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Review Article

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Clinical development of oral semaglutide for the treatment of type 2 diabetes mellitus: focusing on early phase clinical trials

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder often associated with obesity and elevated cardiovascular risks. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become integral to T2DM management due to their clinical benefits of glucose regulation and weight loss. However, their subcutaneous administration presents challenges to patient adherence, limiting their widespread use. Oral semaglutide (Rybelsus®), the first oral GLP-1 RA approved for T2DM, addresses these challenges through an innovative co-formulation with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, which enhances gastric absorption and stability. This review provides a comprehensive overview of the clinical development of oral semaglutide, with a focus on early-phase trials. Phase 1 studies investigated pharmacokinetics, pharmacodynamics, safety, and dose-response relationships, demonstrating a dose-dependent reduction in hemoglobin A_{1c} (HbA_{1c}) and body weight with an acceptable safety profile. Additionally, pharmacological evaluations of interactions with food, dosing condition, disease states, and concomitant medications supported the determination of an optimal dosing regimen for further clinical studies. Phase 2 dose-finding trials confirmed significant HbA_{1c} and weight reductions comparable to subcutaneous semaglutide, which guided dose selection for phase 3 trials. Phase 3 trials, including the Peptide InnOvatioN for Early diabEtes tReatment program, demonstrated significant reductions in HbA_{1c}, weight loss, and cardiovascular safety, positioning oral semaglutide as a transformative option in diabetes care. The study highlights comprehensive clinical strategies and provides an insight into the future development of oral GLP-1 RAs and other oral peptide drugs.

Keywords: Semaglutide; Glucagon-Like Peptide-1 Receptor Agonists; Type 2 Diabetes Mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by impaired glucose regulation due to inadequate insulin production and insulin resistance [1]. A common comorbidity is obesity, which contributes to a high risk of cardiovascular complication and increased mortality [2]. Current glucose-lowering agents used to manage T2DM are associated with undesirable events, such as hypoglycemia and weight gain [1].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as effective therapeutic options for the management of T2DM. As peptide-based drugs, GLP-1 RAs are designed to mimic the actions of the endogenous hormone GLP-1, which plays a crucial role in glucose homeostasis [3]. This class of drug activates GLP-1 receptors, resulting in glucose-dependent stimulation of insulin secretion and suppression of glucagon secretion [3,4]. These mechanisms make GLP-1 RAs highly effective in regulating blood glucose levels, with a low risk of hypoglycemia due to their glucose-dependent mode of action. Additionally, GLP-1 RAs promote weight loss by reducing appetite and food intake, increasing satiety, which is particularly beneficial for patients with T2DM and obesity [4].

Despite their clinical benefits, the adoption of GLP-1 RAs has been constrained by limitations in their delivery systems. Most GLP-1 RAs are available as subcutaneous injections, administered once daily or weekly, due to a poor oral absorption of peptide drugs (**Table 1**). The peptide structure of GLP-1 and its analogs makes them highly susceptible to enzymatic degradation, particularly by dipeptidyl peptidase-4 (DPP-4), resulting in a short half-life ($t_{1/2}$). This pharmacokinetic (PK) limitation, combined with the need for frequent injections, lead to challenges in treatment adherence and suboptimal therapeutic outcomes [5].

Semaglutide, a GLP-1 analog with 94% sequence homology to native GLP-1, addresses several of these challenges through strategic structural modifications. Three key changes extend its $t_{1/2}$ to approximately one week: enhanced resistance to DPP-4 degradation, increased affinity for albumin binding, and structural refinements preventing non-specific binding of its C18 fatty acid moiety [6]. Semaglutide exhibits high plasma protein binding (> 99%) and is primarily distributed within the plasma compartment, with extensive metabolism before excretion via urine and feces. These attributes have positioned semaglutide as a leading therapeutic option among GLP-1 RAs.

Building on the success of subcutaneously injectable semaglutide (Ozempic®), oral semaglutide (Rybelsus®) has emerged as the first oral GLP-1 RA approved for T2DM management [7]. This novel formulation combines semaglutide with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). SNAC facilitates gastric absorption by transiently increasing the transcellular permeability of the gastric epithelium to semaglutide and providing localized pH modulation that protects the peptide from proteolytic degradation in the stomach [8]. These advancements overcome the traditional barriers to oral peptide drug delivery, enabling effective systemic absorption. The oral

Table 1. Summary of US Food and Drug Administration approved glucagon-like peptide-1 receptor agonists for the treatment of T2DM and obesity

Drug	Brand	Indication	Route of administration	Regimen	Approval date*	Company
Exenatide	Byetta®	T2DM	SC	Twice-daily	2005.04	*Amylin & Eli Lilly*
	Bydureon®	T2DM	SC	Once-weekly	2012.01	*Amylin & Eli Lilly*
Liraglutide	Victoza®	T2DM	SC	Once-daily	2010.01	*Novo Nordisk*
	Saxenda®	Obesity	SC	Once-daily	2014.12	*Novo Nordisk*
Albiglutide (withdrawn)	Tanzeum®	T2DM	SC	Once-weekly	2014.04	*GlaxoSmithKline*
Dulaglutide	Trulicity®	T2DM	SC	Once-weekly	2014.09	*Eli Lilly*
Lixisenatide	Adlyxin®	T2DM	SC	Once-daily	2016.07	*Sanofi*
Semaglutide	Ozempic®	T2DM	SC	Once-weekly	2017.12	*Novo Nordisk*
	Rybelsus®	T2DM	Oral	Once-daily	2019.09	*Novo Nordisk*
	Wegovy®	Obesity	SC	Once-weekly	2021.06	*Novo Nordisk*
Tirzepatide	Mounjaro®	T2DM	SC	Once-weekly	2022.05	*Eli Lilly*
	Zepbound®	Obesity	SC	Once-weekly	2023.11	*Eli Lilly*

SC, subcutaneous injection; T2DM, type 2 diabetes melitus.
*The first approved date.

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administration of semaglutide offers significant advantages, including reduced burden associated with injections, which contributes to improved patient compliance. Clinical studies evaluating safety, PKs, pharmacodynamics (PDs), and efficacy of oral semaglutide have demonstrated its potential to treatment options, leading to regulatory approval for T2DM management.

In addition to oral semglutide, several other oral GLP-1 RAs, such as danuglipron and orforglipron, are currently in various stages of clinical development. Danuglipron, a small-molecule GLP-1 RA, demonstrated glucose-lowering effects in a phase 2 clinical trial, in which twice-daily administration for 16 weeks resulted in a hemoglobin A_{1c} (HbA_{1c}) reduction (−1.16%) in the high-dose group [9]. However, gastrointestinal (GI) adverse events (AEs), including nausea and vomiting, were frequently reported, and weight loss effect (−4.17 kg) was modest compared to competitors, leading to the discontinuation of the twice-daily formulation [9]. Currently, an extended-release formulation for once-daily dosing is underdevelopment to enhance tolerability and efficacy, with ongoing clinical trials evaluating its potential benefits. Unlike peptide-based GLP-1 RAs, the non-peptide nature of danuglipron may improve its oral bioavailability and ease of manufacturing. Orforglipron, another non-peptide GLP-1 RA, has demonstrated robust glucose-lowering efficacy in phase 2 clinical trials. After 26 weeks of once-daily dose treatment, HbA_{1c} levels were significantly reduced (−2.1%) [10]. Additionally, after 36 weeks, patients experienced a weight reduction (−14.7%) [11], positioning orforglipron as a promising oral GLP-1 receptor agonist for both glycemic control and weight management. Currently, orforglipron is undergoing phase 3 trials, including the ATTAIN-2 study (NCT05872620), which aims to assess its efficacy and safety in T2DM patients.

This review aims to provide a comprehensive summary of the clinical developments and their results of oral semaglutide. By examining its pharmacological properties, clinical trial data, and therapeutic potential, this paper highlights the transformative impact of oral semaglutide in advancing diabetes care and offers an insight into the future clinical development of oral GLP-1 RAs or other oral peptide drugs.

CLINICAL DEVELOPMENT

Phase 1 clinical trials

Single ascending dose study

The first-in-human trial was conducted in healthy male subjects (n = 135) to evaluate the PKs, safety and tolerability of oral semaglutide [12]. Subjects were randomized to receive a single dose of oral semaglutide (2, 5, 10, or 20 mg) co-formulated with varying amounts of SNAC (150, 300, 450, or 600 mg) or placebo with SNAC [12]. The semaglutide exposure was maximized when co-formulated with 300 mg of SNAC, which was subsequently selected as the optimal SNAC dose for further development [12]. PK analysis revealed that maximum concentration (C_{max}) increased less than dose-proportionally, whereas the area under the concentration-time curve (AUC_{0-504h}) increased more than dose-proportionally with escalating doses [12]. Notably, SNAC exposure remained consistent regardless of semaglutide dose (5 or 10 mg) [12]. Among the subjects who received a single dose of oral semaglutide, headaches were commonly reported, but no severe or serious AEs occurred, and all subjects recovered from the AEs [12]. Other safety profiles were consistent with the known effects of GLP-1 receptor agonists; GI AEs such as nausea, vomiting, and diarrhea were reported, but no significant safety concerns were identified [12].

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Multiple ascending dose (MAD) study

A 10-week MAD study assessed the safety, tolerability, and PK/PD profiles of once-daily oral semaglutide in healthy males (n = 84) and males with T2DM (n = 23) [12]. Subjects were randomized to four cohorts in a semi-parallel design: three cohorts of healthy subjects with maintenance doses of 20 mg, 40 mg, or 60 mg, while a fourth cohort of T2DM patients with a 60 mg as maintenance dose [12]. A stepwise dose escalation scheme was used to mitigate GI AEs. Once-daily dosing began at 5 mg in week 1, increased to 10 mg in week 2, and escalated to 20 mg by week 3. Higher doses of 40 mg and 60 mg were introduced incrementally from weeks 5 and 7, contingent on safety evaluations [12]. After escalating to 40 mg, it was determined that further escalation to 60 mg would result in unacceptable occurrence of AEs [12]. Consequently, the study was completed with healthy subject receiving 40 mg (n = 32) and 20 mg (n = 16), and subjects with T2DM receiving 40 mg (n = 11) [12]. The semaglutide exposure at a steady state was approximately two-fold higher with the 40 mg dose compared to the 20 mg dose [12]. No significant difference in exposure was observed between healthy subjects and subjects with T2DM receiving the 40 mg dose, underscoring consistent PK behavior across populations [12]. In subjects with T2DM, once-daily dosing of 40 mg oral semaglutide for 10 weeks led to a HbA_{1c} reduction of 1.5% and a body weight reduction of 5.4 kg compared to placebo [12]. The results suggest the therapeutic potential of oral semaglutide for the treatment of T2DM. The PK and PD evaluation in this study was limited to lower dose cohorts (20 mg and 40 mg) due to safety concerns, which rendered it difficult to establish a clear PK/PD relationship. However, both PK and PD demonstrated dose-dependent profiles, supporting the investigation of the dose-response relationship across multiple dosing regimens (2.5–40 mg) in the subsequent phase 2 clinical trial.

Drug-food and -dosing conditions interaction studies

The food-effect study in healthy subjects (n = 78) demonstrated that measurable semaglutide exposure was observed in subjects who received oral semaglutide in a fasted state (n = 26), whereas limited or undetectable under a fed state condition (n = 25) [13].

The dosing conditions study evaluated the effects of water volume and post-dose fasting duration on the oral semaglutide PK in healthy males (n = 158) [13]. Subjects were randomized into eight treatment groups receiving 10 mg oral semaglutide once-daily for 10 days, with either 50 or 120 mL of water and post-dose fasting durations of 15, 30, 60, or 120 minutes [13]. The oral semaglutide absorption increased with longer post-dose fasting periods, especially from 15 to 30 minutes, and was comparable when administered with either 50 or 120 mL of water [13].

These findings informed the phase 2 and phase 3 study recommendations to administer oral semaglutide in the fasted state with up to 120 mL water and wait for 30 minutes post-dose before eating or taking other oral medications.

Drug-disease interaction studies

The effects of renal impairment and haemodialysis, common comorbidities in T2DM patients, on the oral semaglutide PK were evaluated in 71 subjects with normal renal function (n = 24), and mild (n = 12), moderate (n = 12), severe (n = 12) renal impairments, as well as end-stage renal disease (n = 11) [14]. Subjects received once-daily oral semaglutide (5 mg for 5 days, followed by 10 mg for 5 days) [14]. Consistent patterns in semaglutide exposure were observed across the groups. The $t_{1/2}$ and time to reach C_{max} were similar in all the patients regardless of renal functions, and haemodialysis did not affect the semaglutide PK [14].

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Similarly, the effect of hepatic impairment, another potential comorbidity in T2DM patients, on the oral semaglutide PK was studied in 56 subjects with normal hepatic function (n = 24), and mild (n = 12), moderate (n = 12) and severe (n = 8) hepatic impairment [15]. No significant relationship between hepatic function and semaglutide exposure was observed [15].

Considering that oral semaglutide is expected to be primarily absorbed in the stomach, the effects of upper GI disease on its PK were assessed in 55 T2DM patients with (n = 36) and without (n = 19) upper GI disease [16]. No significant differences in semaglutide exposure were observed [16].

These studies provided evidence supporting the inclusion of these populations in late phase clinical studies and suggested that dose adjustment is not required in these specific populations.

Drug-drug interaction study

Given the pH dependent absorption of oral semaglutide in the stomach, the effects of co-administered drug, such as gastric acid inhibitors, on oral semaglutide PK was evaluated in healthy subjects. Co-administration with omeprazole resulted in a slight increase in semaglutide exposure which was not clinically significant [17]. However, co-administration with five placebo tablets resulted in a 32–34% decrease in semaglutide exposure, supporting the recommendation to take semaglutide at least 30 minutes prior to food, beverages, or other medications [18].

The mechanism of action of oral semaglutide may also affect the PKs of other drugs due to its delaying effect on gastric emptying. The effects of oral semaglutide on other drugs, commonly used in T2DM patients, were assessed. No significant changes in the exposure were observed for lisinopril, warfarin, digoxin, ethynilestradiol and levonorgestrel [19,20]. Small changes in the exposure of metformin, furosemide and rosuvastatin were noted, but these are not considered to be clinically significant [19,20]. However, co-administration with levothyroxine resulted in a 33% increase in total thyroxine exposure (AUC) without affecting C_{max} [18]. Consequently, when co-administering levothyroxine with oral semaglutide, it is recommended to closely monitor thyroid parameters.

Phase 2 clinical trial

Dose-finding study

A phase 2 dose-finding study evaluated the dose-response relationship on glycemic control (HbA_{1c}) level of five doses (2.5, 5, 10, 20, and 40 mg) of once-daily oral semaglutide compared with placebo in a double-blind design and once-weekly subcutaneous semaglutide 1 mg in patients with T2DM in an open-label design (n = 632) over 26 weeks [21]. The dose titration scheme was applied to reduce the risk of GI AEs with a 4-week dose escalation.

Oral semaglutide demonstrated significant reductions in HbA_{1c} and body weight compared to placebo. Mean HbA_{1c} levels decreased from baseline to week 26 in a dose-dependent manner (from −0.7 to −1.9%) with oral semaglutide, and these reductions were significantly greater compared with placebo (−0.3%) [21]. The decreases in HbA_{1c} achieved with the two highest doses of once-daily oral semaglutide (20 and 40 mg) were similar to those achieved with subcutaneous semaglutide 1 mg once-weekly (−1.9%) [21]. Reductions in body weight were also significant in 10 mg, 20 mg, and 40 mg doses of oral semaglutide compared to placebo [21]. As expected for a GLP-1RA, the most common AEs were mild-to-moderate GI disorders, including nausea, vomiting and diarrhea, with higher incidence at doses of 20 mg and 40 mg

[21]. Nausea events appeared to occur less frequently when patients were initiated at a lower dose (2.5 mg) compared to a higher dose (5 mg) of oral semaglutide [21]. Based on these findings, three optimal doses (3, 7, and 14 mg) were selected for phase 3a trials, which were expected to have the optimal benefit-risk profile.

Phase 3 clinical trials

The Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) clinical trial program was designed to confirm the efficacy and safety of oral semaglutide in a broad population of patients with T2DM. A total 9,543 patients were enrolled in 10 trials, each study addressing different clinical questions related to the efficacy of oral semaglutide and its comparison with other glucose-lowering agents or placebo.

In PIONEER 1 (n = 703), oral semaglutide at doses of 3, 7, and 14 mg demonstrated significant reductions in HbA_{1c} and body weight compared to placebo in patients managed with diet and exercise [22]. PIONEER 2 (n = 822) [23], PIONEER 3 (n = 1,864) [24], and PIONEER 4 (n = 711) [25] compared semaglutide to empagliflozin, sitagliptin, and liraglutide, respectively, showing superior or non-inferior glycemic control and weight loss. PIONEER 5 (n = 822) [26], PIONEER 6 (n = 3,138) [27], and PIONEER 8 (n = 731) [28] targeted specific populations, including those with moderate renal impairment, cardiovascular risk factors, and insulin-treated patients, confirming efficacy and safety of oral semaglutide across various clinical scenarios. PIONEER 7 (n = 504) [29,30] explored flexible dose adjustments, enhancing tolerability and glycemic outcomes. PIONEER 9 (n = 243) [31] and PIONEER 10 (n = 458) [32], conducted in Japan, confirmed the clinical benefits of semaglutide in comparison to placebo, liraglutide, and dulaglutide. Across the whole trials, oral semaglutide consistently achieved significant, dose-dependent HbA_{1c} and weight reductions, establishing itself as a highly effective treatment option for T2DM.

DISCUSSION

The clinical development of oral semaglutide has shown a strategic approach to addressing the limitations of peptide therapeutics for T2DM. Several key considerations were integral to its successful clinical development, reflecting both scientific rigor and patient-centric design.

The early inclusion of T2DM patients during phase 1 trials is a notable feature of the oral semaglutide in clinical development. This approach allowed researchers to directly assess the PK, PD, and safety profiles in the target population, accelerating the translation of findings into clinical practice. It also facilitated an early understanding of how the drug's absorption and metabolic parameters may vary between healthy individuals and T2DM patients. Early involvement of the intended patient group not only enhanced the clinical relevance of the findings but also informed optimal dosing strategies that accounted for the disease-specific physiological variations.

The clinical development of oral semaglutide involved comprehensive evaluations of its interactions with food, disease and concomitant drugs (**Table 2**), considering its pharmacological properties and therapeutic application. Food-effect studies informed the importance of fasting conditions for optimal absorption, while studies on disease interactions demonstrated consistent PK profiles across varying patient conditions, eliminating the need for dose adjustments. Drug-drug interaction studies assessed

Table 2. Overview of clinical studies of oral semaglutide

Design or type	Population	No. of subjects	Treatment	Regimen/duration	Results being analyzed	ClinicalTrials.gov identifier
Phase 1 study						
Single ascending dose [12]	Healthy male	155	Oral semaglutide 2, 5, 10, 15, 20 mg, placebo	-	PK, safety	NCT01037582
Multiple ascending dose [12]	Healthy and T2DM male	107	Oral semaglutide 20, 40 mg, placebo	Once-daily for 10 wk	PK, PD, safety	NCT01686945
Dosing conditions [13]	Healthy	158	Oral semaglutide 10 mg	Once-daily for 10 d	PK, safety	NCT01572753
Food effect [13]	Healthy	78	Oral semaglutide 10 mg	Once-daily for 10 d	PK, safety	NCT02172313
RI [14]	Normal, mild, moderate, severe RI, ESRD	71	Oral semaglutide 10 mg	Once-daily for 10 d	PK, safety	NCT02014259
HI [15]	Normal, mild, moderate, severe HI	56	Oral semaglutide 10 mg	Once-daily for 10 d	PK, safety	NCT02016911
Upper GI disease [16]	T2DM with or without upper GI disease	55	Oral semaglutide 7 mg	Once-daily for 10 d	PK, safety	NCT02877355
Metformin and digoxin DDI [19]	Healthy	32	Oral semaglutide 20 mg, metformin 850 mg, digoxin 500 μg	Once-daily for 10 d	PK, safety	NCT02249910
Lisinopril and warfarin DDI [19]	Healthy	52	Oral semaglutide 20 mg, lisinopril 20 mg, S-warfarin 25 mg	Once-daily for 10 d	PK, PD, safety	NCT02070510
Oral contraception DDI [20]	Healthy postmenopausal female	25	Oral semaglutide 14 mg, ethinylestradiol/levonorgestrel 0.03/0.15 mg	Once-daily for 10 d	PK, safety	NCT02845219
Furosemide and rosuvastatin DDI [20]	Healthy	41	Oral semaglutide 14 mg, furosemide 40 mg, rosuvastatin 20 mg	Once-daily for 10 d	PK, safety	NCT03010475
Levothyroxine and 5 drugs DDI [18]	Healthy	45	Oral semaglutide 14 mg, levothyroxin 40 mg, placebo (5 tablets)	Once-daily for 10 d	PK, safety	NCT02920385
Omeprazole DDI [17]	Healthy	54	Oral semaglutide 10 mg, omeprazole 40 mg	Once-daily for 10 d	PK, safety	NCT02249871
Probenecid and cyclosporine DDI	Healthy	21	Oral semaglutide 3 mg, probenecid 500 mg, cyclosporine 600 mg	Once-daily for 10 d	PK, safety	-
Phase 2 study						
Dose finding [21]	Healthy male	155	Oral semaglutide 2, 5, 10, 15, 20 mg, placebo, SC semaglutide 1 mg	Once-daily (Oral) and once-weekly (SC) for 26 wk	Efficacy, safety	NCT01923181
Phase 3 study						
PIONEER 1 [22]	T2DM	703	Oral semaglutide 3, 7, 14 mg, placebo	26 wk	Efficacy, safety	NCT02906930
PIONEER 2 [23]	T2DM	822	Oral semaglutide 14 mg, empagliflozin 25 mg	52 wk	Efficacy, safety	NCT02863328
PIONEER 3 [24]	T2DM	1,864	Oral semaglutide 3, 7, 14 mg, sitagliptin 100 mg	78 wk	Efficacy, safety	NCT02607865
PIONEER 4 [25]	T2DM	711	Oral semaglutide 14 mg, liraglutide 1.8 mg, placebo	52 wk	Efficacy, safety	NCT02863419
PIONEER 5 [26]	T2DM with RI	324	Oral semaglutide 3, 7, 14 mg, placebo	26 wk	Efficacy, safety	NCT02827708
PIONEER 6 [27]	T2DM	3,183	Oral semaglutide 14 mg + SOC, placebo + SOC	83 wk	Efficacy, safety	NCT02692716
PIONEER 7 [29,30]	T2DM	504	Oral semaglutide 3, 7, 14 mg, sitagliptin 100 mg	52 wk	Efficacy, safety	NCT02849080
PIONEER 8 [28]	T2DM	731	Oral semaglutide 3, 7, 14 mg, placebo	52 wk	Efficacy, safety	NCT03021187
PIONEER 9 [31]	T2DM Japanese	243	Oral semaglutide 3, 7, 14 mg, liraglutide 0.9 mg, placebo	52 wk	Efficacy, safety	NCT03018028
PIONEER 10 [32]	T2DM Japanese	458	Oral semaglutide 3, 7, 14 mg, dulaglutide 0.75 mg	52 wk	Efficacy, safety	NCT03015220

PK, pharmacokinetic; T2DM, type 2 diabetes mellitus; PD, pharmacodynamic; RI, renal impairment; ESRD, end-stage renal disease; HI, hepatic impairment; GI, gastrointestinal; DDI, drug-drug interaction; SC, subcutaneous injection; PIONEER, Peptide InnOvatioN for Early diabEtes tReatment; SOC, standard of care.

medications commonly co-administered in the management of T2DM and those potentially affect the gastric pH, given the mechanism of its absorption enhancer, SNAC. These investigations informed the development of practical dosing regimens, enhancing the safety, efficacy, and real-world applicability of oral semaglutide in the treatment of T2DM.

The dose escalation schemes implemented in MAD and subsequent studies were crucial for mitigating GI AEs, which is a common concern with GLP-1 RAs. By adopting a gradual dose titration strategy, the trials ensured better tolerability, minimizing dropout rates and enhancing patient adherence. This strategy underscores the importance of balancing efficacy with safety to optimize patient outcomes in chronic disease management.

In conclusion, oral semaglutide represents a paradigm shift in the treatment of T2DM, offering a novel oral alternative to injectable GLP-1 RAs. The clinical development of oral semaglutide highlights the importance of tailoring clinical strategies to the unique pharmacological and therapeutic profiles of new drugs. These successful development of oral semaglutide, as summarized in this review, serve as a valuable reference model for future development of oral GLP-1 RAs and other oral peptide drugs.

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