INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Rybelsus (Semaglutide): Revolutionizing Type 2 Diabetes Therapy - A Systematic Review Of Clinical Evidence And Future Prospects

Harshitha G.*[1], Surendra Vada[2], P. Aswathy[3], K. Keerthana[4]

[1,2,3,4] *Department of Pharmacology, Acharya & BM Reddy College of Pharmacy, Soldevanahalli, Bengaluru-560107, Karnataka, India.*

ARTICLE INFO

Published: 29 July. 2026
Keywords:
Type-2 Diabetes, Semaglutide, Obesity, DPP4-Ihibitor, Rybelsus, Oral administration.
DOI:
10.5281/zenodo.21671030

ABSTRACT

The Oral semaglutide (Rybelsus) marks a significant advancement in managing Type 2 Diabetes Mellitus (T2DM). The GLP-1 RA class receives a groundbreaking addition through Oral semaglutide which utilizes sodium N-(8-amino) caprylate (SNAC) to enhance stomach absorption and resolve previous challenges in oral peptide drug delivery. The results of various clinical trials specifically the PIONEER program show that the drug records effective HbA1c level reduction alongside weight loss. The drug is equal in safety profile to its injectable counterparts. The validity of such concepts is further supported by findings emanating from different population subgroups. Recent research demonstrates that glucose control improves with medication compliance when the patients use comparative medications instead of sitagliptin and empagliflozin and provides a more convenient injection-free alternative. Cardiovascular disease and renal impairment risk patients benefit from the promising results of oral semaglutide. Patient satisfaction assessments indicate that this medication improves long-term diabetes treatment outcomes and medication compliance. The arrival of oral semaglutide is a milestone in the science of medicine that provides a new standard for patient-focused management of long-term disease.

INTRODUCTION

Overview of Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus is a common metabolic disease that permanently increases blood glucose concentration due to insulin insensitivity and beta-cell failure.[1] Type 2 diabetes pathophysiology obliges cells within the body to be resistant to insulin despite the fact that the pancreas produces this vital regulates blood sugar. The pancreas will end up at the stage where it will no longer produce sufficient insulin to keep pace with the reduction in sensitivity. The inability to control high blood

***Corresponding Author:** Harshitha G
Address: *Department of Pharmacology, Acharya & BM Reddy College of Pharmacy, Soldevanahalli, Bengaluru-560107, Karnataka, India.*
Email : harshithag.23.phcl@acharya.ac.in

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

sugar will initiate several complications for the body.[2] Type 2 diabetes keeps growing globally due to two main causes: increased population ages accompanied by physical inactivity and increasing rates of obesity.[1]

Type 2 Diabetes Mellitus should be strictly controlled since it minimizes the risk of cardiovascular disease and complications such as nephropathy, neuropathy and retinopathy. Individuals with Type 2 diabetes are at high risk of death due to cardiovascular diseases which comprise heart attacks and strokes. Patients with nephropathy develop kidney failure that causes them to require dialysis treatment or a kidney transplant. Neuropathy initiates nerve injury which causes diverse painful symptoms in extremities and produces gastrointestinal and cardiac rhythm abnormalities. Physicians use the term for total blindness due to retinopathy as the disorder in which injury is caused in the veins of the retina.[3]

The Emergence of GLP-1 Receptor Agonists (GLP-1 RAs) in T2DM Management

Blood glucose control and weight loss benefits have positioned GLP- 1 RAs as essential elements in Type 2 diabetes management.[4] GLP-1 RAs mimic the structure of the hormone naturally released by the intestines during meal digestion. The therapeutic benefits of GLP-1 RAs tackle the main components of Type 2 diabetes hence making effective disease management possible.[5]

GLP-1 RAs demonstrate their biological effects through three main pathways which involve glucagon suppression and gastric emptying reduction as well as insulin secretion enhancement following glucose intake.[6] The release of insulin occurs exclusively during high blood glucose periods because GLP-1 RAs prevent hypoglycemic conditions in people with diabetes. The drug creates optimal glycemic control by blocking glucagon secretion which normally raises blood glucose levels. The medication delays stomach emptying which could help control blood sugar spikes after meals and make people feel fuller.[7]

These medications present benefits to patients who have reached the stage of kidney failure while experiencing microvascular disease-related complications. Large clinical trials have demonstrated both the safety and tolerability of GLP-1 RA therapy while showing positive renoprotective effects in people with deteriorating kidney function. The glucose-independent function of GLP-1 RAs provides benefits to type 2 diabetes patients who face potential microvascular complications such as retinopathy and nephropathy.[8]

Addressing the Limitations of Injectable GLP-1 RAs with Oral Semaglutide

Patients who experience discomfort and anxiety as well as inconvenience due to injections tend to discontinue their prescribed drugs as instructed. The diminished effectiveness of treatment as well as the increased type 2 diabetes risk is due to this problem.[9]

Oral semaglutide (Rybelsus) continues to be the first approved oral GLP-1 RA for type 2 diabetes because its formulation contains sodium N-(8-amino) caprylate (SNAC).[4] The emerging drug delivery system improves patient use of valuable drugs by means of a more convenient access to GLP-1 RAs. The use of oral semaglutide as a pharmaceutical treatment for type 2 diabetes is a major breakthrough in the treatment of type 2 diabetes.[8]

The efficiency of the stomach's absorption process is enhanced through the use of SNAC while extending the stability of semaglutide.

Semaglutide's gastrointestinal absorption as well as protection from stomach acids results from SNAC chemical properties. Semaglutide's combination with this chemical makes the drug bypass stomach degradation through oral intake.[10]

Development and Mechanism of Action of Oral Semaglutide

Overcoming Oral Peptide Delivery Challenges

Delivery of peptides via the oral route is still a significant challenge since they face poor absorption through the intestinal lining and enzymatic breakdown within the digestive system. [11] Their large size and complex structure makes it difficult for peptides to diffuse through the intestinal wall into the bloodstream as digestive enzymes readily break them down. The route of administering therapeutic peptides via oral route is proven to be challenging. [12]

Semaglutide and SNAC have superior stomach absorption by their joint formulation that addresses the current issues. SNAC operates to shield stomach mucosa against enzyme breakdown and allows semaglutide absorption via this barrier. The delivery method allows sufficient semaglutide to enter the bloodstream at therapeutic concentrations to realize its health benefits. [13]

The innovative delivery strategy facilitated the development of oral semaglutide that proved to be a successful treatment option for type 2 diabetes patients. Patients get improved access to this life-changing drug via the oral route since it is patient-compliant and offers more convenient delivery compared to injectable forms. Oral semaglutide delivery system is a significant breakthrough in peptide drug delivery. [11]

Mechanism of Action of Semaglutide

Semaglutide aligns genetically with human GLP-1 at a rate of 94%. The high genetic resemblance between semaglutide and natural GLP-1 allows the drug to connect with identical receptors to produce comparable effects. Activation of the GLP-1 receptor by semaglutide results in desirable control of hunger as well as glucose metabolism in various ways.[14]

The drug acts by increasing glucose-stimulated insulin secretion, decreasing the rate of stomach emptying, and lowering glucagon hormone release. Semaglutide suppresses glucagon discharge through its action in inducing pancreatic insulin secretions only when blood glucose is elevated thereby preventing episodes of hypoglycemia.[6] Through its mechanism of action on blood glucose control semaglutide inhibits the release of glucagon for superior glycemic management. The transit time of the stomach is reduced upon administration of semaglutide which results in decreased blood glucose variability after food intake and improved satiety.[15]

Upon binding to blood albumin, semaglutide reduces the metabolism of the protein which consequently prolongs the time the drug exerts its therapeutic effect. The oral delivery of semaglutide once a day provides type 2 diabetes patients with an effective solution for treatment. The long half-life of semaglutide allows it to stay in the body long enough to exert its desired therapeutic action. [14]

The Role of SNAC in Enhancing Oral Absorption

The absorption facilitator Sodium N-(8-amino)caprylate (SNAC) allows semaglutide to cross the membrane of the stomach. The pharmaceutical acts as an essential element whereby oral semaglutide can be administered as it addresses challenges in peptide absorption

within the digestive system. Orally administered semaglutide is effective contingent upon SNAC supplementation.[8]

Semaglutide attains paracellular absorption by the combined effects of pH increase along with cell membrane destruction. SNAC acts by pH increase close to the stomach lining to improve semaglutide absorption conditions.[11] Semaglutide absorption is enhanced by the action of SNAC on the cell membrane. Semaglutide gains access to the bloodstream by intercellular movement due to this paracellular absorption method. [16]

SNAC is fundamental to the development of semaglutide since it has a mere 1% oral bioavailability. Semaglutide does reach therapeutic levels and has beneficial effects on glucose homeostasis as well as hunger control despite its poor capability to be absorbed. Without SNAC, there would be semaglutide's poor oral bioavailability that would rule out its utility as an oral drug.[10]

Clinical Development: Early Phase Trials

Phase 1 Studies: Pharmacokinetics, Pharmacodynamics, and Safety

Phase 1 studies used human subjects to evaluate the safety profiles and pharmacological characteristics and dose-dependent trends of orally administered semaglutide. Early human studies are important in finding out how new drugs are absorbed and carried around the body and metabolized and excreted while demonstrating their effects.[4]

The study team proved that body weight loss and HbA1c reduction were greater when patients took higher dosages of oral semaglutide which estimate blood glucose average concentrations over the last three months. The safety assessment of oral semaglutide established acceptable outcomes since almost all adverse effects occurred as mild or moderate in severity.[17]

Pharmacological assessment examined the effects of food consumption and dosing intervals and illness and medication use to create the optimal prescription schedule. The examination of these factors is required to understand how oral semaglutide absorption function under various conditions. The study seeks to determine the optimal dose timing regimen that provides maximum treatment effects with least detrimental consequences.[18]

Phase 2 Dose-Finding Trials

The dose-finding phase 2 trials revealed oral semaglutide resulted in significant weight loss and HbA1c reduction amounts to those reported by subcutaneous semaglutide. The trials followed the detection of safe effective oral semaglutide levels of dosage for use in ensuing clinical studies. Findings revealed oral semaglutide resulted in body weight and HbA1c reduction rates equal to those of its injectable counterpart.[19]

The outcomes of the study decided the optimal doses of oral semaglutide for phase 3 trials through assessment of each dose's efficacy and safety. Scientists made up their minds to proceed with advancing the 3 mg, 7 mg, and 14 mg doses from the phase 2 trial to the larger phase 3 trials due to their safety as well as effectiveness balance.[20]

The dose selection of 3 mg, 7 mg, and 14 mg doses proceeded to clinical development on the basis of their satisfactory results. The phase 2 trials showed that these dosages provided an acceptable balance between safety and efficacy which led to them being chosen. 7 mg and 14 mg were developed for patients who required more intensive glycemic

control measures while 3 mg was the starting amount of treatment.[21]

Optimal Dosing Regimen

Two dosing rules are fundamental in deciding the correct schedule of medication: take the medication between meals and drink a certain quantity of water. Therapeutic success of semaglutide demands that these administration rules be followed strictly. The digestion of semaglutide in the stomach needs uninterrupted time since nutritional consumption and excess water interfere with its digestive process.[22]

The clinical responses of patients undergoing oral semaglutide therapy improve when they fast. The optimal method to enhance semaglutide absorption is by sustaining fasting states after drug administration. Drug absorption is reduced since semaglutide competes with food in the stomach to gain entry into the bloodstream via absorption routes.[16]

The patients must adhere to best therapeutic practice which comprises correct stomach absorption to ensure maximum treatment benefits. To reach full therapeutic benefits from oral semaglutide patients must follow their medical professional's guidance.[23]

Pivotal Phase 3 Clinical Trials: The PIONEER Program

Overview of the PIONEER Trial Program

A phase 3 clinical trial program named Peptide Innovation for Early Diabetes Treatment served as the platform for verifying the efficacy and safety of oral semaglutide. The PIONEER program demonstrated that oral semaglutide stands as a first-line treatment option for type 2 diabetes.[24]

The PIONEER program engaged over 9500 patients that had other forms of diabetes types and a number of differing periods of the condition and past history of drug administration. The PIONEER program guarantees its data will be generalizable to all T2DM patients owing to its comprehensive standards of patient involvement. Patient diversity within the study population brought about findings which could be made applicable across patient populations.[25]

The PIONEER trials conducted tests which paired oral semaglutide against placebo and three common glucose-lowering drugs known as sitagliptin, empagliflozin, and liraglutide. The study facilitated the evaluation of oral semaglutide safety as well as its treatment effectiveness compared to standard type 2 diabetes management. The most commonly prescribed type 2 diabetes medications functioned as active comparators for this study.[21]

The reduction of body weight effects of oral semaglutide were comparable to those of empagliflozin but exceeded placebo and sitagliptin and liraglutide. The findings of this study illustrated the weight loss benefits that oral semaglutide offers to patients with T2DM who want to lose weight from their treatment.[26]

Cardiovascular Safety and Other Benefits

Patients with type 2 diabetes are at highest risk of death from cardiovascular disease hence this information is critical. The primary aim of the PIONEER research program was to assess the cardiovascular safety of oral semaglutide.[25]

The study findings indicated that oral semaglutide is not associated with clinically meaningful benefits for the reduction of cardiovascular event but does demonstrate a potential to decrease cardiovascular and all-cause mortality. The

findings indicate that oral semaglutide has a potential to prolong the duration of life.[9]

Patients with type 2 diabetes with moderate kidney impairment show favorable results when they take oral semaglutide. Type 2 diabetic patients tend to develop kidney disease as they grow older.Oral semaglutide has been found to work well for patients with impaired renal function which indicates its potential application in various types of T2DM patients.[21]

Real-World Evidence and Observational Studies

Clinical Outcomes in Routine Clinical Practice

The exploration of oral semaglutide performance using real-world studies builds on the controlled trials by measuring both the safety and efficacy of the drug in diverse clinical settings. Real-world clinical practice data are an important tool for learning how patients utilize oral semaglutide and its impact on outcomes in typical healthcare environments.[27]

Real-world research allows researchers to study patients who have different age groups with varied ethnic backgrounds and health conditions that are different from the usual clinical trial participants.[28] Real-world research allows researchers to acquire in-depth information regarding the benefits and limitations of oral semaglutide among different patient groups.[29]

The clinical impacts from oral administration of semaglutide came from PIONEER REAL studies in the Netherlands, UK, Switzerland, Sweden and Canada. Through studies in various cultures and medical environments these trials gave vital information on safety, efficacy and patient satisfaction from oral semaglutide treatment.[30]

Effectiveness in Reducing HbA1c and Body Weight

The present study is in line with the findings of the PIONEER clinical trial program that established efficacy of oral semaglutide for glycemic control and weight reduction support. Varying study designs and diverse patient populations have contributed to similar findings that augment the evidence base for oral semaglutide. [31] The PIONEER REAL Netherlands trial results show that oral semaglutide provides significant advantages of glycemic control and weight loss in real clinical practice. Clinically significant improvement can be attained by patients suffering from type 2 diabetes with these changes.[32]

A study performed in India proved that oral semaglutide patients lost on average 5.03 kg of body weight and achieved a 1.81% reduction in HbA1c levels in 12 months of treatment. The study corroborates earlier studies by proving that oral semaglutide reduces effectively HbA1c and body weight among various patient groups. The findings of the research directly have significance for the medical professionals in India since type 2 diabetes is a major public health concern in the country.[28]

Patient Satisfaction and Adherence

The overall agreement of patients shows that oral semaglutide is an effective tool for managing type 2 diabetes. When patients are more satisfied with their treatment they get better health outcomes and have improved adherence to their plan.[31] Most participants report easy management of oral semaglutide administration hence achieving improved adherence. Patients get a critical benefit of treatment with oral semaglutide since it gives them easy administration compared to injectable GLP-1 RAs that have complicated use that leads to poor treatment adherence. The drug in its oral

form demonstrates to offer improved glucose control and fewer complications for patients who adhere to the prescribed treatment regimen.[33]

Oral agents tend to demonstrate higher patient acceptance and compliance rates compared to their injectable equivalents especially for injectable-unwilling patients. A substitute for injectable semaglutide exists for individuals who would rather take their medication orally. The oral delivery of the drug eliminates barriers that are present for GLP-1 RA treatment thereby widening therapeutic application in the treatment of type 2 diabetes.[34]

Comparative Analysis with Other Antidiabetic Agents

Head-to-Head Comparisons in Clinical Trials

Clinical trials assessed the performance of oral semaglutide through direct comparisons with antidiabetic drugs sitagliptin, empagliflozin and liraglutide to determine their therapeutic effects.[21] Through clinical trials that evaluate oral semaglutide against sitagliptin and empagliflozin researchers obtain fundamental safety data as well as essential therapeutic results about these traditional diabetes drugs. Medical professionals base their treatment decisions on these study results to determine the most effective therapy for their patients.[26]

Medical studies have shown that oral semaglutide yields better results in glycemia control than sitagliptin and empagliflozin. The findings show that oral semaglutide yields higher effects of lowering blood glucose than these antidiabetic drugs. Better glycemic control achieved by oral semaglutide can lead to lower risks of developing diabetic complications that are long-term in nature in type 2 diabetes.[35]

Oral semaglutide patients have equivalent results when compared to empagliflozin but have better weight loss when compared to sitagliptin and placebo. The research illustrates that oral semaglutide is an excellent tool for weight loss among type 2 diabetes patients. Weight loss is responsible for enhanced insulin sensitivity and lower cardiovascular disease risk.[36]

GLP-1 RAs versus DPP-4 Inhibitors

The incretin mechanism functions as a unifying system for GLP-1 receptor agonists together with dipeptidyl peptidase-4 inhibitors but these drugs produce different clinical effects. The two pharmaceutical groups which function along the incretin pathway boost hormone activity to generate both insulin production and glucagon suppression. GLP-1 RAs accomplish this process more effectively while slowing stomach emptying.[37]

The glycemic effect of GLP-1RAs is greater than that of DPP4is and results in weight loss and cardiovascular advantages. Evidence has shown that GLP-1 RAs are more effective for lowering blood glucose and weight than DPP4is. Certain clinical trials depict the cardiovascular event reduction benefits of GLP-1 Ras.[7]

Oral delivery of semaglutide has the potential to provide new opportunities for the application of GLP-1RAs in the treatment of diabetes by providing an oral alternative. The release of oral semaglutide overcomes existing barriers which will make more patients with type 2 diabetes have access to therapeutic drugs. Oral semaglutide administration brings about enhanced cardiovascular protection as well as weight reduction and blood sugar control improvements for more patients.[38]

Oral Semaglutide versus Injectable Semaglutide

Both routes of semaglutide administration yield significant weight loss outcomes in addition to enhanced control of blood glucose in clinical use. Patients with type 2 diabetes may select either of the two forms to manage their condition effectively. Patients can make their choice between injectable and oral semaglutide depending on their preferences and various medical considerations.[29]

The reduction of weight and HbA1c obtained with oral semaglutide for six months of treatment is equal to that obtained with injectable semaglutide. Many T2DM patients will be able to switch to oral semaglutide because this option offers an acceptable alternative to injectable semaglutide. The similar efficacy of these two products makes it possible for healthcare providers and patients to choose among different treatment options.[39]

Patients make their choice between injectable and oral semaglutide based on individual medical needs as well as their capacity to tolerate injections. The two methods are chosen based on the individual personal condition and medical situation of the patient.[22] Patients feel differently about tolerance, which can lead one formulation to have worse side effects than the other. The choice between oral and injectable semaglutide is based on specific clinical conditions such as the need for more aggressive glucose control and the presence of specific concomitant medical conditions.[40]

Safety and Tolerability Profile

Common Adverse Events

The most common adverse effects of oral semaglutide are GI disorders expressed as nausea, vomiting and diarrhea. The side effects of GLP-1 RAs are similar to those seen in other drug classes of the same category and are due to their effect on stomach emptying rates. The common gastrointestinal side effects that happen during treatment will usually lessen and resolve by themselves in the majority of instances.[25]

These shared gastrointestinal side effects are usually mild at first but slowly build up in intensity over the first period of treatment before they ultimately resolve. These side effects will lessen by means of using non-prescription drugs or by making dietary and lifestyle adjustments based on patient feedback.[41]

In order to minimize GI side effects of both injectable and oral formulations of semaglutide, patients must begin with higher doses. Small doses at initiation followed by gradual dose escalation over time serve to minimize the occurrence and severity of GI side effects. Adaptation to medication using this technique reduces discontinuation of medication.[22]

Risk of Hypoglycemia

The oral administration of semaglutide has an infrequent risk of hypoglycemia especially when the patients use it with metformin. Semaglutide acts by causing insulin release only when blood glucose increases thereby reducing the likelihood of hypoglycemia due to overcorrection. Some antidiabetic medications have greater risks of hypoglycemia than sulfonylureas in comparison with oral semaglutide.[13] Patients taking sulfonylureas in combination with semaglutide and other agents lowering blood glucose should be cautioned that they have an increased risk of hypoglycemia. Physicians should carry out ongoing monitoring for hypoglycemia when patients combine oral semaglutide with sulfonylureas. [26] The education program should include the warning signals for hypoglycemia such

as shaking and sweating and confusion and dizziness and also educate on the immediate glucose treatment. Health practitioners need to educate patients on how to prevent hypoglycemia by taking regular meals along with planned snacks and controlling drinking alcohol.[23]

Long-Term Safety Considerations

Based on safety information from clinical trials and real-world evidence, patients generally have good tolerability when taking oral semaglutide. The safety profile of oral semaglutide is not compromised for long-term use in individuals with type 2 diabetes since the scientific evidence base supports its safety. Post-market surveillance together with ongoing monitoring is an essential system for the detection of any potential long-term safety threats. [13] The correlation of GLP-1 RAs with several diseases has provided ambivalent evidence in medicine. More studies are needed to establish if there's a causal relationship.[42]

Post-market surveillance and ongoing monitoring are both needed to investigate the long-term safety profile of oral semaglutide. Reading up-to-date medical literature throughout observational research and adverse event data collection constitutes this monitoring process. Post-market surveillance serves to pick up on any rare or uncommon side effects that went unnoticed during clinical trials.[43]

Special Populations and Specific Clinical Scenarios

Patients with Renal Impairment

The oral use of semaglutide has beneficial results when administered to patients that have type 2 diabetes and a moderate degree of renal impairment. Beneficial results of oral semaglutide on patients with renal impairment indicate its possible application for the treatment of a vaster number of T2DM patients.[21]

Diabetic kidney disease (DKD) patients have good tolerance when they undergo oral semaglutide as per studies. The findings indicate that oral semaglutide can be an effective therapeutic agent in patients who possess T2DM and DKD. Physicians have to exercise more caution when they prescribe to patients who illustrate extreme renal impairment.[44]

The oral semaglutide administration does not cause any changes in renal metrics among chronic kidney disease (CKD) patients who take the drug throughout their follow-up period. The findings suggest that oral semaglutide does not have renal function changes among patients suffering from chronic kidney disease that offers positive findings. The patients should be subjected to ongoing renal function tests based on medical standards.[45]

Elderly Patients

Older patients with type 2 diabetes and depression can lose weight rapidly and reduce HbA1c levels when treated with oral semaglutide. Elderly patients with T2DM and symptoms of depression may benefit from oral semaglutide as a potential cure solution. The speed at which the weight and HbA1c drop will improve health and quality of life among these patients.[46]

The dramatic therapeutic effect may be due to longer medication fasting times combined with lifestyle changes along with better psychosomatic conditions. The therapeutic efficacy of oral semaglutide in geriatric patients is based on several factors. Medication absorption increases with longer fasting times while therapeutic impacts enhance through lifestyle changes and better psychosomatic conditions.[47]

The treatment with this medication in old patients' needs health practitioners to exercise caution due to the side effects as well as pre-existing medical conditions. Old patients are at a higher risk of gastrointestinal adverse effects and other side effects from the administration of oral semaglutide. Patients with various medical conditions can develop side effects from the medication. Doctors need to perform a detailed evaluation regarding the advantages and disadvantages of giving oral semaglutide to older patients while monitoring side effects closely.[48]

Patients with Cardiovascular Disease

The oral semaglutide clinical trials found its cardiovascular safety profile in high-risk individuals as well as those with cardiovascular disease. The primary cause of this study is that cardiovascular disease takes the highest number of lives of individuals suffering from type 2 diabetes.[25] GLP-1RAs and semaglutide exhibit cardiovascular safety in addition to their antihyperglycemic activity in producing better cardiac outcomes. The benefits of the drugs may be accompanied by reduced inflammation as well as weight loss and blood pressure regulation.[42]

Type 2 diabetic patients can expect positive benefit ratios from these drugs when they have atherosclerotic cardiovascular disease or high risk of developing it. According to research findings GLP-1 RAs such as oral semaglutide show better cardiovascular benefits than risks for all type 2 diabetic patients with cardiovascular disease.[48]

Future Directions and Emerging Therapies

Combination Therapies and Personalized Medicine

The future management of type 2 diabetes seems to consist of personalized medicine approaches in addition to oral semaglutide and other drugs. Administration of more than one drug with different mechanisms of action assists oral semaglutide to bring about improved blood glucose control and disease complication regulation. Personalized medicine methods allow healthcare providers to create individualized treatment plans which are tailored to fit the unique patient needs and biological profiles.[49]

The new diabetes drug tirzepatide acts as a dual GIP and GLP-1 receptor agonist to not only manage blood sugar but also assist patients in losing weight. The dual action of activating GLP-1 and GIP receptors via tirzepatide results in better effects on blood glucose control and weight reduction compared to single GLP-1 RAs. The newly developed drug shows promising indications for augmenting current treatment regimens in patients suffering from type 2 diabetes.[1]

Patient health outcomes improve when their individualized medical conditions and attendant factors are given personalized management that conforms to their long-term quality of life. The treatment strategy has to combine all elements of patient goals with their disease risk profile. Patients' prescription treatment plans ought to incorporate both drug therapies in addition to lifestyle adjustments involving dietary changes and exercise regimens. The health outcomes of the patients will be enhanced by the integration of drug therapies and lifestyle modifications such as diet change and exercise regimen.[50]

Expanding Indications and Clinical Applications

The therapeutic potential of semaglutide therapy is being further supported through research analysing cardiovascular outcomes alongside diabetic retinopathy and prevalent T2D

comorbidities such as obesity and chronic kidney disease and non-alcoholic steatohepatitis. The future studies will determine more information regarding the advantages of semaglutide for patients within these particular medical categories. The increasing body of evidence will allow medical professionals to make informed decisions about semaglutide use in several therapeutic uses.[22]

Rybelsus, Wegovy and Ozempic all of which are semaglutide-based drugs hold promise for the treatment of obesity. The effect of weight loss on these drugs has been established in research among individuals who have type 2 diabetes as well as those without. The research combined with clinical use of semaglutide in obesity is undergoing rapid growth.[50]

GLP-1 family medications exhibit impressive protective qualities in clinical trials of Parkinson's disease and Alzheimer's disease. The findings of the studies indicate that GLP-1 RAs could be bringing with them some further advantages beyond blood glucose levels and body weight regulation. Further studies are needed to confirm this and determine the most appropriate methods of application for GLP-1 RAs in these medical conditions.[51]

Novel Oral Formulations and Delivery Systems

Advances in oral peptide delivery must continue to make oral semaglutide and other similar peptide drugs more therapeutic. Developers of medicine must design new and improved ways of delivering peptides orally to maximize bioavailability and improve efficacy which would make it easier for patients to access. Present research directions indicate considerable focus on this specific area.[10]

New formulation creation methods with permeation enhancers have the potential to increase the absorption rate and therapeutic effectiveness of peptide therapy by oral administration. Researchers are investigating several approaches that involve drug composition adjustments and changes in permeation enhancers to increase peptide absorption in the gastrointestinal tract. These processes have the potential to generate sophisticated solutions for delivering peptides orally.[11]

The advancement in oral formulation development enables one to increase the application of peptide-based drugs via oral route. The present market scenario demands most peptide drugs to be administered via injections which hampers patients and reduces their usage. The use of oral drug formulations for such treatments would facilitate easier management by patients in adhering to their therapy while enhancing medical accessibility.[52]

CONCLUSION

The introduction of Semaglutide in oral form marks a significant advancement in managing type 2 diabetes because it provides an injectable GLP-1 receptor agonist that works well without requiring injections. The newly developed drug delivery system of Semaglutide uses SNAC to solve traditional issues of oral peptide drugs which leads to enhanced absorption and extended therapeutic effects. Both trial data and real-world evidence validate the therapeutic benefits of semaglutide for the control of blood glucose with weight loss advantages in all patient groups and preservation of cardiovascular and renal protection across various population profiles. Oral semaglutide is anticipated to become a fundamental medication in present-day diabetes management because it offers patients an improved drug experience together with better medication adherence. Research teams plan to establish oral semaglutide as a mandatory therapy

for personalized diabetes management by developing new extended-duration drug therapies which will be available in widespread clinical settings.

REFERENCES

1. Caturano A, Galiero R, Rocco M, Tagliaferri G, Piacevole A, Nilo D, Di Lorenzo G, Sardu C, Vetrano E, Monda M, Marfella R, Rinaldi L, Sasso FC. Modern Challenges in Type 2 Diabetes: Balancing New Medications with Multifactorial Care. Biomedicines 2024; 12(9):2039.
2. Su J, Luo Y, Hu S, Tang L, Ouyang S. Advances in Research on Type 2 Diabetes Mellitus Targets and Therapeutic Agents. International Journal of Molecular Sciences 2023; 24(17):13381.
3. Deol R, Bashir S. Exploring the complications of type 2 diabetes mellitus: pathophysiology and management strategies. EPRA International Journal of Research and Development (IJRD) 2024; 9(7):173-82.
4. Won H, Cho JY, Lee S. Clinical development of oral semaglutide for the treatment of type 2 diabetes mellitus: focusing on early phase clinical trials. Translational and Clinical Pharmacology 2025; 33(1):1-9.
5. Bando H. Useful oral administration of glucagon-like peptide 1 receptor agonist (GLP-1RA) as Semaglutide (Rybelsus) for Type 2 diabetes mellitus (T2DM). Asploro Journal of Biomedical and Clinical Case Reports 2022; 5(1):38.
6. Bandyopadhyay I, Dave S, Rai A, Nampoothiri M, Chamallamudi MR, Kumar N. Oral Semaglutide in the Management of Type 2 DM: Clinical Status and Comparative Analysis. Current Drug Targets 2022; 23(3):311-27.
7. Campos C, Unger J. Primary care management of type 2 diabetes: a comparison of the efficacy and safety of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Postgraduate Medicine 2021; 133(8):843-53.
8. Selvarajan R, Subramanian R. A Peptide in a Pill - Oral Semaglutide in the Management of Type 2 Diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2023; 16:1709-20.
9. Sofogianni A, Tziomalos K. Oral Semaglutide, A New Option in the Management of Type 2 Diabetes Mellitus: A Narrative Review. Advances in Therapy 2020; 37(10):4165-74.
10. Asano D, Takakusa H, Nakai D. Oral Absorption of Middle-to-Large Molecules and Its Improvement, with a Focus on New Modality Drugs. Pharmaceutics 2023; 16(1):47.
11. Kim JC, Park EJ, Na DH. Gastrointestinal Permeation Enhancers for the Development of Oral Peptide Pharmaceuticals. Pharmaceuticals (Basel) 2022; 15(12):1585.
12. Fagan A, Bateman LM, O'Shea JP, Crean AM. Elucidating the Degradation Pathways of Human Insulin in the Solid State. Journal of Analysis and Testing 2024; 8(3):288-99.
13. Andersen A, Knop FK, Vilsbøll T. A Pharmacological and Clinical Overview of Oral Semaglutide for the Treatment of Type 2 Diabetes. Drugs 2021; 81(9):1003-30.
14. Miyasaka K. New drug for type 2 diabetes: introduction of oral Semaglutide (Rybelsus® tablets), an oral GLP-1 receptor agonist. Nihon Yakurigaku Zasshi 2022; 157(2):146-54.
15. Tilinca MC, Tiuca RA, Niculas C, Varga A, Tilea I. Future perspectives in diabesity treatment: Semaglutide, a glucagon-like peptide 1 receptor agonist (Review). Experimental and Therapeutic Medicine 2021; 22(4):1167.

16. Hayashi K, Bando H, Miki K, Yasuoka E, Kamoto A, Yasuoka T. Fasting period after Rybelsus administration influences clinical benefit. International Journal of Complementary and Alternative Medicine 2022; 15(3):151-2.
17. Aroda VR, Aberle J, Bardtrum L, Christiansen E, Knop FK, Gabery S, Pedersen SD, Buse JB. Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in adults with type 2 diabetes (PIONEER PLUS): a multicentre, randomised, phase 3b trial. The Lancet 2023; 402(10403):693-704.
18. Bækdal TA, Borregaard J, Hansen CW, Thomsen M, Anderson TW. Effect of Oral Semaglutide on the Pharmacokinetics of Lisinopril, Warfarin, Digoxin, and Metformin in Healthy Subjects. Clinical Pharmacokinetics 2019; 58(9):1193-203.
19. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. Journal of the American Medical AssociationJAMA 2017; 318(15):1460-70.
20. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. The Lancet Diabetes & Endocrinology 2018; 6(4):275-86.
21. Rodbard HW, Dougherty T, Taddei-Allen P. Efficacy of oral semaglutide: overview of the PIONEER clinical trial program and implications for managed care. American Journal of Managed Care 2020; 26(16):335-43.
22. Gallwitz B, Giorgino F. Clinical Perspectives on the Use of Subcutaneous and Oral Formulations of Semaglutide. Frontiers in Endocrinology (Lausanne) 2021; 12:645507.
23. Isaacs DM, Kruger DF, Spollett GR. Optimizing Therapeutic Outcomes With Oral Semaglutide: A Patient-Centered Approach. Diabetes Spectrum 2021; 34(1):7-19.
24. Bandō H. Effective oral formulation of semaglutide (Rybelsus) for diabetes and obesity due to absorption enhancer development. International Journal of Endocrinology and Diabetes 2022; 5(1):130.
25. Thethi TK, Pratley R, Meier JJ. Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: The PIONEER programme. Diabetes, Obesity and Metabolism 2020; 22(8):1263-77.
26. Lavernia F, Blonde L. Clinical review of the efficacy and safety of oral semaglutide in patients with type 2 diabetes compared with other oral antihyperglycemic agents and placebo. Postgraduate Medicine 2020; 132(2):15-25.
27. Kick A, M'Rabet-Bensalah K, Acquistapace F, Amadid H, Ambühl RA, Braae UC, Item F, Schultes B, Züger T, Rudofsky G. Real-World Use of Oral Semaglutide in Adults with Type 2 Diabetes: The PIONEER REAL Switzerland Multicentre, Prospective, Observational Study. Diabetes Therapy 2024; 15(3):623-37.
28. Bhattacharyya S. 809-P: Oral semaglutide in Indian type 2 diabetes mellitus patients (SOLID) study—twelve months follow-up. Diabetes 2024; 14:73
29. Roy Chowdhury S, Sadouki F, Collins E, Keen F, Bhagi R, Lim YSJ, Cozma SL, Bain SC. Real-World Use of Oral and Subcutaneous Semaglutide in Routine Clinical Practice in the UK: A Single-Centre, Retrospective

Observational Study. Diabetes Therapy 2024; 15(4):869-81.
30. Jain AB, Reichert SM, Amadid H, Braae UC, Bradley RM, Kim JW, Soo V, Yale JF. Use of once-daily oral semaglutide and associated clinical outcomes among adults with type 2 diabetes in routine clinical practice in Canada: A multicentre, prospective real-world study (PIONEER REAL Canada). Diabetes, Obesity and Metabolism 2024; 26(5):1799-807.
31. Saravanan P, Bell H, Braae UC, Collins E, Deinega A, Dhatariya K, Machell A, Trent A, Strzelecka A. PIONEER REAL UK: A Multi-Centre, Prospective, Real-World Study of Once-Daily Oral Semaglutide Use in Adults with Type 2 Diabetes. Advance Therapy 2024; 41(11):4266-81.
32. van Houtum W, Schrömbges P, Amadid H, van Bon AC, Braae UC, Hoogstraten C, Herrings H. Real-World Use of Oral Semaglutide in Adults with Type 2 Diabetes in the PIONEER REAL Netherlands Multicentre, Prospective, Observational Study. Diabetes Therapy 2024; 15(8):1749-68.
33. Catrina SB, Amadid H, Braae UC, Dereke J, Ekberg NR, Klanger B, Jansson S. PIONEER REAL Sweden: A Multicentre, Prospective, Real-World Observational Study of Oral Semaglutide Use in Adults with Type 2 Diabetes in Swedish Clinical Practice. Diabetes Therapy 2024; 15(9):2079-95.
34. Evans M, Morgan AR, Bain SC, Davies S, Hicks D, Brown P, Yousef Z, Dashora U, Viljoen A, Beba H, Strain WD. Meeting the Challenge of Virtual Diabetes Care: A Consensus Viewpoint on the Positioning and Value of Oral Semaglutide in Routine Clinical Practice. Diabetes Therapy 2022; 13(2):225-40.
35. Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SØ, Lingvay I, Søndergaard AL, Treppendahl MB, Montanya E; PIONEER 2 Investigators. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care 2019; 42(12):2272-81.
36. Wehler E, Lautsch D, Kowal S, Davies G, Briggs A, Li Q, Rajpathak S, Alsumali A. Budget Impact of Oral Semaglutide Intensification versus Sitagliptin among US Patients with Type 2 Diabetes Mellitus Uncontrolled with Metformin. Pharmacoeconomics 2021; 39(3):317-30.
37. Ahrén B, Schmitz O. GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. Hormone and Metabolic Research 2004; 36(11-12):867-76.
38. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. New England Journal Medicine 2016; 375(19):1834-44.
39. Klobucar S, Belancic A, Bukša I, Moric N, Rahelic D. Effectiveness of oral versus injectable semaglutide in adults with type 2 diabetes: results from a retrospective observational study in Croatia. Diabetology 2024; 5:60–8.
40. Meier JJ. Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation. Frontiers in Endocrinology (Lausanne) 2021; 12:645617.
41. Huang X, Wu M, Lin J, Mou L, Zhang Y, Jiang J. Gastrointestinal safety evaluation of semaglutide for the treatment of type 2 diabetes mellitus: A meta-analysis. Medicine (Baltimore) 2024; 103(21):e38236.
42. Oliveira BV, Franco PHM, Nogueira MC, Faria M. Investigation of clinical outcomes on the oral or injectable use of semaglutide and

cardiovascular risks: a systematic review. International Journal of Nutrology 2025; 18(2).
43. Du Y, Zhang M, Wang Z, Hu M, Xie D, Wang X, Guo Z, Zhu J, Zhang W, Luo Z, Yang C. A real-world disproportionality analysis of semaglutide: Post-marketing pharmacovigilance data. Journal of Diabetes Investigation 2024; 15(10):1422-33.
44. Mima A, Kidooka S, Nakamoto T, Kido S, Gotoda H, Lee R, Murakami A, Lee S. Effects of Oral Semaglutide on Renal Function in Diabetic Kidney Disease: A Short-term Clinical Study. In Vivo 2024; 38(1):308-312.
45. Marques Vidas M, López-Sánchez P, Sánchez-Briales P, López Illazquez MV, Portolés J. Efficacy and Safety in a Real-World Study of the New Oral Formulation of Semaglutide in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus. Journal of Clinical Medicine 2024; 13(17):5166.
46. Bandō H, Hayashi K, Sumitomo K, Miki K, Kamoto A. Rapid reduction of HbA1c and weight in elderly patient with type 2 diabetes (T2D) and depression by oral semaglutide (Rybelsus). Asploro Journal of Biomedical and Clinical Case Reports 2022; 5(2):73-8.
47. Anderson SL, Beutel TR, Trujillo JM. Oral semaglutide in type 2 diabetes. Journal of Diabetes and Its Complications 2020; 34(4):107520.
48. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC; PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine 2019; 381(9):841-51.
49. Tilinca MC, Tiuca RA, Niculas C, Varga A, Tilea I. Future perspectives in diabesity treatment: Semaglutide, a glucagon-like peptide 1 receptor agonist (Review). Experimental and Therapeutic Medicine 2021; 22(4):1167.
50. Humphrey CD, Lawrence AC. Implications of Ozempic and Other Semaglutide Medications for Facial Plastic Surgeons. Facial Plastic Surgery 2023; 39(6):719-21.
51. Hölscher C. Glucagon-like peptide-1 class drugs show clear protective effects in Parkinson's and Alzheimer's disease clinical trials: A revolution in the making? Neuropharmacology 2024; 253:109952.
52. Mikkola I, Hagnäs M, Hartsenko J, Kaila M, Winell K. A Personalized Care Plan Is Positively Associated With Better Clinical Outcomes in the Care of Patients With Type 2 Diabetes: A Cross-Sectional Real-Life Study. Canadian Journal of Diabetes 2020; 44(2):133-8.

HOW TO CITE: Harshitha G., Surendra Vada, P. Aswathy, K. Keerthana, Rybelsus (Semaglutide): Revolutionizing Type 2 Diabetes Therapy - A Systematic Review Of Clinical Evidence And Future Prospects, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 5522-5536. https://doi.org/ 10.5281/zenodo.21671030