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## Oral GLP-1 Treatment for Type II Diabetes Mellitus - A Review



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### ABSTRACT

Glucagon-like peptide 1 receptor agonists (GLP1-RA) are prominent agents in the therapeutics of type 2 diabetes mellitus due to their exemplary efficacy in both preprandial and postprandial glycemia, their safety, low risk of hypoglycemia, their multilevel pathophysiological superiority, weight loss and importantly the observed benefits in cardiovascular disease reduction. Their major **drawback** is the subcutaneous route of administration, constituting a barrier to adoption and reason for treatment discontinuation. Thus, the development of an oral GLP1-RA agent would promote medication adherence and quality of life, further consolidating its beneficial effects in real-life clinical practice. However, this task is hampered by suboptimal gastrointestinal protein absorption. Yet, the introduction of oral semaglutide, a modified form of semaglutide with the addition of a carrier sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, may have provided a safe and effective way to reach systemic circulation while other molecules are in development. Whether this molecule still has the impressive cardiovascular effects demonstrated with the use of its precursor remains to be explored. However, to date, its efficacy and safety have already been showcased in a randomized trial. More research is warranted in order to further consolidate these findings across different type 2 diabetes mellitus (T2DM) subpopulations, and adequately powered studies with a longer follow-up that would allow the exploration of microvascular and macrovascular complications are needed. Finally, studies comparing oral semaglutide and similar molecules with other currently established antidiabetic agents to evaluate the relative efficacy, the cost-effectiveness and further understand its place in T2DM therapeutic algorithm are needed. This review focuses on the development of oral GLP1-RA agents and summarizes the challenges, milestones and expected benefits associated with a successful introduction.

## INTRODUCTION

### DIABETES

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes.

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:

- i. Type 1 diabetes results from the pancreas's failure to produce enough insulin due to loss of beta cells. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The loss of beta cells is caused by an autoimmune response. The cause of this autoimmune response is unknown.
- ii. Type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses, a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The most common cause is a combination of excessive body weight and insufficient exercise.
- iii. Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

### Other types

Maturity onset diabetes of the young (MODY) is a rare autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production. It is significantly less common than the three main types, constituting 1-2% of all cases. The name of this disease refers to early hypotheses as to its nature. Being due to a defective gene, this disease varies in age at presentation and in severity according to the

specific gene defect; thus there are at least 13 subtypes of MODY. People with MODY often can control it without using insulin.<sup>[1]</sup>

### **SIGNS AND SYMPTOMS**

- ❖ Unintended weight loss, polyuria (increased urination),
- ❖ Polydipsia (increased thirst), and polyphagia (increased hunger)
- ❖ Weight loss
- ❖ Tiredness.

### **TREATMENT**

The major goal in treating type 1 and type 2 diabetes is to control blood sugar (glucose) levels within the normal range, with minimal excursions to low or high levels.

Type 1 diabetes is treated with:

- insulin,
- exercise, and
- type 1 diabetes diet.

Type 2 diabetes is treated:

- First with weight reduction, a type 2 diabetes diet, and exercise
- Diabetes medications (oral or injected) are prescribed when these measures fail to control the elevated blood sugars of type 2 diabetes.
- If other medications become ineffective treatment with insulin may be initiated.<sup>[2]</sup>

The FDA approved an oral formulation of semaglutide, to be sold under the brand name Rybelsus, for treatment of type 2 diabetes in adults. Oral semaglutide thus becomes the first glucagon-like peptide-1 (GLP-1) agonist to reach market, and comes at doses of 7 mg and 14 mg.

Before this approval, patients did not have an oral GLP-1 option to treat their type 2 diabetes, and now patients will have a new option for treating type 2 diabetes without injections.<sup>[3]</sup>

#### **GENERAL SIDE EFFECTS ARE**

- ❖ Nausea and diarrhea
- ❖ Low blood sugar
- ❖ Weight gain
- ❖ Increased risk of heart failure
- ❖ Anemia
- ❖ Joint pain
- ❖ Increase your risk of pancreatitis.

New Oral GLP-1 Receptor Agonist establishes a safe and effective management of Type 2 Diabetes.

#### **THE DEVELOPMENT OF AN ORAL GLP-1 RECEPTOR AGONIST FOR THE MANAGEMENT OF TYPE 2 DIABETES**

Diabetes is a group of metabolic disorders characterized by high blood sugar levels over a prolonged period. Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced.

There are three main types of diabetes mellitus:

- Type 1: Insulin Dependent Diabetes Mellitus or Juvenile Onset Diabetes Mellitus
- Type 2: Non-insulin Dependent Diabetes Mellitus
- Gestational Diabetes

## THE FIRST LINE DRUGS USED

➤ Metformin (Glucophage, Glumetza, others). Generally, metformin is the first medication prescribed for type 2 diabetes. It works by lowering glucose production in the liver and improving your body's sensitivity to insulin so that your body uses insulin more effectively.

Nausea and diarrhea are possible side effects of metformin. These side effects may go away as your body gets used to the medicine or if you take the medicine with a meal. If metformin and lifestyles changes aren't enough to control your blood sugar level, other oral or injected medications can be added.

➤ Sulfonylureas. These medications help your body secrete more insulin. Examples include glyburide (DiaBeta, Glynase), glipizide (Glucotrol) and glimepiride (Amaryl). Possible side effects include low blood sugar and weight gain.

Now a new drug has been introduced which is having a low risk of adverse effects and can be taken orally.

### Oral GLP-RA

Glucagon-like peptide 1 receptor agonists (GLP1-RA) constitute a class of antidiabetic medications with unique a set of characteristics. Despite within class variations in terms of clinical efficacy due to different biochemical structures and pharmacokinetics profiles, all members of GLP1-RA class (liraglutide, albiglutide, dulaglutide, lixisenatide and semaglutide) have shown significant hypoglycaemic efficacy. Second, their safety profile is overall satisfactory considering the low risk of serious adverse events. Moreover, their supplementary effects on satiety and weight loss are essential in the management of type 2 diabetes mellitus (T2DM) to the extent that liraglutide has already been repurposed as an anti-obesity medication, and the 3 mg dose is already approved and used in clinical practice. Last but not least, their favourable cardiovascular (CV) properties in blood pressure, endothelial function and myocardial metabolism exemplified in the LEADER trial and other studies, in which a significantly lower risk of CVD events was demonstrated with liraglutide in patients with T2DM, are of major clinical importance when considering the increased risk of CV and all-cause mortality in patients with T2DM.

On top of the above hard clinical outcomes, the use of GLP1-RA is associated with unique beneficial effects from the pathophysiological perspective as well. This class has a glucose-dependent nature of action and is admittedly one of the most efficacious amongst glucose-lowering agents in addressing GLP-1 resistance and hyperglucagonemia, thus combating in multiple ways the multifactorial components of T2DM.

Considering the above, it comes as no surprise that several formulations of GLP1-RA have been tested and developed and several members of the family have been introduced in everyday practice with different pharmacokinetic properties. In 2005, US Food and Drug Administration (FDA) approved exenatide for the treatment of type 2 DM. Long-acting liraglutide was approved in 2009 and 2010 by the European Medicines Agency and FDA, respectively, followed by lixisenatide (2013 EMA, 2016 FDA), albiglutide (2014 for both EMA and FDA) and dulaglutide (2014 for both EMA and FDA)<sup>8</sup> On December 5, 2017, semaglutide was approved in the USA for its use as subcutaneous injection, while in Europe, semaglutide was approved by the EMA on February 8, 2018.

However, notwithstanding the above admittedly well-grounded benefits associated with the use of GLP1-RA, both the adoption and adherence to treatments may be considered as low<sup>11</sup> in the real world. One of the major reasons is the high dropout rate, possibly due to the nausea-related side effects and importantly the fact that these formulations are till date injectable. The recent introduction of weekly instead of daily injection schemes is an advance, but still, the injectable therapy places a significant psychological and practical burden to patients, who may prioritize ease of use associated with an oral formulation over superior pathophysiological properties. On top of this, oral formulations do not require specific conditions of sterility and other precautions against possible particle contamination, which may also have cost implications.

The above issues should be addressed by the development and introduction of oral GLP1-RA formulations, which are preferable by patients and related to better compliance and convenience. This is why the recent advances with semaglutide, the first and more advanced form of oral GLP1-RA, are considered a major step forward in the therapeutics of diabetes.<sup>1</sup> These steps will be summarized in this review.

The injectable formulation of semaglutide has an increased affinity for native human GLP1. Semaglutide molecule resembles native GLP1 sharing a 94% structural homology and is

modified at 3 positions; position 8, where alanine is substituted by alpha-aminoisobutyric acid and thus increasing resistance to DPP-4 degradation, position 34, where lysine is changed by arginine and thus, preventing wrong binding of C-18 fatty acid, and position 26, where lysine is acylated with a glutamate spacer to provide specific binding to albumin. The semaglutide molecule differs from its precursor molecule liraglutide in two positions; alanine at the second position is replaced by  $\alpha$ -aminoisobutyric acid and lysine 26 residue is acylated with a stearic diacid instead of palmitate. These changes result in extending semaglutide half-life to approximately 1 week, thus permitting a weekly delivery dosage scheme. The strong affinity for albumin also contributes to the long duration of action. The spacer region (glutamic acid moiety) between the C-18 fatty di-acid side chain and the peptide is considered to be important for potency, whereas the fatty acid is considered to be important for both potency and protraction.

The metabolism of semaglutide takes place in two steps: the first step is the proteolytic cleavage of the peptide backbone and the second one is  $\beta$ -oxidation (involving dehydrogenation, hydration, dehydrogenation, thiolytic cleavage) of the fatty di-acid chain, procedures that are not confined to specific organs. Following  $\beta$ -oxidation, semaglutide degradation products are excreted mainly via urine and to lesser extent via the feces, involving hepatic metabolism in part. Amongst semaglutide metabolites, the most dominant metabolite is traceable up to 7.7% of all semaglutide material and found to consist of several co-eluting components.

Moreover, the pharmacokinetics of semaglutide are not significantly affected by renal or hepatic impairment and thus, no dose adjustment is required in these populations. Of note, the kidney function appears to be unaffected by the use of semaglutide. The level of creatine clearance also does not appear to affect the pharmacokinetics of semaglutide, yet clinical experience in patients with end-stage renal disease is limited and thus not recommended. No significant drug interactions were detected when semaglutide was coadministered with metformin, warfarin, digoxin, atorvastatin, ethinylestradiol and levonorgestrel in healthy adults.

The efficacy and safety of injectable semaglutide was explored in the SUSTAIN trials program. Overall, semaglutide was associated with improved glycaemic control, when used either as monotherapy or as add-on therapy in patients with T2DM against both placebo and active comparators (including other GLP-1 RAs). The results of the published SUSTAIN

trials are summarized in Table 1. Compared with placebo, a significant decrease in HbA1c with both dosages (1.45% and 1.55% for 0.5 mg and 1.0 mg, respectively) was observed in SUSTAIN 1. Moreover, body weight reduced significantly by 3.73 kg and 4.53 kg with 0.5 mg and 1.0 mg, respectively. The magnitude of this effect is considered exceptionally high.

**Table No. 1: Effectiveness of semaglutide versus control in HbA1c and weight reduction**

Study	Duration (weeks)	Route	Dose (mg)	Comparator	HbA1c (%) Reduction	Weight (kg) Reduction
SUSTAIN 1 <sup>25</sup>	30	subcutaneous	0.5 1.0	Placebo	-1.43* -1.53*	-2.75* -3.56*
SUSTAIN 2 <sup>27</sup>	56	subcutaneous	0.5 1.0	Sitagliptin 100 mg	-0.77* -1.06*	-2.35* -4.2*
SUSTAIN 3 <sup>28</sup>	56	subcutaneous	1.0	Exanatide ER	-0.62*	-3.78*
SUSTAIN 4 <sup>29</sup>	30	subcutaneous	0.5 1.0 (+insulin)	Glargine U100	-0.38* -0.81*	-4.62* -6.33*
SUSTAIN 5 <sup>31</sup>	30	subcutaneous	0.5 1.0 (+insulin)	Placebo	-1.35* -1.75*	-2.31* -5.06*
SUSTAIN 6 <sup>26</sup>	104	subcutaneous	0.5 1.0	Placebo	-0.7* -1.0*	-2.9* -4.3*
SUSTAIN 7 <sup>30</sup>	40	subcutaneous	0.5 1.0	Delaglutide: 0.75 1.5	-0.4* -0.41*	-2.26* -3.55*
Davies et al <sup>10</sup>	26	Per Os	2.5 5.0 10.0 20.0 40.0	Placebo	-0.4* -0.9* -1.2* -1.4* -1.6*	-0.9 -1.5 -3.6* -5.0* -5.7*

**Abbreviations:** SUSTAIN, semaglutide unabated sustainability in treatment of type 2 diabetes; s.c, subcutaneous; p.os, per os; HbA1c, glycated haemoglobin A1c.

Adult patients with T2DM treated by metformin, thiazolidinediones/rosiglitazone or both without adequate glycaemic control after 3 months were enrolled in SUSTAIN 2 trial to explore the comparative effectiveness of semaglutide against sitagliptin.

The primary outcome was the mean HbA1c change from baseline to 56 weeks, which was significantly reduced in both semaglutide groups against sitagliptin. Notably, body weight reduced up to ~6.0% for the highest dosage of semaglutide.

SUSTAIN 3 trial compared semaglutide 1.0 mg with exenatide extended release 2 mg in adults with T2DM not controlled on one or two oral antidiabetic agents. After 56 weeks, Hb1Ac and body weight were significantly decreased in the semaglutide group. The results



were similar when semaglutide was compared to insulin glargine and dulaglutide, but importantly, fewer hypoglycaemic episodes were recorded with semaglutide.

In addition to its glucose- and weight-lowering efficacy, semaglutide, when used as add-on standard care in patients with T2DM and high cardiovascular disease, was found to be associated with significantly lower risk of cardiovascular death, nonfatal myocardial infarction, stroke and new or worsening nephropathy compared to placebo. This finding is regarded as of paramount importance in the long-term clinical care of patients with T2DM.

Similar to other GLP-1 RA, nausea and other gastrointestinal (GI)-related symptoms were the most common complications reported in the SUSTAIN trials. Nausea was reported up to a quarter of patients receiving semaglutide (placebo group 8%). Diarrhea was less frequent; it was reported to 13% of patients receiving 0.5 mg semaglutide and 11% of patients receiving 1 mg semaglutide (placebo group 2%). No case of pancreatitis or pancreatic or medullary cancer was documented, while cases of cholelithiasis were rare.<sup>25</sup> In a large population consisting of 3297 patients (SUSTAIN 6 trial), the incidence of the above GI disorders was found to be similar. Of note, the rates of malignant neoplasms were similar in the pooled semaglutide groups (0.5 and 1.0 mg) compared to placebo, although the highest rate was noted in the semaglutide group receiving 1.0 mg. Microvascular outcomes related to diabetic retinopathy complications were found to be higher in semaglutide group compared to the placebo group, as expected in the context of rapid HbA1c reductions. These events were mostly mild or moderate and recorded mainly in patients with significant background diabetic retinopathy. This imbalance in retinopathy outcomes was absent in SUSTAIN 1–5 trials, yet not infrequently reported following abrupt glycaemic improvement (such as in Diabetes Control and Complications Trial and in newly diagnosed patients with T2D in the UK Prospective Diabetes Study (UKPDS 33), or in introduction of insulin in everyday clinical practice). On the other hand, the incidence of new or worsening nephropathy was significantly decreased in the semaglutide group compared to placebo.

## **ORAL SEMAGLUTIDE**

### **Oral semaglutide: safety and efficacy data from trials**

A Phase II, 26-week randomized multicenter, open-label clinical trial, in which oral semaglutide was compared with subcutaneous semaglutide and placebo, was designed and finally recruited 1106 participants. The design involved multiple dosing schemes of oral

semaglutide, including once-daily dosages of 2.5 mg, 5 mg, 10 mg, 20 mg or 40 mg. Moreover, two additional 40-mg dosages were evaluated: the slow escalation extending over 8 weeks (5 mg as first dose for 8 weeks and doubling dose every 8 weeks until 40 mg) and the fast escalation of 2 weeks (5 mg for the first 2 weeks and doubling dose every 2 weeks until 40 mg). The most common adverse events were reported from the GI system. In the standard-dose escalation of oral semaglutide, GI adverse events were similar to the subcutaneous semaglutide, yet lower compared to placebo. In the oral semaglutide group, the percentage of patients reported GI adverse events were approximately doubled in the case of fast escalation compared to the standard dose of 2.5 mg and 5 mg. Generally, the severity of adverse events was higher in the high-dose oral semaglutide, compared to the subcutaneous or placebo group. This may explain the higher rates of treatment discontinuation in these cases. Surprisingly enough, episodes of hypoglycemia were less common in both the oral and subcutaneous semaglutide groups compared to the placebo, a finding that may constitute an advantage over other hypoglycaemic agents.

With regard to its efficacy, oral semaglutide was found to be of comparable efficacy in reducing HbA1c with the subcutaneous form, associated with a reduction up to 1.9% in HbA1c and 6.9 kg in body weight.<sup>41</sup> The reduction of HbA1c and weight from the oral administration of semaglutide compared with placebo or other treatments is summarized in Table 2.

**Table No. 2 Effectiveness of oral semaglutide versus control in glyceimic control and weight reduction**

Study	Duration (weeks)	Semaglutide Dose (mg)	Comparator	HbA1c (%) change	Weight change (kg)
PIONEER 1 <sup>41</sup>	26	3 7 14	Placebo	-0.7* -1.2* -1.4*	-0.2 -1.0* -2.6*
PIONEER 2 <sup>42</sup>	52	14	Semaglutide 25 mg	-0.5*	-0.9*
PIONEER 3 <sup>43</sup>	78	3 4 17	Sitagliptin 100 mg	0.1 -0.3* -0.7*	-0.8* -1.6* -2.4*
PIONEER 4 <sup>44</sup>	52	14	Placebo Liraglutide 1.8 mg	-1.4* -0.3*	-3.8* -1.9*
PIONEER 5 <sup>46</sup>	25	14	Placebo	-1*	-2.6*
PIONEER 7 <sup>44</sup>	52	On the basis of glycaemic control	Sitagliptin 100 mg	N/A	-2.1*
Davies et al <sup>40</sup>	26	2.5 5.0 10.0 20.0 40.0	Placebo	-0.4* -0.9* -1.2* -1.4* -1.6*	-0.9 -1.5 -3.6* -5.0* -5.7*

**Abbreviation:** HbA1c, glycated haemoglobin.

A Phase III, 26-week, randomized, double-blinded, placebo-controlled trial, the PIONEER 1, exploring the oral form of semaglutide at 3-mg, 7-mg and 14-mg doses in patients with T2DM is currently ongoing and it is soon expected to be concluded. Novo Nordisk announced a preliminary analysis from PIONEER 1 trial in February 2018; the oral semaglutide group achieved a 0.8%, 1.3% and 1.5% reduction in HbA1c and a weight loss of 1.7 kg, 2.5 kg and 4.1 kg at doses 3 mg, 7 mg and 14 mg, respectively. Further results and secondary end points are expected to be published after the completion of PIONEER 1 trial.

Following this announcement regarding the placebo-controlled PIONEER 1 trial, the main results from an active-controlled RCTs (trials in which oral semaglutide is compared to already approved antidiabetic medications) were also made public. These active comparators included SGLT2i empagliflozin (PIONEER 2), inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitor) sitagliptin (PIONEER 7) and GLP1-RA liraglutide (PIONEER 4).

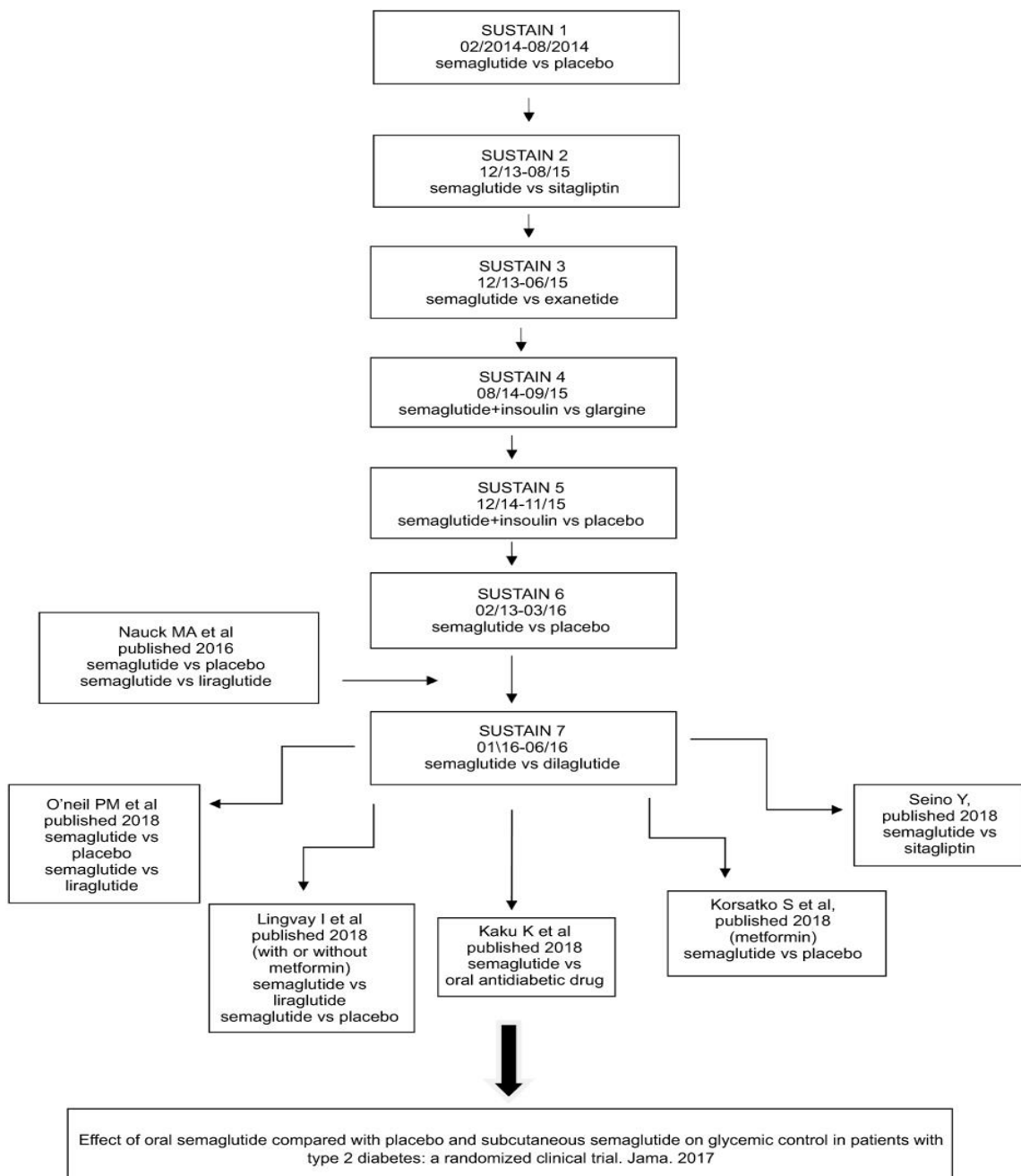
In the 52-week PIONEER 2 trial, the main aim was to compare oral semaglutide with empagliflozin, in 421 patients inadequately controlled with metformin. Oral semaglutide was found to provide a significantly greater reduction in HbA1c and body weight compared to

empagliflozin at 52 weeks. Fourteen milligrams of oral semaglutide resulted in a 1.3% improvement of HbA1c and 4.7 kg weight loss, while empagliflozin 25 mg achieved a 0.8% decrease in HbA1c and 3.8 kg weight loss. The superiority of oral semaglutide in reducing HbA1c was observed as early as at week 26. In the PIONEER 3 trial, similar results were reported showing the superiority of oral semaglutide at 78 weeks (7 mg and 14 mg achieved: 0.7% and 1.1% HbA1c reduction, 2.7 kg and 3.5 kg weight loss) compared to the 100 mg sitagliptin (0.4% HbA1c reduction, 1.1 kg weight loss) in patients with T2DM inadequately controlled with metformin, with or without sulfonylurea. Analyses from PIONEER 4 and 7, both with 52-week duration, were also announced. In PIONEER 4, 14 mg oral semaglutide was compared with 1.8 mg liraglutide (1.2% vs 0.9% HbA1c reduction, 5 kg vs 3.1 kg weight loss) and was found to provide comparable glycemic control and significant weight loss. In the open-label PIONEER 7, flexible once-daily adjustable dose of oral semaglutide (3 mg, 7 mg, 14 mg; n=253) was compared to 100 mg sitagliptin in patients whose type 2 diabetes was uncontrolled with one to two oral glucose-lowering medication. Flexible dose adjustment of oral semaglutide led to superior glycemic control and weight loss at week 52 versus sitagliptin and was well tolerated. Adverse events were more frequent in patients receiving oral semaglutide, yet generally mild and consistent with the GLP-1 receptor antagonist class (nausea). Discontinuation due to adverse events was more frequent for oral semaglutide (PIONEER 4: 11%, PIONEER 7: 9%) compared to liraglutide (9%) and sitagliptin (3%) users.

Oral semaglutide was further investigated against placebo with regard to its cardiovascular safety (PIONEER 6) in patients considered to be at high cardiovascular risk, safety and efficacy in patients with moderate renal impairment (PIONEER 5), and safety and efficacy as an add-on therapy to insulin-treated patients (PIONEER 8). In PIONEER 6 trial, 3183 patients with T2DM were randomized to either oral semaglutide or placebo were observed for cardiovascular events up to a median of approximately 16 months. Major adverse cardiovascular events occurred in 61 of 1591 patients (3.8%) in the oral semaglutide group and in 76 of 1592 (4.8%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.57–1.11;  $p < 0.001$  for noninferiority). Despite its relative short duration and low number of events, the cardiovascular risk profile of oral semaglutide appears to be (at least) not inferior to that of placebo. In a 26-week RCT (PIONEER 5), involving 163 patients randomized to oral semaglutide (14 mg once daily) and 161 patients to the placebo, oral semaglutide was shown to provide a superior glycemic control (estimated treatment difference of 0.8%) and

body weight loss (estimated treatment difference of  $-2.5$  kg) than placebo and was found not to affect renal function. As an add-on to insulin with or without metformin (PIONEER 8), oral semaglutide (at doses of 3, 7 and 14 mg) was shown to be associated with superior HbA1c and body weight reductions versus placebo as early as at week 26 and achieved further reduction in insulin need (except dose 3 mg) at week 52, without significantly increasing the rate of hypoglycemia.

The evolution of research starting from the first SUSTAIN trial to the creation of the new oral form of semaglutide is depicted in Figure. [5]



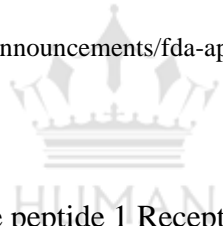
## CONCLUSION

Type 2 diabetes is the most common form of diabetes, occurring when the pancreas cannot make enough insulin to keep blood sugar at normal levels. GLP-1, which is a normal body hormone, is often found in insufficient levels in type 2 diabetes patients. Glucagon-like peptide-1 and GLP-1 analogs have many advantages over existing therapies for the treatment of T2DM, including a superior ability to increase glucose-dependent insulin secretion and glucose-dependent glucagon suppression with consequent low risk of hypoglycemia. As oral delivery of proteins and peptides is still a great challenge for the modern pharmaceutical industry, oral delivery of GLP-1 and its analogs is a promising new scheme therapy.

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## ABBREVIATIONS LIST



GLP1-RA	-	Glucagon-like peptide 1 Receptor Agonist
HbA1c	-	Hemoglobin A1c
T2DM	-	Type 2 Ddiabetes Mellitus
CV	-	Cardiovascular
FDA	-	Food and Drug Administration
EMA	-	European Medicines Agency
SNAC	-	Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate
GIP	-	Gastric Inhibitory Polypeptide. <sup>[5]</sup>