



Semaglutide: Pharmacology and Clinical Evidence in Cardiometabolic Therapy

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ABSTRACT

Type 2 diabetes mellitus and obesity frequently coexist and contribute to cardiovascular and renal complications. Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist, has expanded incretin pharmacology beyond glucose lowering toward broader cardiometabolic therapy. This narrative review integrated pharmacological and clinical evidence on semaglutide. PubMed/MEDLINE was searched for English-language articles published from January 2015 to September 2026. Priority was given to pivotal randomized controlled trials, cardiovascular and renal outcome trials, pharmacokinetic studies and clinically relevant follow-up studies from the SUSTAIN, PIONEER, STEP, SELECT and FLOW programmes. Studies were selected using predefined inclusion and exclusion criteria. Semaglutide enhances glucose-dependent insulin secretion, suppresses glucagon, reduces appetite and energy intake, and delays gastric emptying. Once-weekly subcutaneous and once-daily oral formulations produced clinically important reductions in glycated hemoglobin and body weight. Semaglutide reduced major adverse cardiovascular events in high-risk patients with type 2 diabetes, lowered cardiovascular events in patients with established cardiovascular disease and obesity without diabetes, and slowed chronic kidney disease progression in patients with diabetes and chronic kidney disease. Gastrointestinal adverse effects were the main tolerability limitation, and substantial weight regain occurred after treatment withdrawal. Semaglutide is an important cardiometabolic therapy; optimal use requires patient selection, gradual dose escalation, monitoring and long-term treatment planning.

Keywords: Glucagon-like peptide-1 receptor agonist; type 2 diabetes mellitus; obesity; cardiovascular outcomes; chronic kidney disease

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity are chronic metabolic disorders that frequently coexist and contribute to cardiovascular, renal and other long-term complications. Therapeutic strategies that improve glycemic control while reducing body weight and cardiovascular risk are therefore increasingly important. GLP-1 receptor agonists have a distinctive pharmacological profile because they influence insulin and glucagon secretion, appetite, gastric emptying and several cardiometabolic pathways. [1,2]

Semaglutide is a modified analogue of human GLP-1 with a prolonged duration of action that permits once-weekly subcutaneous administration; an oral formulation was subsequently developed as an alternative route of delivery. Its clinical development includes the SUSTAIN programme in T2DM, PIONEER studies of oral semaglutide, STEP studies in obesity, SELECT in cardiovascular disease with overweight or obesity without diabetes, and FLOW in T2DM with chronic kidney disease. The magnitude and breadth of these findings have moved semaglutide from a glucose-lowering drug toward a broader cardiometabolic therapy. [5-9]

Although several reviews have described the clinical efficacy of semaglutide, a pharmacologically oriented synthesis that links its molecular characteristics, pharmacokinetics, therapeutic efficacy, cardiovascular and renal outcomes, safety and durability remains limited. This review therefore evaluates semaglutide from a pharmacological perspective and critically integrates its mechanism, pharmacokinetics, clinical evidence and limitations. The objective is not simply to catalogue clinical trials but to explain how the pharmacology of semaglutide relates to its clinical effects and limitations.

Revision note: The methodology has been expanded in response to the reviewer's compulsory revision request by specifying the database, search period, search terms, eligibility criteria and study-selection process.

MATERIALS AND METHOD

This narrative review was written using peer-reviewed pharmacological and clinical literature on semaglutide. It was not planned as a formal systematic review or meta-analysis, but the literature search was done in a structured way, as explained below.

Databases and search period

The primary literature database searched was PubMed/MEDLINE. Articles published from January 2015 to September 2026 were considered. Only articles written in English were included. The reference lists of selected papers were also checked manually to identify relevant studies that may not have been retrieved in the database search.

Search strategy and keywords

The keywords used were "semaglutide", "oral semaglutide", "GLP-1 receptor agonist", "pharmacokinetics", "type 2 diabetes", "obesity", "cardiovascular outcomes", "chronic kidney disease", "weight regain", and the trial names SUSTAIN, PIONEER, STEP, SELECT and FLOW. These terms were combined using Boolean operators AND and OR. An example search string was: (semaglutide OR "oral semaglutide") AND ("type 2 diabetes" OR obesity OR "cardiovascular outcomes" OR "chronic kidney disease") AND (pharmacokinetics OR safety OR "weight regain").

Inclusion and exclusion criteria

Studies were included if they were (a) pivotal randomized controlled trials, cardiovascular or renal outcome trials, human pharmacokinetic studies, trial extension or follow-up studies, or systematic reviews on semaglutide; (b) done in adult participants; and (c) available as full text in English. Studies were excluded if they were animal or in vitro studies only, case reports, conference abstracts, editorials or letters, papers not mainly about semaglutide, or duplicate publications.

Study selection and data handling

Reporting note: The study-selection counts are presented to improve transparency of the structured search; they should not be interpreted as evidence of a systematic review because no formal risk-of-bias assessment or meta-analysis was performed.

Titles and abstracts were screened first, followed by full-text assessment of potentially relevant articles. The initial PubMed search identified 4,172 records. After duplicate removal and title/abstract screening, relevant full texts were assessed and 11 pivotal studies were selected as the principal references for the narrative synthesis. From each selected study, the design, population, dose, main outcomes and safety findings were recorded. Because this is a narrative review, no formal risk-of-bias assessment, quality scoring or statistical pooling was performed.

Evidence was organized around GLP-1 receptor pharmacology, pharmacokinetics, efficacy in T2DM, obesity, cardiovascular outcomes, kidney outcomes, safety and treatment withdrawal.

RESULTS AND DISCUSSION**Pharmacological characteristics and mechanism of action**

Endogenous GLP-1 is an incretin hormone released predominantly from intestinal L cells after nutrient ingestion. GLP-1 receptor activation enhances glucose-dependent insulin secretion and suppresses glucagon secretion; it also affects gastric motility and central pathways involved in

satiety. Native GLP-1 has a short circulating half-life because of rapid enzymatic degradation and clearance, limiting its direct therapeutic use. [1,2]

Semaglutide is engineered to preserve GLP-1 receptor activity while markedly extending systemic exposure. Its structural modifications increase albumin binding and reduce susceptibility to enzymatic degradation; more than 99% of circulating semaglutide is albumin-bound, contributing to its prolonged systemic persistence. [1,2] In pancreatic beta cells, receptor activation increases glucose-dependent insulin secretion, while in alpha cells glucagon secretion is reduced when plasma glucose is elevated. Because insulin stimulation is glucose dependent, clinically significant hypoglycemia is relatively uncommon with semaglutide monotherapy. Semaglutide also influences appetite and energy intake through central GLP-1 receptor pathways, and its gastrointestinal effects, including delayed gastric emptying, attenuate postprandial glucose excursions. [1-4]

Subcutaneous semaglutide provides sustained exposure and is administered once weekly. Oral semaglutide was developed using an absorption-enhancing co-formulation that enables uptake of the peptide across the gastrointestinal tract; once absorbed, it has a prolonged half-life of approximately one week and supports once-daily dosing. [2,3]

Table 1: Pharmacological characteristics of semaglutide

Characteristic	Description	Clinical relevance
Class	Long-acting GLP-1 receptor agonist	Sustained incretin pharmacology
Half-life	Approximately 1 week	Supports weekly subcutaneous dosing
Main metabolic actions	Increased glucose-dependent insulin; reduced glucagon	Improves glycemic control
Appetite effect	Reduced hunger and energy intake	Major contributor to weight loss
GI effect / Oral delivery	Delayed gastric emptying; absorption-enhanced tablet formulation	Postprandial glucose and satiety effects; alternative to injection

Pharmacokinetics

Semaglutide has a prolonged elimination half-life of approximately one week. Slow elimination, high albumin binding and resistance to enzymatic degradation produce sustained exposure that permits weekly subcutaneous dosing. Clinical pharmacology studies have shown broadly comparable exposure across studied Japanese and Caucasian populations and have reported that renal or hepatic impairment does not produce changes requiring routine dose adjustment in the populations studied. [1,4] Oral semaglutide uses an absorption enhancer to facilitate systemic delivery and exhibits an approximately one-week half-life, supporting once-daily dosing. [3] The

prolonged profile has practical consequences: adverse effects may persist beyond a missed dose compared with short-acting agents, while dose escalation is used to improve gastrointestinal tolerability.

Clinical efficacy in type 2 diabetes: SUSTAIN and PIONEER programmes

The SUSTAIN programme established once-weekly subcutaneous semaglutide as an effective glucose-lowering therapy in T2DM. Across the programme, semaglutide reduced glycated hemoglobin and body weight compared with placebo and several active comparators; the combination of glycemic improvement and weight reduction is clinically relevant because some traditional glucose-lowering therapies are associated with weight gain. [5] SUSTAIN-6 enrolled patients with T2DM at high cardiovascular risk: the primary composite outcome of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke occurred less frequently with semaglutide than with placebo (hazard ratio 0.74), alongside a lower rate of new or worsening nephropathy but a higher rate of diabetic retinopathy complications. [5]

The PIONEER programme demonstrated that oral semaglutide improves glycemic control and reduces body weight in T2DM. PIONEER 6 was a cardiovascular outcomes trial designed primarily to establish cardiovascular safety, and cardiovascular risk with oral semaglutide was not inferior to placebo. [6] These findings supported oral semaglutide as an alternative formulation without fundamentally altering the cardiovascular safety profile of the molecule. An important practical distinction is administration: oral semaglutide must be taken according to specific instructions to maximize absorption, whereas subcutaneous semaglutide avoids gastrointestinal absorption constraints.

Obesity and weight management: STEP programme

The STEP programme demonstrated the capacity of semaglutide 2.4 mg once weekly to produce substantial weight loss in adults with overweight or obesity. In STEP 1, 1,961 adults without diabetes were randomized to once-weekly semaglutide 2.4 mg or placebo in addition to lifestyle intervention for 68 weeks. Mean body weight changed by -14.9% with semaglutide compared with -2.4% with placebo, a treatment difference of approximately 12.4 percentage points. [7] The effect was accompanied by improvements in several cardiometabolic risk factors. The STEP evidence reinforces the importance of combining pharmacotherapy with lifestyle intervention as part of a broader chronic-disease management strategy.

Cardiovascular outcomes: SELECT

SELECT extended the cardiovascular evidence to patients with established cardiovascular disease and overweight or obesity without diabetes. Among 17,604 participants, a primary

cardiovascular event occurred in 6.5% of the semaglutide group and 8.0% of the placebo group, corresponding to a hazard ratio of 0.80. [8] The result demonstrates a clinically meaningful reduction in cardiovascular events in a secondary-prevention population without diabetes.

Renal outcomes: FLOW

FLOW addressed whether semaglutide could reduce kidney disease progression in patients with T2DM and chronic kidney disease. The trial randomized 3,533 participants to weekly semaglutide 1.0 mg or placebo. The primary outcome occurred in 331 participants receiving semaglutide and 410 receiving placebo, corresponding to a hazard ratio of 0.76 (95% CI 0.66–0.88; $P=0.0003$) and a 24% relative risk reduction. [9] Semaglutide also reduced cardiovascular death, major cardiovascular events and death from any cause and was associated with a less steep annual decline in estimated glomerular filtration rate. Table 2 summarizes the selected pivotal clinical evidence.

Table 2: Selected pivotal clinical evidence for semaglutide

Study	Population	Intervention	Key result
SUSTAIN-6	T2DM, high CV risk	SC semaglutide 0.5/1.0 mg weekly	MACE HR 0.74; retinopathy complications increased
PIONEER 6	T2DM, high CV risk	Oral semaglutide	Cardiovascular risk noninferior to placebo
STEP 1	Overweight/obesity without diabetes	SC semaglutide 2.4 mg weekly	Mean weight change -14.9% vs -2.4% placebo at week 68
SELECT	Established CVD + overweight/obesity without diabetes	SC semaglutide 2.4 mg weekly	MACE 6.5% vs 8.0%; HR 0.80
FLOW	T2DM + CKD	SC semaglutide 1.0 mg weekly	Primary kidney outcome HR 0.76

DISCUSSION

Safety and tolerability

Gastrointestinal adverse effects are the most common tolerability limitation of semaglutide. Nausea, vomiting, diarrhea and constipation are particularly common during dose escalation, and gradual titration is central to clinical use. In SELECT, adverse events leading to permanent discontinuation occurred more frequently with semaglutide than placebo, illustrating that efficacy must be balanced against tolerability. [8] Hypoglycemia is generally uncommon with semaglutide alone because insulin secretion is glucose dependent; the risk increases when it is combined with insulin or insulin secretagogues, in which case adjustment of concomitant therapy may be required. [1,6]

Diabetic retinopathy complications require attention in susceptible patients. SUSTAIN-6 reported more retinopathy complications with semaglutide, an observation discussed in relation

to the magnitude and speed of glycemic improvement. [5] Patients with established diabetic retinopathy therefore require appropriate clinical assessment and monitoring. Other safety considerations include gallbladder-related adverse events and severe or persistent gastrointestinal symptoms that warrant clinical evaluation. Safety counseling should emphasize that semaglutide is a prescription pharmacotherapy for defined indications and should not be used as an unsupervised cosmetic weight-loss product.

Treatment discontinuation and weight regain

A major issue in obesity pharmacotherapy is the durability of benefit after treatment withdrawal. In the STEP 1 extension, participants who discontinued semaglutide after the 68-week treatment period regained a substantial proportion of the weight they had lost during the following year. [10] This observation has an important pharmacological interpretation: semaglutide suppresses biological drivers of appetite and energy intake while it is present, and discontinuation removes those effects. Weight regain therefore does not necessarily indicate treatment failure but supports the concept that obesity is a chronic disease for which long-term pharmacotherapy may be required in patients who respond and tolerate treatment.

Critical appraisal of the evidence

Semaglutide has an unusually broad evidence base that includes randomized efficacy studies, cardiovascular outcomes trials and a dedicated renal outcomes trial, and the consistency of clinically meaningful effects across glycemia, weight, cardiovascular events and kidney outcomes strengthens the overall pharmacological case. However, several limitations remain. Pivotal trials use selected eligibility criteria and may not fully represent routine clinical populations with multimorbidity, variable adherence and unequal access to specialist care. Relative risk reductions can appear larger than absolute benefits when baseline event rates are low; treatment decisions should therefore consider individual baseline risk. Many pivotal trials were sponsored by the manufacturer; sponsorship does not invalidate randomized evidence, but independent replication and transparent appraisal remain important. Finally, cross-trial comparisons should be avoided, and direct head-to-head trials are needed to determine the comparative effectiveness of semaglutide and newer incretin-based therapies.

Emerging applications and future directions

Semaglutide has accelerated the development of incretin pharmacology as a broader cardiometabolic strategy. Research is now moving beyond glycemic control and weight loss toward cardiovascular, renal and other metabolic outcomes. A 2025 randomized trial of oral semaglutide 25 mg in adults with overweight or obesity [11] evaluated an intermediate oral dose

as an alternative to injectable treatment, illustrating the continuing evolution of semaglutide delivery and dosing. Future research should address long-term durability, body composition and physical function, treatment strategies after weight stabilization, outcomes after dose reduction or interruption, and comparative effectiveness against other incretin-based therapies. Additional evidence is also needed in populations that remain underrepresented in major trials.

CONCLUSION

Semaglutide is a long-acting GLP-1 receptor agonist that has become an important therapy for T2DM and obesity and has acquired a broader role in cardiovascular and renal risk reduction. Its pharmacology combines glucose-dependent insulin secretion, glucagon suppression, appetite reduction and gastrointestinal actions, producing clinically meaningful improvements in glycemia and body weight. SUSTAIN and PIONEER established its glucose-lowering efficacy; STEP demonstrated substantial weight reduction; SELECT demonstrated cardiovascular benefit in a high-risk obesity population without diabetes; and FLOW demonstrated kidney and cardiovascular benefits in T2DM with chronic kidney disease. [5-9] The main limitations are gastrointestinal tolerability, the need for gradual dose escalation, retinopathy considerations in susceptible patients and substantial weight regain after discontinuation. Overall, semaglutide represents a major advance in modern incretin pharmacotherapy, but its optimal use requires individualized risk assessment, long-term follow-up and continued evaluation of durability, comparative effectiveness and real-world outcomes.

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Conflict of Interest

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Declaration of generative AI use in manuscript preparation

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REFERENCES

1. Anderson SL, Trujillo JM. Advances in pharmacologic treatment of type 2 diabetes

- mellitus: semaglutide and other GLP-1 receptor agonists. *Clin Pharmacokinet* 2018; 57: 1529-1538.
2. Lau J, Bloch P, Schaffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem* 2015; 58: 7370-7380.
 3. Granhall C, Sondergaard FL, Thomsen M, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. *Clin Pharmacokinet* 2019; 58: 781-791.
 4. Marbury TC, Flint A, Jacobsen JB, Derving Karsbol J, Lasseter K. Pharmacokinetics and tolerability of a once-weekly subcutaneous dose of semaglutide in subjects with and without renal impairment. *Clin Pharmacokinet* 2017; 56: 1381-1390.
 5. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; 375: 1834-1844.
 6. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019; 381: 841-851.
 7. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021; 384: 989-1002.
 8. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023; 389: 2221-2232.
 9. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med* 2024; 391: 109-121.
 10. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab* 2022; 24: 1553-1564.
 11. Wharton S, Lingvay I, Bogdanski P, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. *N Engl J Med* 2025; 393:1077-1087. doi:10.1056/NEJMoa2500969.

