with up to half a glass of water equivalent to 120 mL.
- Do not split, crush or chew the tablet.
- Wait at least 30 min before the first meal or drink of the day or taking other oral medicinal products. Waiting less than 30 min may decrease the absorption of semaglutide.

If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day [48]. Patient counselling on the administration of the drug is crucial for the effectiveness of orally administered semaglutide.

ORAL GLP-1 RA IN DEVELOPMENT

The success of orally administered semaglutide in clinical trials has led to the development of other oral formulations. OWL833 is a new orally active non-peptide GLP-1 RA licensed by Eli Lilly. In preclinical studies conducted on cynomolgus monkeys it has shown agonistic activity to human and cynomolgus GLP-1 receptors and improved glucose tolerance by

stimulating insulin secretion, and it exhibited an anti-feeding activity like exenatide. Further human clinical trials will help in better understanding the drug in the treatment of diabetes [49]. Another oral GLP-1 RA, which is a non-peptide molecule, under development is TTP273 from vTv Therapeutics; this drug has recently completed phase 2a clinical trials with promising results in reducing HbA1c without any nausea [50].

CONCLUSION

GLP-1 RAs are an important class of glucose-lowering drugs. Though their use is supported by various professional guidelines, their injectable route of administration has been considered a barrier to widespread adoption. The development of semaglutide, an oral GLP-1 RA, overcomes this barrier. Already approved for prescription in Europe, USA, Canada, Australia, Japan and Switzerland, orally administered semaglutide has been shown to be effective, safe and well tolerated. The drug should emerge as a first-line therapy for persons with type 2 diabetes and associated overweight/obesity as well as atherosclerotic cardiovascular disease. It should also be helpful in persons at high risk of hypoglycaemia, and those who prefer the advantage of oral over injectable administration. Further clinical trials and experience will help improve our understanding of the benefits of this drug.

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