Volume 9, Issue 6, June – 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

Oral Anti-Diabetic Semaglutide: A GLP-1 RA Peptide

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Abstract:- T2DM has emerged as a global disorder. Although there are many treatment options available for T2DM patients, still several patients complaint about inadequate blood sugar levels. Diabetes management is not limited to just lowering of blood glucose level, it needs a multifactorial approach in treatment. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a new category of T2DM drugs that acts on various targets such as body weight reduction, renal and cardiovascular benefits. Despite of being so beneficial the major drawback of semaglutide has been its subcutaneous route of administration. Majority of the patients are unable to continue semaglutide for long because of their reluctance towards daily injectable. To avoid this oral semaglutide is introduced. Oral semaglutide is a GLP-1RA which is displays high glycaemic control. However, in order to increase its bioavailability, it needs to be co formulated with sodium N-(8-[2-hydroxybenzyol] amino) caprylate (SNAC). Oral semaglutide has gone through a very intense series of clinical trials known as, Peptide Innovation for Early Diabetes Treatment (PIONEER). These trials have established benefits of oral semaglutide regarding reduction in glycaemic levels and body weight. It is deemed to be fit for regular consumption. In this review we discuss many aspects of oral semaglutide such as, its chemical structure, route of administration, challenges associated with the oral form of semaglutide, dosage, mechanism of oral bioavailability, robust indications, its placement in the line of defence, drug-drug interaction, various clinical trials (Phase trials and PIONEER studies) including their results. It also summarizes the benefits of oral semaglutide beyond glycaemic control and some future scope of research in the field.

I. INTRODUCTION

➢ *Background*

According to the reports of International Diabetes Federation (IDF), 463 million people were confirmed diabetics in 2019. This number is expected to reach 700 million by 2045. Although prevalence statistics of diabetes may vary among different countries, regions, lifestyles and food habits but Asia has emerged as an epicenter of diabetes disorder. Precisely, China and India houses 139.9 million and 65 million diabetics.Whereas in the USA, 34 million (approximately) people suffer from diabetes. Above all the prevalence rate of type II diabetes (T2DM) mellitus is 95% (Yusufi 2023, Niman et al 2021).

In normal conditions, glucose homeostasis is maintained by insulin which is secreted by the pancreatic beta cells. In case of diabetes, beta cells get dysfunctional resulting in impaired insulin secretion or insulin resistance, which further causes imbalanced glucose homeostasis (Niman et al 2021). Uncontrolled T2DM may cause macro and micro-vascular complications. These may include cardiovascular diseases (CVD), coronary artery diseases (CAD), peripheral arterial diseases or diabetic neuropathy/retinopathy. T2DM may also cause stiffness in the blood vessels resulting in hypertension. To avoid such repercussions, strict maintenance of blood sugar levels is highly recommended. Although changes in the food habits and lifestyle and regular exercise may catalyse the improvement in glycaemic control but anti-hyperglycemic medicaments are imperative to sustain appropriate glucose levels. Metformin has been and continues to be the first choice for treatment of T2DM. However, the American Diabetes Association Guideline for Pharmacologic Approaches to Glycaemic Treatment: Standards of Medical Care in Diabetes advices an alternate treatment along with metformin for cases where in metformin doesn't show the desired results (ADA 2020). This add-on treatment accounts to glucagon-like peptide-1 receptor agonist (GLP-1RA) and/or a sodium-glucose cotransporter-2 inhibitor (in cases with CVD).

The US Food and Drug Administration has approved and allowed commercial marketing of five GLP-1RAs, exenatide, liraglutide, dulaglutide, lixisenatide, and subcutaneous semaglutide. These are applicable for long-term T2DM management (ADA 2020). Among the GLP-RA drug class, there are variations in the molecular structures, dosing, glycemic controllability, and immunogenicity and tolerability levels. However, GLP-1RA has proven to lower the HbA1c level by 1.9% and also reduce the body weight by 5-10 lbs (Niman et al 2021). These results make them a promising candidate for antihyperglycemic medication.

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Inspite of having a vast plethora of advantages, GLP-RAs are not the first choice of medication amongst the patients. This is due to their injectable administration (Niman et al 2021, Bucheit et al 2020). After years of research and efforts, first orally admissible GLP-RA, "Semaglutide", is introduced. It is expected to overcome the limitation. Numerous clinical trials and studies have been conducted to validate and verify the efficiency of oral semaglutide on an individual level. However, there are very few reviews that could summarize these studies and add substantially to the relevant literature.

Diabetes mellitus has emerged as a global health issue worldwide. About 10% of the adult population is suffering from diabetes and 90% cases correspond to T2DM. The prevalence rate of T2DM is exponential; it is highly prevalent in South America, Estern Europe and Asia. Specifically is China and India (Eliaschewitz and Canani 2021). Nevertheless there are many treatment options available in the market, still hyperglycaemia remains a challenge. Discovery of GLP-1RA has come as a hope for the physicians. It can be used alongside of metformin. GLP-1 is one of the major incretin hormones in human body. It is involved in various biochemical pathways such as suppression of hepatic gluconeogenesis; augmented (glucose-dependent) insulin secretion and inhibition of glucagon release (Mahapatra et al 2022).

Semaglutide belongs to the class of Glucagon-like peptide 1 receptor agonists (GLP-1RAs) drugs. These are classified as important antidiabetic drugs, primarily involved in T2DM management. Many prominent pathophysiologies (atleast six out of eight), such as pancreatic cells (α and β), brain, liver, muscles, incretin are targets of GLP-1RAS. It has shown to have remarkable safety benefits for CV patients. It has also proven significant HbA1c and weight reduction in T2DM patients. The only limitation associated with it is the subcutaneous route of administration. Over decades of research, finally an oral GLP-1RA, Semaglutide is developed and is available for clinical studies (Kalra et al 2020). Currently, **Ozempic®** (available in 0.5, 1.0 mg dose subcutaneous injection, weekly-once) and **Rybelsus®** (available in 3, 7, 14 mg dose, oral tablets, once-daily) are launched by Novo Nordisk and are approved by USFDA, Health Canada, European Medicines Agency, Japanese Health ministry. However, it's under review at many health regulatory authorities (Rosenstock et al 2020, Novo Nordisk assessment 2020).

This review summarizes various aspects of Semaglutide such as, its chemical structure, route of administration, challenges related to oral peptides, dosage, mechanism of oral bioavailability, robustness involved, drug-drug interaction, various clinical trials and their results.

II. CHEMICAL STRUCTURE

Semaglutide is known as a 'human homologue' of native GLP-1RA because its structure is 94% similar to the GLP-1RA. The chemical formula is C187H291N45O59, it's hydrophilic and has molecular weight of 4113.58 g/mol. It has 31 amino acid forming peptide structures. semaglutide molecule is modified at three places: 8, 26 and 34 positions (Kalra et al 2020). These modifications increase the half-life by 160 hours. At the 8th position, alanine is replaced by 2-aminoisobutyric acid (Aib). This replacement protects the peptide from degradation by dipeptidyl peptidase-4 (DPP-4) enzymes. The second modification is at 26th position, where lysine is placed. This lysine residue is acylated by C18 fatty acid chain. This diacid chain is attached through "γGlu-2xOEG" (hydrophilic linker sequence).this modification increases systemic half-life by reducing renal clearance and enhancing albumin binding. The third modification is at the 34th position of the peptide sequence. The lysine residue at the 34th position is substituted by an arginine residue. This replacement avoids mis-binding of C18 fatty acid chain and is helpful in producing GLP-1 by recombinant methods (Fig1) (Mahapatra et al 2022 and Kalra et al 2020]

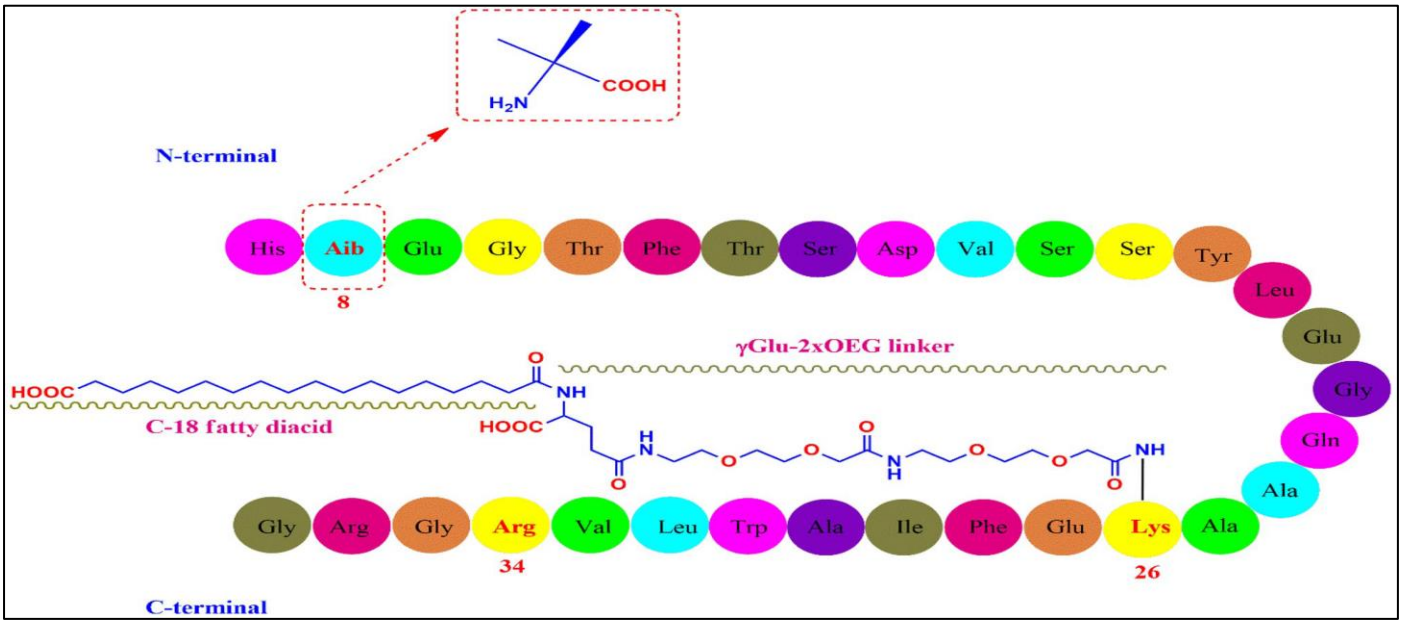

Fig 1 Chemical Structure of Oral Semaglutide (Mahapatra et al 2022)

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

➢ *Challenges of Oral Peptide*

Peptides are less than 100 amino acid long monomeric chain. Due to their small size they can be used as a potential therapeutics. Many positive factors make peptides capable for therapeutic usage. Some of them are low toxicity, low tissue accumulation, broad range of targets (high chemical and biological diversity binding), higher efficiency, tolerability and safety. However, scientists had to face many difficulties during their research. Some of them are high cost of production, low oral bioavailability, low metabolic stability, short half-life and rapid clearance. The nature of the peptide also posed several challenges such as poor membrane permeability, presence of immunogenic sequences and affinity towards aggregate formation (Eliaschewitz and Canani 2021**)**.

To approach against these challenges researchers made multiple strategies. Some of the approaches are as under (Drucker 2020):

- Development of permeation enhancers that specifically worked on the transcellular /paracellular routes causing improved permeability.
- Direct inhibition of enzymes using precise inhibitors
- Alteration of pH
- Use of devices such as milliposts/ microneedles was encouraged to maintain bioavailability and to reduce the side effect of protein size.
- Reducing cleavage susceptibility by enzyme attack through removal of exposed N and C termini from the peptide by cyclization of peptide.
- To enhance peptide passage through mucus membrane barriers, mucus permeating agents were used.
- To deliver the peptides across the cell membrane, glycosaminoglycan interacting peptides were deployed to penetrate the cell through exocytosis.
- To protect the drug from degradation by local enzymes, while placing it near absorptive epithelium, intestinal patches were used.
- For prolonged sustenance of the drug within the gut region and in presence of constant enzymatic resistance, facilitating hydrogels were used. Hydrogels also prolong the shelf time of the peptide.

➢ *Development of Oral Semaglutide: a GLP-1 RA Peptide*

GLP-1, an intestinal hormone (from incretin family) plays an important role in numerous biological processes. It induces physiological satiety by many ways. Through the central nervous system, it signals satiety through the hypothalamus. Here GLP-1 mimics a neurotransmitter. Peripherally, it regulates appetite by inducing a sense of fullness and reducing hunger. Biochemically, it is involved in suppression of glucagon release, amplification of insulin secretion, reduces insulin resistance and delays gastric emptying (Drucker 2020, Reed et al 2020).

No doubt, GLP-1RA is potential therapeutic candidates for the T2DM treatment but they are only available as a parenteral formulation. Its limited bioavailability has been a major challenge to introduce it as an oral medication. To overcome this challenge researchers developed a coformulation of semaglutide with a transcellular permeation enhancer, sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC). Conjugated SNAC enhanced the permeation and ensured the bioavailability of oral semaglutide. Along with semaglutide (10 mg), SNAC (300 mg) predominantly transits through the gastric epithelium. The absorption of ingredients occurs in the epithelium 1-2 hours after the ingestion of the tablet. This was applicable for 10 mg. In order to enhance the bioavailability, patients are recommended to have an oral semaglutide empty stomach in the morning with 120 ml of normal water. Gradual increase in the dose can be considered as per requirement to avoid gastric issues. Dose begins from 3 mg daily (for a month) to 14 mg daily dose (Drucker 2020).

However, Semagltide is marketed as long acting, subcutaneous, once a week dosage treatment for T2DM (Aroda et al 2019). During clinical trial phase III, subcutaneous semaglutide was found to have greater reduction in the HbA1c levels and body weights and higher safety standards as compared to placebo (and other standard medicines) for T2DM treatment. But, since patients prefer to have oral dosage, the idea of transformation of semaglutide from injectable to oral medication was conceived.

The first oral formation of the drug was approved by Food and Drug Administration (FDA) on 20TH September 2019, by Brazilian Health Regulatory Agency (ANVISA) on 20th October 2020. This was decided on the bases of remarkable efficiency and safety provided by oral semaglutide as compared to the standard of care medication (and placebo) in the results of PIONEER program (phase III clinical trial) (FDA report 2019).

➢ *Mechanism of Oral bioavailibilty*

Low bioavailability has been the major issue for acceptance of semaglutide as an oral medicine. Oral administration of GLP-1RA accounts to near negligible bioavailability i.e. 0.01% (Drucker 2020). Semaglutide gets degraded due to low pH and proteolytic enzyme action. Additionally, permeation through the epithelium is difficult due to its molecular weight. These factors constitute to low absorption and finally lead to low bioavailability.

However, conjugation of semaglutide with SNAC has improved bioavailability by100 folds. SNAC is a fatty acid chain, which facilitates easy permeation through the gastric epithelium. It protects the tablet from local proteolytic degradation and also increases the pH around the periphery. It transcellularly transits the tablet. SNAC works in a time and concentration-dependent manner. SNAC conjugate is analyzed from 150 mg to 600 mg, and the peak absoption with maximum bioavailability is found at 300 mg (Kalra et al 2020). Table 1 summarizes the pharmacokinetics of semaglutide (injectable Vs oral)

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Table 1 Pharmacokinetics of Injectable Semaglutide Vs Oral Semaglutide.

Characteristic		Inj. Semaglutide	Oral Semaglutide
Concentration time	**Steady state**	4-5 weeks	4-5 weeks
	maximum	1-3 days	1 hour
Distribution	**Protein binding**	>99%	>99%
	Distributed volume	12.5 litres	8 litres
Absorption	**Absolute bioavailability**	89%	0.4-1%
	Steady state plasma concentration	65 ng/ml (0.5 mg once weekly)	6.7 nmol/L (7 mg once daily)
		123 ng/ml (1 mg once weekly)	14.6 nmol/L (14 mg once daily)
Elimination profiling	**Half time**	1 week	1 week
	Rate of clearance	0.05 litres/hour	0.04 litres/hour
Metabolic pathway involved		Proteolytic degradation and later fatty acid oxidation	Proteolytic degradation and later fatty acid oxidation

III. CLINICAL TRAILS

Any drug or medication that is entitled for human consumption for treatment has to go through a robust sequence of clinical trials. Oral semaglutide also went through many clinical trials and evaluation studies. Wherein, it was assessed multiple times and compared to a number of potential contemporaries. The clinical trials were very carefully designed keeping in mind the entire necessary requirement needed for the approval of any medication (for human consumption). These series of clinical trials included a phase I study, phase II study and phase III study, which comprises of a series of PIONEER studies.

➢ *Phase I*

Phase I clinical trial was the first clinical study in the cascade of clinical trials planned for oral semaglutide. It was completed by *Granhall et al.* This study was meant to assess the tolerability and safety of the oral semaglutide. It also analyzed the pharmacokinetics and pharmacodynamics traits of multiple doses of the oral semaglutide with SNAC. The study population consisted of healthy individuals and people with T2DM. The primary objective of the study was to study the adverse effects that occur due to the treatment in both the study groups. The secondary objective was to study the area under the curve (concentration-time) to evaluate plasma concentration, fasting glucose level, insulin and HbA1c. The study was also divided into 2 types: the single dose study and multiple dose study.

In case of single dose study; In order to determine the optimum amount of SNAC required for largest systemic absorption of oral semaglutide, many combinations were attempted (oral semaglutide ranging from 2mg to 20 mg). Subjects were divided into 3 groups and randomized accordingly. In all the dose study groups, subjects were randomized either with oral semaglutide or placebo having equal amounts of SNAC. The healthy male subjects were administered with 1 of the 3 parts. [part 1a had 4 ascending order doses of SNAC, PART 1b had included 3 additional doses and Part 2 had 3 of the doses used in part 1 which were chosen to be repeated in part 2 as a parallel design].

On the other hand, multiple-dose study was conducted. It consisted of 2 groups of patients. The study enrolled 107 male subjects, out of which 84 were healthy and 23 had T2DM (being treated with controlled diet, regular exercise or metformin). The healthy were given oral semaglutide (20 mg and 40 mg) one tablet each day and T2DM patients were given oral semaglutide 40 mg once daily. Both groups had additive SNAC 300 mg.

In terms of adverse events (AE), mild AEs were reported in case of single dose study, which usually included GI disorders and headaches. As a result of part 1a and 1b, 300 mg SNAC was found to be the most suited adjunct for the tested range of semaglutide. In addition to this body weight reduction was also noted in the study. However, body weight reduction was statistically significant in oral semaglutide Vs placebo (Granhall et al 2018).

On the other hand, 662 AEs were reported in the multiple dose study. Similar to the single dose study, majority of AEs reported were GIs. Interesting fact noted was that severity of AEs was directly proportional to the dose of oral semaglutide. However, the AEs were resolved after dose correction (Niman et al 2021).

➢ *Phase II*

The Phase II clinical study was designed to assess the efficiency and efficacy of oral semaglutide in comparison to the injectable (subcutaneous) semaglutide over the glycemic control. The study was conducted by Davies et al. The study enrolled 632 patients with T2DM. The enrolled subjects were treated with diet control and regular exercise or metformin. The HbA1c level of the enrolled patients was from 7% to 9.5%.The Phase II clinical study comprised of 9 study groups on the basis of the oral semaglutide dose. The patients were randomized with 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg of oral semaglutide, 40 mg with slow (8 weeks) dose escalation, 40 mg with fast (2 weeks) dose escalation, open label subcutaneous semaglutide and a placebo. The subcutaneous dose was administered once a week and the oral medications were given once every day. A mean reduction of 1.8% in the HbA1c levels was noted within 26 week in the oral semaglutide 40 mg dose as compared to the placebo. The patients with oral semaglutide showed HbA1c reduction, 0.4% in 2.5 mg group, 0.9% in 5 mg in group, 1.2% in 10 mg group, 1.4% in 20 mg group, 1.6% in 40 mg group. Patients in the oral semaglutide group also showed significant loss in the body weight in a dose dependent manner. Statistically significant body weight reduction was

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

reported, 2.1 kg (for oral semaglutide 2.5 mg, $p = 0.25$), 2.7 kg (for oral semaglutide 5 mg $p = 0.06$), 4.8 kg (for oral semaglutide 10 mg, $p < 0.001$), 6.1 kg (for oral semaglutide 20 mg, $p < 0.001$), and 6.9 kg (for oral semaglutide 40 mg standard escalation, $p < 0.001$) as compared to 1.2 kg with placebo. The phase II clinical trial established that oral semaglutide anti diabetes medicine is a better option as compared to the placebo and the subcutaneous semaglutide (Niman et al 2021, Davies et al 2017).

- *Phase III*

On the basis of the data generated and the success rate of the Phase II clinical trials, a series of 8 metacentric, randomized phase III clinical trials were meticulously designed. The PIONEER clinical study programs were aimed to evaluate the safety and efficacy of the oral semaglutide. Every PIONEER study has a different set of patients to evaluate. The set of patients evaluated has differing associated prevailing medical conditions, duration of diabetes, HbA1c levels and some anti-diabetes medication involved (Eliaschewitz and Canani 2021).

Later, the trials were extended upto 12 phase III clinical trials. These trials included 9542 T2DM patients (as of 2020). Enrollment and analysis of the PIONEER study1 to 8 has been complete, whereas, analysis and research of the PIONEER study 9, 10, 11 and 12 are still ongoing. The PIONEER clinical study evaluates safety and efficacy using the treatment policy estimand and trial product estimand. Here the trial product is the oral semaglutide. The treatment policy estimand is defined as the impact of treatment upon the patient, regardless of the discontinuation of the trial product or use of the rescue medication. The trial product estimand is defined as effect of the treatment on the patients if all the enrolled patients used the trial product and none of them has opted to use the rescue medication. There are trials still being conducted. However, this review summarizes the PIONEER 1 to 8 (Kalra et al 2020).

- *Pioneer Study 1*

PIONEER 1 clinical study was the first step in the long series of rigorous clinical trials designed for oral semaglutide. This clinical study involved 703 patients of T2DM. All the involved patients had uncontrolled diabetes with and average HbA1c from 7.0% to 9.5%, but were treated only with diet modifications and regular exercise. The average age of the enrolled patients was 55 years. This trial was conducted to evaluate efficacy and safety of semaglutide in comparison to placebo. The enrolled patients were randomized with oral semaglutide 3 mg, 7 mg and 14 mg and placebo, in the ratio 1:1:1:1. Patients randomized with semaglutide were given dose escalation every 4 weeks (if needed). All the patients who were on oral semaglutide showed reduction in the HbA1c level as compared to placebo within 26 weeks ($P< 0.001$ all) and higher number of patients attained the desired HbA1c level (55.1%, 68.8%, or 76.9%, respectively vs 31.0%). Statistically significant difference was noted in the results of oral semaglutide 14 mg Vs placebo; however oral semaglutide 3 mg and 7 mg Vs placebo was note statistically different. PIONEER 1 clinical study indicated that oral semaglutide can be used to treat diabetes and can be placed in the first line of defence medications (Kalra et al 2020, Niman et al 2021).

- *Pioneer Study 2*

PIONEER 2 clinical trials was a multicenter clinical study. It was an open-label, parallel group and randomized trial. It included 822 T2DM subjects. The average duration diabetes for this trial was 7.4 years. T2DM patients, who were on metformin baseline treatment (at least for 90 days with level ≥1500 mg or maximal tolerated) and had HbA1c between 7% to 10.5 % were selected for the study. Subjects were randomized with semaglutide (14 mg) and empagliflozin 25 mg (in the ratio1:1). Oral semaglutide (14 mg) displayed significant reduce in the body weight (−0.9 kg [95% CI: −1.6, −0.2 kg]) and HbA1c (−0.5% [95% CI: −0.7%, −0.4%]) levels as compared to empagliflozin (25 mg) within 52 weeks. Additionally, 71.62% subjects attained target glycemic control with oral semiglutide 14 mg in comparison to empagliflozin 25 mg (Rodbard et al 2019, Niman et al 2021).

- *Pioneer Study 3*

PIONEER 3 clinical trials was a multicentre and multinational clinical trial. It was double-blind, double-dummy, randomized, parallel-group clinical trial. The average duration of diabetes included in PIONEER 3 trial was 8.6 years. This study included 1864 T2DM patients who were on metformin (with or without sulphonylurea minimum for 90 days) and had HbA1c levels from 7% to 10.5%. This study made a comparative assessment between oral semaglutide and sitagliptin, comparing their safety, efficacy, tolerability and long term adverse events (AE). All these were done as an add-on medication to metformin ± sulphonylurea in patients with T2DM.the participating patients were randomized with oral semaglutide 3, 7, 14 mg or sitagliptin 100 mg once daily (1:1:1:1) for 78 weeks. Patients on oral semaglutide (7 and 14 mg) showed greater reductions in HbA1c versus sitagliptin across HbA1c subgroups (≤8.0%, >8.0–≤9.0%, >9.0%). A greater number of patients in the semaglutide 3- and 7-mg groups attained desired HbA1c <7% levels in comparison to patients on sitagliptin. Also, significant weight reduction was noted in the patients with oral semaglutide as compared to sitagliptin (at weeks 26, 52 and 78) (Rosenstock et al 2019, Niman et al 2021).

- *Pioneer Study 4*

PIONEER 4 clinical trials is a multicenter based, random, double-blind, parallel group, double dummy and a placebo controlled clinical study. It was a 52 week long study. The average duration of T2DM for this was 7.6 years. This included 722 patients with an average HbA1c between 7 to 9.5%. Patients were on metformin (with or without SGLT2 inhibitor) .This clinical trial compared the efficacy and safety of oral semaglutide with liraglutide (injectable GLP-1RA) and a placebo. Patients were randomized with oral semaglutide (14 mg) once daily, liraglutide (1.8 mg) once daily or placebo (2:2:1). At the final stage of the clinical trial (52 weeks), the oral semaglutide had superior baseline reduction in HbA1c as compared to liraglutide (−0.3% [95% CI: −0.4%, −0.1%]). Higher percentage of

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

patients attained HbA1c <7% as compared to the liraglutide and placebo groups. Similar was noted in case of body weight reduction (at 26 weeks, with a reduction of 4.7, 3.2 and 0.7 kg, respectively) (P < 0.0001 for all comparisons). Since, most of patients are reluctant towards regular use of injectable, oral semaglutide was a better option for intensified regular treatment. Hence, PIONEER 4 clinical trial proved oral semaglutide as a better option over injectable liraglutide in terms of better HbA1c reduction, weight loss and patient compliance (Kalra et al 2020 and Niman et al 2021).

- *Pioneer Study 5*

PIONEER 5 clinical trials was a multinational, multicenter based, randomized, double blind, parallel group and placebo-controlled clinical study. It included 324 patients with T2DM with estimated glomerular filtration rate (eGFR) 30–59 mL/min/1.73 m2, and was taking stable doses of 1–2 oral antidiabetic drugs (OADs). These could be metformin or SU with basal insulin for ≥ 90 days. Among the enrolled patients, 60% had an eGFR of 45 to <60 mL/min/1.73 m2. The average duration of T2DM was 14 years. Oral semaglutide displayed a remarkable loss of weight and reduction in HbA1c levels. Incidence of nausea was reported in 15% -20% of the subjects. Despite of incidence of nausea, patients did not opt for discontinuation of the medicine. Patients were counselled for the dosing adjustment and methodology. Advisories and dose education have been helpful for management of adverse events (Kalra et al 2020, Niman et al 2021).

- *Pioneer Study 6*

PIONEER 6 clinical trials were mainly meant for patients with cardiovascular issues. It was also known as a Cardiovascular Outcome Trial (CVOT). It was 16 months long trial which included multiple events. These were basically designed to compare the CV safety and efficacy of semaglutide to placebo. This clinical trial enrolled 3183 patients. All the enrolled patients had uncontrolled T2DM and were either ≥50 years old (established CV disease or CKD) or ≥60 years old (with CV risk factors). Patients were randomized with oral semaglutide (14 mg) and placebo. This trial included 137 events; nevertheless 122 events were initially planned. Towards the end of the trial, 21% reduction was noted in 3-point major cardiovascular event (3P-MACE) [for non-inferiority HR: 0.79 (0.57; 1.11) P value for non-inferiority: <0.0001; P value for superiority: 0.1749]. Previously, the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 6 trial has reported a significant reduction of 26% in 3P-MACE, while comparing subcutaneous semaglutide to placebo (Husain et al 2019).

- *Pioneer Study 7*

PIONEER 7 clinical trials was an open-label clinical study. It was a 52 weeks long trial. For PIONEER 7, the average duration of diabetes was 8.8 years and HbA1c was kept between 7.5 -9.5%. 504 patients were enrolled in this trial. This trial was mainly a comparative study for efficacy and safety, between oral semaglutide and DPP-4 inhibitor sitagliptin (as an additional medication to an existing anti-diabetes medicine). The anti-diabetes a medication may also include metformin, thiazolidinediones, SGLT-2 inhibitors etc. This trial also considered the dose adjustment with patients on the basis of their existing HbA1c and tolerability criteria. Patients were randomized as two arms - a flexible dose of oral semaglutide (3 mg for 8 weeks, followed by continues 3, 7 or 14 mg) and sitagliptin 100 mg once daily. As a result of this trial, greater percentage (63%) of patients on oral semaglutide attained a satisfactory HbA1c level <7% whereas, only 28% patients with sitagliptin could attain lowered HbA1c. Also, significant lose in the body weight (-1.9, 95% CI -2.6 to -1.2; P < 0.0001) and HbA1c level (-0.5, 95% CI -0.7 to -0.4; P < 0.0001) was noted within 52 weeks. This trial proved the superiority of flexible-dose adjustment of oral semaglutide (in comparison to sitagliptin). Dose adjustment is very important as it is widely followed across all treatment patterns (Pieber et al 2019, Niman et al 2021)

- *Pioneer Study 8*

PIONEER 8 was a double-blind, randomized clinical study, including place-control and parallel-group evaluations. This clinical trial was spread across many nationals and many clinical research centers. The average duration of diabetes in this study was 15 years. This study enrolled 731 patients who had T2DM. Majority of these subjects were on insulin but had imappropriate control over T2DM and managed it by metformin or any other oral antidiabetic medication. These were randomized with oral semaglutide dose (3/7/14 mg once a day) or a placebo once a day. Interestingly, 51 subjects enrolled in this clinical trial were Indians. All the doses of oral semaglutide return good results. The HbA1c level was found to be reduced in all the doses of oral semaglutide. Similar reduction was also noted in the body weight. These resukts were in comparision to the placebo (at 26 and 52 weeks). The PIONEER 8 clinical trial establishes that oral semaglutide is applicable (effective and safe to use) for late stage of diabetes. Also, it can be used as an intensification medicament along with metformin (Zinman et al 2019, Niman et al 2021).

IV. POSOLOGY/DOSING

Dose conditions for oral administration of semaglutide have been optimized by multiple clinical trials and pharmacological studies. Oral semaglutide is advised to have after approximately 6 hours of fasting, preferable in the morning, empty stomach, with at least 120 ml of water. Water shall neither be warm nor chilled. To avoid gastric issue and maintain absorption, it is recommended not to eat or drink for 30 minutes after intake of oral semaglutide.

During the initial days of oral semaglutide therapy, very low dose (3mg) is recommended for a month. Later, depending on the patient profile the dose may be increased (up to 14 mg).In the phase II of clinical trials, various doses (2.5, 5, 10, 20 and 40 mg) of oral semaglutide were analyzed. However, in the phase III, only 3 mg, 7 mg and 14 mg were selected for further analysis. All these are co formulated with SNAC and had optimal benefit-risk proportion (Kalra et al 2020).

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

➢ *Placement in Line of Therapy (1st, 2nd or 3rd)*

Clinical trials (PIONEER) and studies have respectfully places oral semaglutide across the spectrum of diabetes standard of care medication in 1st, 2nd and 3rd line of therapy. PIONEER study 1 placed oral semaglutide in the 1st line of therapy, as an adjunct to diet modification and regular exercise for early diabetes. Oral semaglutide is also established in the2nd line of therapy along with metformin in adults suffering from T2DM. It is mainly because of the results of PIONEER 2 study, wherein oral semaglutide has caused significant reduction in HbA1c and body weight as compared to empagliflozin. PIONEER 3,4,5,7 and 8 depicted remarkable efficiency, efficacy and tolerability of the drug and placed it in the 2nd and 3rd line of therapy against T2DM (Kalra et al 2020).

➢ *Robust Indication*

The robust indication regarding the oral semaglutide is represented in the figure 2. According to US prescribtion, oral semglutide can be used for patients with CKD (all stages) without any dose adjustment (Kalra et al 2020). Oral semaglutide is advisable for patients with CVDs when intolerance towards SGLT-2 inhiboitors is noted. It is a proven safe medicament for diabetics suffering from liver or kidney dysfunctions. The "Management of Hyperglycaemia in type 2 diabetes" by European Association for the Study of Diabetes consensus report 2019 and the American Diabetes Association 2020, recommend the use of oral semaglutide in cases where immediate and higher glycemic control is required and weight reduction is essential. They also recommend oral semaglutide prior to prescribing insulin (ADA 2020).

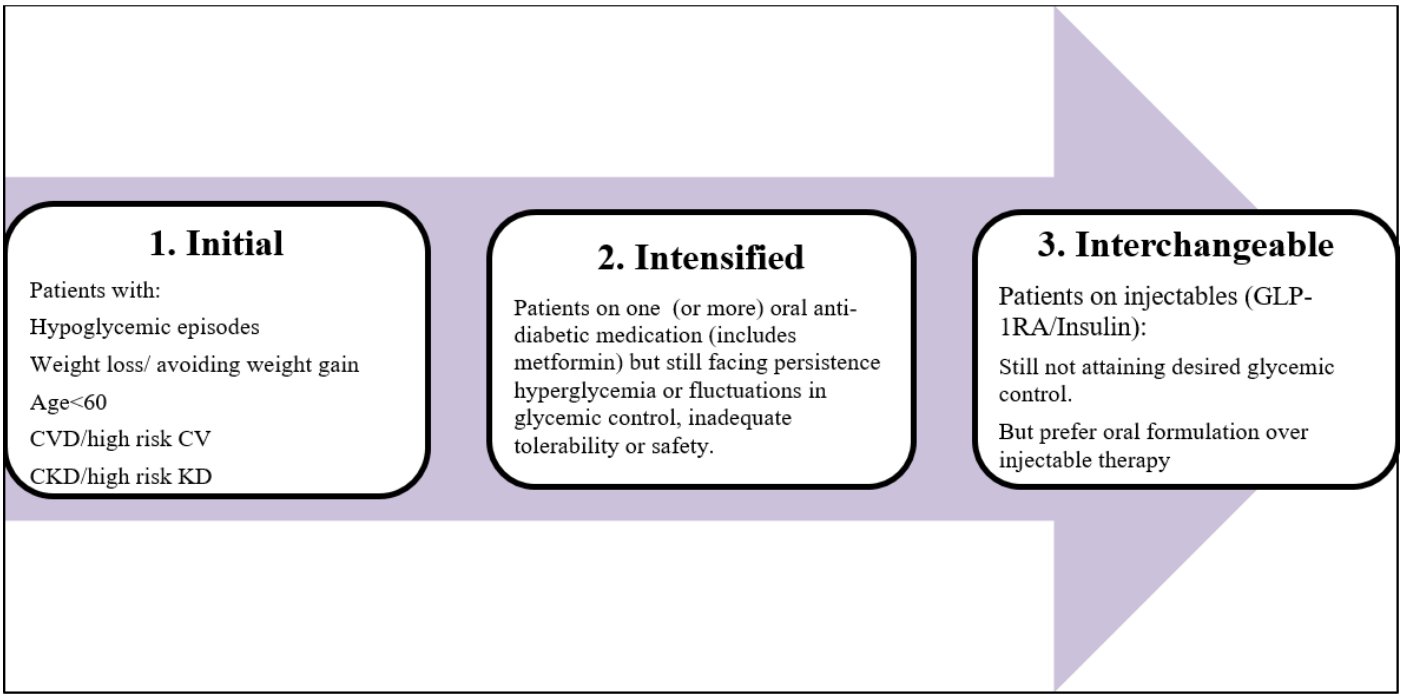

Fig 2 Indication and Placement of Oral Semaglutide

➢ *Drug-Drug Interaction*

Oral semaglutide is rendered a safe drug by several PIONEER clinical trial studies. These tests have been conducted with commonly used baseline drugs. No significant clinical interference is found when oral semaglutide is co administered with the baseline drugs. During the drug-drug interaction studies, no clinically relevant increase has been noted with exposure on omeprazole, metformin, rosuvastatin, Lisinopril, warfarin, furosemide and ethinyloestradiol/levonorgestrel. However, oral semaglutide alomg with levothyroxine caused 33% increased exposure of levothyroxine. Therefore, patients are advised to follow the dosage instruction strictly. Additionally patients with thyroid disorders are advised to take levothyroxine 3 hours after the last meal, likewise interaction can be avoided (Kalra et al 2020, Mahapatra et al 2020).

➢ *Glycemic Control in Pioneer Studies*

- *Glyceamic Efficacy*

An extremely vigorous and sturdy clinical trial programme called Peptide Innovation for Early Diabetes Treatment (PIONEER), has evaluated the glycemic control efficacy of oral semaglutide as an option for diabetes therapeutic. The applicability of oral semaglutide is assed at every stage of diabetes, ranging from early onset, to mid-, and late diabetes. Additionally, it has also been evaluated for its usage for patients with CVD/CKD. In the PIONEER study, 9543 subjects were enrolled and out of them 5707 subjects were randomised to oral semaglutide. The results of the study demonstrated 1.5% reduction in the HbA1c levels, about 70% of the patients attained their targeted HbA1c (<7%) and up to 5 kg of body weight reduction in subjects using oral semaglutide [15, 22 Semaglutide1]. In addition to the main stream PIONEER clinical trial, some post-hoc analyses were also conducted. One of such analysis

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

demonstrated up to 2.6% reduction in HbA1c level among people with HbA1c>9% [23 Semaglut1]. Another study found Asians to be more positively responded towards oral semaglutide. Interestingly, 85% of Asian participants in the PIONEER 8 study were Indians (Mosenzon et al 2019).

- *Early Diabetes Stage*

The results from the PIONEER 1 clinical study trials have advocated placement of oral semaglutide in the first line of treatment for early stage of diabetes, with or after diet and regular exercise. The study was a double-blinded, randomized control clinical trial. Subjects enrolled in this study had diabetes since 3.5 years, Average HbA1c was 8% and body mass index (BMI) 31.8 kg/m2.. This study enrolled 703 subjects and their HbA1c levels were monitored at 26 weeks. Oral semaglutide with dosage 3 mg, 7 mg and 14 mg were compared with the placebo. Significant HbA1c and weight reduction were noted in subjects and 80% subjects having 14 mg oral semaglutide achieved their desired HbA1c (<7%) targets (Aroda and Rosenstock et al 2019).

- *Mid Diabetes Stage*

Mid stage diabetes is covered in the PIONEER 2,3,4 and 7 clinical trial study. The duration of diabetes considered in these studies has been 7.4 to 8.8 years [17-20 semaglut 1]. It included patients who were on metformin but were unable to achieve the desired glycemic control; thereafter these subjects may opt for taking up some additional antihyperglycemic drugs. Recent medical guidelines, recommend using GLP-1RAs, sulphonylureas, Thiazolidinediones, sodium-glucose co-transporter-2 (SGLT2) inhibitors and DPP-4 inhibitors for glycemic control (Garber et al 2020, ADA 2022).

PIONEER 2 clinical trials concluded that oral semaglutide showed good tolerability and efficacy. Also the safety levels were consistent to the GLP-1RAs. Thus, it Can be used in addition to metformin (as compared to empagliflozin) in patients with T2DM (Rodbard et al 2019).

PIONEER 3 clinical trials results proved, as compared to sitagliptin, the oral semaglutide is a better option as an add-on to metformin (with or without sulphonylurea).

PIONEER 4 clinical trials found oral semaglutide to be better medication for treatment of T2DM, in comparision to injectable liraglutide, because it showed better HbA1c reduction and weight reduction. Subsequently, these results also improved patient compliance (Kalra et al 2020).

PIONEER 7 clinical trials stated a superior characteristic feature of dose adjustment for oral semaglutide in comparison to sitagliptin. The concept of dose adjustment is actively followed in the clinical practices (Pieber et al 2019).

- *Late Diabetes Stage*

Late stage of diabetes was covered in the PIONEER 5 and 8 clinical trials study. These clinical trials enrolled the subjects with above 10 years history of T2DM. These patients have been on medications like insulin, with or without metformin but had inadequate glycemic controls. In the PIONEER 5, 6 and 8 study, concepts such as adverse effects (AEs) of the oral semaglutide, dose adjustment (pause dose/ resume dose and accelerate dose) were also included.

PIONEER 8 clinical trials were multicenter and multinational trials. The average duration of diabetes was 15 year. This trial included 731 patients suffering from diabetes, who were on insulin with or without metformin. They had inadequate control over HbA1c levels. The enrolled patients were randomized with oral semaglutide dose of 3, 7 and 14 mg, once daily or placebo once daily. In the results, HbA1c reduction was noted in the patients with renal impairments. Here the researchers have also noted some AEs among the patients. In order to resolve them, the dose of semaglutide were reduced initially and resumed later, after resolving the AEs. However, PIONEER 8 clinical trial study concluded that oral semaglutide is safe and effective for the late stage of diabetes as well. Additionally, oral semaglutide can be used in the intensified treatment therapy as an add-on to insulin (Zinman et al 2019).

PIONEER 5 clinical trials were multicenter and multinational trials. It included 324 subjects. The enrolled patients had T2DM and kidney disorders. The average duration of diabetes was 14 years and majority of patients were on oral antidiabetic drugs (OADs). Patients with oral semaglutide showed a significant reduction in HbA1c and weight. Some patients experienced some side effects such as vomiting or nausea. Dose adjustment was extensively practised in this clinical trial. It was recommended to stop their medication for some time and resume later (Kalra et al 2020).

Table 2 Efficacy and Safety of Oral Semaglutide Versus other GLP-1 RA Drugs

Medicine	Drug	Dose	Reduction in HbA1c
Oral semaglutide 14 mg, once daily	dulaglutide	1.5 mg, once daily	− 0.85%, 95% CI − 1.25 to − 0.45
	exenatide	10 μg, twice weekly	− 0.93%, 95% CI − 1.32 to − 0.54
	exenatide	2 mg, once weekly	0.89%, 95% CI − 1.27 to − 0.51
	liraglutide	1.8 mg, once-daily	(− 0.42%, 95% CI − 0.78 to − 0.05
	lixisenatide	20 μg, once-daily	− 1.32%, 95% CI − 1.74 to − 0.91
	injectable semaglutide	0.5 mg, once-weekly	− 0.32%, 95% CI − 0.72 to 0.08
	injectable semaglutide	1.0 mg, once-weekly	0.08%, 95% CI − 0.32 to 0.47

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

Table 2 summarizes the results of a comparative study of oral semaglutide with other standard of care drugs. The relative efficacy and safety of the drug is calculated using meta-analysis tool. The results prove that oral semaglutide significanty lowered the HbA1c levels. It is also found to be involved in weight reduction as compared to lixisenatide (− 2.39 kg, 95% CI − 3.66 to − 1.14) and exenatide 2 mg (− 2.21 kg, 95% CI − 3.45 to − 0.92).

As per the safety standards, some patients might experience nausea, vomiting or diarrhoea. Therefore, it is recommended to strictly abide to the dosing precautions and methods (Chubb et al 2021).

➢ *Benefits Beyond Glycaemic Control*

- *Weight Control*

PIONEER clinical trial studies have reported weight reduction as one of the effects of semaglutide. In a double blind randomized controlled trial conducted by Wilding et al, impact of semaglutide 2.4 mg dose was analysed.this study enrolled 1961 obese non-diabetic adults. Along with regular exercise, diet and lifestyle changes, semaglutide 2.4 mg and placebo were subcutaneously injected once a week to these subjects. Remarkable differences were shown in the patients taking semaglutide as compared to the placebo group. Results showed that among obese or overweight participants, semaglutide 2.4 mg once a week plus lifestyle interventions correlated with sustained, clinically significant weight loss. From the average baseline weight (105.3 kg), semaglutide 2.4 mg group reported a loss of 15% whereas the placebo group reported a loss of 2.4%. More than 5% of weight loss was reported in 86.5% of the semaglutide 2.4 mg group members whereas only 31.5% members with placebo reported it. Although slight side effects including gastrointestinal problems were reported by the participants, but these were resolved by following the dosing methodology sincerely. Finally, this can be concluded that Semaglutide can be a potential method of treatment for weight loss (Liu and Luo 2022).

- *CVD*

The primary cause of death in patients with T2DM is CVD. The upcoming therapeutics for diabetes must consider the CVD risk factors as well. PIONEER 6 clinical trials were CVD centric. These clinical trials were known to be Cardiovascular Outcome Trial (CVOT) as they were meticulously designed to evaluate CV safety. This trial enrolled 3183 subjects, out of which 206 participants were Indians. The established results of this clinical trial have proved the safety of oral semaglutide. In addition to this, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 6 trial displayed a remarkable reduction of 26% in 3-point major cardiovascular event (3P-MACE) with subcutaneous semaglutide as compared to placebo (Husain et al 2019). Moreover, GLP-1 agonists have shown its cardioprotectin effects in rats by reducing apoptosis in cardiac cells (Iogra et al 2020).

Another post-hoc analysis has reported about 24% reduction in CVD events in patients who were on semaglutide (Husain et al 2020). In another study, Semaglutide is reported to reduce atherosclerosis. According to this study, in proatherogenic apolipoprotein E-deficient mice (ApoE−/−) and low-density lipoprotein receptor deficient mice (LDLr−/−) model, semaglutide negatively regulates multiple inflammatory pathways (Mahapatra et al 2022).

- *Renal*

T2DM is one of major causative reasons for CKD and final stage renal dysfunction. Consequently, it is a major cause of morbidity and mortality across the world. The antidiabetic medications are correlated to the kidney diseases. The dose adjustment depends on the kidney function tests. However, patients with eGFR = 15 ml/min/1.73 m2 may take subcutaneous semaglutide, when the doses are stabilized (Eliaschewitz and Canani 2021).

There have been a number of clinical trials and clinical studies that have considered the importance of the considering renal impairment/ CKD while designing anti-diabetic drugs. Some of them are quoted hereunder:

The most significant of all is the PIONEER 5 clinical trial. it can be conveniently said that it was designed keeping in mind the renal impairments. The enrolled subjects had moderate renal impairments. It was noted that the renal functions remained unchanged in both the comparative study groups (i.e placebo group and the oral semaglutide group). Negligibly, 3 nonserious side-effects were reported by the patients on oral semaglutide and 1 from the placebo group (ClinicalTrials.gov 2021).

- *Contradictions*

Oral semaglutide is not meant for type 1 diabetes and gestational diabetes. Also, it is yet to be discovered if it is applicable for patients with history of pancreatitis. Additionally, its applicability is questionable in patients with personal or family history of medullary thyroid cancer (MTC). It is also not explored in patients with multiple endocrine neoplasia syndrome type 2 (MEN2) (Kalra et al 2020).

- *Future Scope/ Trials*

Although semaglutide has given satisfactory results in the preliminary trials, there are certain aspects yet to be explored. A clinical trial named, NCT04524832 is been designed to explore and analyse steady state plasma concentration (Cmax and Tmax) for higher potency of oral semaglutide (25 mg and 50 mg). Another important aspect of oral semaglutide that is yet to be discovered is its applicability for patients between the ages of 10 to 17 years. To address this issue a clinical trial named, PIONEER TEEN is being conducted. In addition to this a clinical trial named, PIONEER REAL is being run as a global non-interventional single arm real world based, global prospective study. A clinical study EVOKES and EVOKE PLUS also has its trials running. This study primarily focuses on the efficacy and safety of oral semaglutide for the

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1950

subjects suffering from Alzheimer's disease. Also, a special clinical study is ongoing, named SOUL, which is CV centric. It investigates the CV benefits of oral semaglutide. As an important aspect of all upcoming therapeutics, effect of the medication with COVID-19 complications need to be studied. Therefore, a clinical study named, SEMPATICO (NCT04615871) is being designed. This is a phase II clinical trial which aims to investigate and reduce the mortality and morbidity rates among subjects with COVID-19. It analysis the low dose and gradually acceleration of oral semaglutide doses (0.25 mg on day 0, then 0.5 mg on day 7, 14 and 21) with the aim to minimize myocardial injury in subject with COVID -19. This study also includes patients with elder age, obesity, history of CVD/established CVD, high troponin levels or hypertension (Kalra et al 2020, Mahapatra et al 2022).

V. SUMMARY

Oral semaglutide is the first of its kind GLP-1RA that is developed as an oral medication for diabetes. It has gone through robust clinical trials and proved itself as a potential anti-diabetic drug. It has shown significant weight and HbA1c reduction as well as management. It has proved its efficiency, efficacy, safety and tolerability is various stages of clinical trials. This review has summarized the background, introduction, chemical structure, challenges in oral peptide, development of oral semaglutide, mechanism of oral bioavailability, an elaborate discussion of the involved clinical trials, posology/ dosing of the drug, its placement in the line of therapy, the involved robust indication, drug-drug interactions, the glycemic in early, mid and late stages of diabetes, its benefits other than the glycemic control such as Weight loss, CVD and renal disease management. This review also includes comparison of the efficacy and safety between oral semaglutide and other GLAP-1RAs, contradictions and future scope of semaglutide research.

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