




Brief Reviews

Current Insights, Advantages and Challenges of Small Molecule Glucagon-like Peptide 1 Receptor Agonists: A Scoping Review

Eder Luna Ceron¹, Sparsha Duvuru Reddy¹, Lakshmi Kattamuri¹, Durga Mounika Muvva¹, Luis Chozet², Tamis Bright² 

¹ Department of Internal Medicine, Texas Tech University Health Sciences Center,

² Division of Endocrinology, Texas Tech University Health Sciences Center

Journal of Brown Hospital Medicine

Vol. 4, Issue 2, 2025

Article Information

Keywords: GLP-1 receptor agonists,

Obesity, Diabetes, Danuglipron,

Orforglipron, Aleniglipron

<https://doi.org/10.56305/001c.132255>

Submitted: December 28, 2024

EDT

Accepted: March 11, 2025

EDT

Published: April 01, 2025 EDT

Abstract

Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition with significant morbidity and mortality, largely due to its vascular complications. The emergence of novel pharmacological agents, particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs), has revolutionized T2DM management by addressing glycemic control and comorbidities such as cardiovascular and renal diseases. Traditionally, GLP-1RAs require subcutaneous injection, presenting challenges in patient adherence and limiting combination therapy options. Recent advancements have introduced orally available small-molecule GLP-1RAs, which retain the physiological benefits of peptide-based GLP-1RAs, such as promoting insulin secretion, reducing appetite, and improving weight loss. These small molecules offer enhanced tissue permeability, extended half-lives, and the potential for fixed-dose combinations, addressing limitations of injectable formulations. This review explores the preclinical and clinical progress of small-molecule GLP-1RAs, highlighting their potential to redefine diabetes care by improving convenience, adherence, and accessibility for patients.

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a chronic condition that affects millions of patients worldwide, posing significant challenges to both patients and healthcare systems.¹ T2DM remains as one of the leading causes of disability and death worldwide mainly due to its long-term vascular complications.¹ The management of T2DM is becoming increasingly complex with the availability of more pharmacologic drug classes and the completion of high-quality clinical trials.² The development of and approval of new antihyperglycemic medications has favored the use of different pharmacological families with remarkable properties for the management of additional comorbidities such as renal disease, cardiovascular disease, and non-alcoholic fatty liver disease, that are highly prevalent in this subset.² Treatment for type 2 diabetes is initiated based on (glycated hemoglobin) HbA1C levels, treatment goals, and cardiovascular, renal, as well as hypoglycemia risk. First-line therapies, including metformin, sodium-glucose cotransporter-2 inhibitors (SGLT-2i), and Glucagon-like peptide-1 (GLP-1) receptor agonists, are selected according to patient-specific risk factors.^{3,4} American Association of Clinical Endocrinology guidelines recommend treatment with GLP-1RA in T2DM patients with coexisting ASCVD, high-risk for ASCVD, heart failure, or chronic kidney disease regardless of their glycemic control due to their organ protective effects.⁵

These guidelines align with the American Diabetes Association (ADA) standards of care which also provide strong recommendations based on robust clinical trial data supporting the cardiovascular benefits of GLP-1RAs, particularly in patients with established cardiovascular disease and chronic kidney disease (CKD).⁴ For example, ADA and KDIGO joint group has recommended that for patients with T2DM and CKD who do not achieve their glycemic target with metformin and/or an SGLT2i or cannot use them, a GLP-1RAs with proven cardiovascular benefit is recommended.⁶ Similarly, as GLP-1RAs significantly reduced the risk of MACE, mortality from CV causes, when compared with placebo, ADA has suggested that these medications should be used in patients with underlying cardiovascular disease.⁴ ⁷ In this regard, this addition ensures a more comprehensive discussion aligned with current expert consensus on risk mitigation strategies.^{4,6}

A key issue in the physiology of type 2 diabetes (T2DM) is the reduced incretin effect, which mainly results from decreased activity of the primary incretin hormones, GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic peptide).⁸ GLP-1 is produced by L cells in the lower part of the small intestine and the colon.⁸ When GLP-1 receptors are activated, they promote insulin release and decrease glucagon secretion in response to glucose levels.^{3,8} Additional effects of

GLP-1 include slowing gastric emptying, reducing appetite, and aiding in weight loss.³

The development of GLP-1 receptor agonists has shown promising results in improving metabolic markers.⁹ Notably, these agents have also led to a significant decrease in major cardiac events, regardless of their effect on blood glucose, indicating a dual benefit for both cardiac health and diabetes management.¹⁰ Recently, several clinical trials have shown the potential effects of these medications in not only in glycemic control but also in the improvement of cardiovascular outcomes, weight loss, osteoarthritis,¹¹ metabolic dysfunction-associated steatohepatitis (MASH),¹² Parkinson's disease,¹³ chronic kidney disease (CKD)¹⁴ and obstructive sleep apnea.¹⁵ Of important interest was their effects in weight loss even in non-diabetic patients.¹⁶

Particularly the effects of these medications have covered importance in diseases closely related to obesity and DM such as CKD, cardiovascular disease and MASH. For example, the LEADER trial showed that Liraglutide significantly reduced the risk of major adverse cardiovascular events (MACE) by 13% and cardiovascular death by 22% in comparison to placebo.¹⁷ Moreover, other trials as the SUSTAIN-6 trial showed that semaglutide, another GLP-1RA also reduced the risk of MACE by 26% and non-fatal stroke by 39% in patients with T2DM.¹⁸ In the same line, the SELECT trial showed that semaglutide administered once weekly reduced the risk of MACE by 20% compared to placebo in individuals with established cardiovascular disease but no DM.¹⁶ Nonetheless, other GLP-1 RAs such as albiglutide has also shown reductions on MACE risk up to 22% as demonstrated by the HARMONY trial.¹⁹ In regard to CKD, these clinical trials have also shown positive effects in the composite renal outcomes. For example, the LEADER trial showed positive renal effects with the use of liraglutide primarily by the reduction of macroalbuminuria.¹⁷ In addition to these findings, the SUSTAIN-6 trial also showed that semaglutide can offer a significant reduction in the risk of new or worsening nephropathy including persistent macroalbuminuria, increase in serum creatinine or the need of renal replacement therapy.¹⁸ Similarly, the FLOW trial proven that semaglutide showed a 24% reduction in the risk of major kidney disease events in patient with underlying T2DM and CKD.¹⁴ Finally, multiple clinical trials have demonstrated the benefits of using GLP-1RAs in MASH. For example, a phase 2 trial showed that tirzepatide, a dual Gastric Inhibitory Polypeptide (GIP) and GLP-1 RA, significantly improved MASH.²⁰ After 52 weeks, steatohepatitis resolved without fibrosis progression in 44%, 56%, and 62% of participants receiving tirzepatide at doses of 5 mg, 10 mg, and 15 mg, respectively, compared to 10% in the placebo group.²⁰ Similarly, A phase 2 trial of 320 patients with biopsy-confirmed MASH found that daily subcutaneous

semaglutide (0.4 mg) achieved steatohepatitis resolution without fibrosis progression in 59% of patients vs. 17% with placebo, though fibrosis stage did not significantly improve.²¹ Given this critical findings, The ADA advises using GLP-1 RAs to treat type 2 diabetes in adults with MASH, citing histological benefits demonstrated in the mentioned phase 2 randomized controlled trials.²²

With the exception of oral semaglutide, available GLP-1 receptor agonists (RA) require subcutaneous injection due to their peptide-based structure.³ While effective, this method can be inconvenient for many patients and may result in lower adherence compared to oral medications.²³ This need for injection can limit patient use and may also restrict the possibility of combining these drugs in fixed-dose treatments with other therapies for cardio-metabolic conditions.^{15,23} This issue has been addressed by the synthesis of small molecule GLP-1RA that have smaller molecular sizes and can be administered orally offering a more convenient and acceptable option to patients.²⁴ Small molecules may offer advantages such as improved tissue permeability, longer half-lives, and lower production costs.²⁴ In this review, we discuss the benefits and challenges associated with the small-molecule GLP-1 RA drugs from pre-clinical and clinical studies.

METHODOLOGY

We conducted a search for English-language original studies and meta-analyses published between 2010 and 2024 using PubMed, Medscape, and MEDLINE. The search included terms such as “small molecule GLP-1 receptor agonists,” “oral GLP-1 receptor agonists,” “Danuglipron,” “Orforglipron,” and “Aleniglipron.” Additionally, information on ongoing clinical trials involving small molecule GLP-1 receptor agonists was retrieved from the [ClinicalTrials.gov](https://clinicaltrials.gov) database using the same keywords. This scoping review was carried out in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews) guidelines.

GLP-1 AND ITS MECHANISMS OF REGULATION AND SYNTHESIS

GLP-1 is a peptide hormone produced by the enzymatic breakdown of proglucagon.²⁴ This hormone is mainly synthesized in L-cells of the intestinal lining. However, further studies have revealed that α -cells in the pancreatic islets, and neurons in the nucleus of the solitary tract are also able to produce GLP-1.²⁵ As an endocrine hormone, GLP-1 is secreted by enteroendocrine L-cells in the distal jejunum, ileum, and colon in response to food intake and neuroendocrine signals.²⁶ Originating from the proglucagon precursor, it is processed in intestinal L-cells

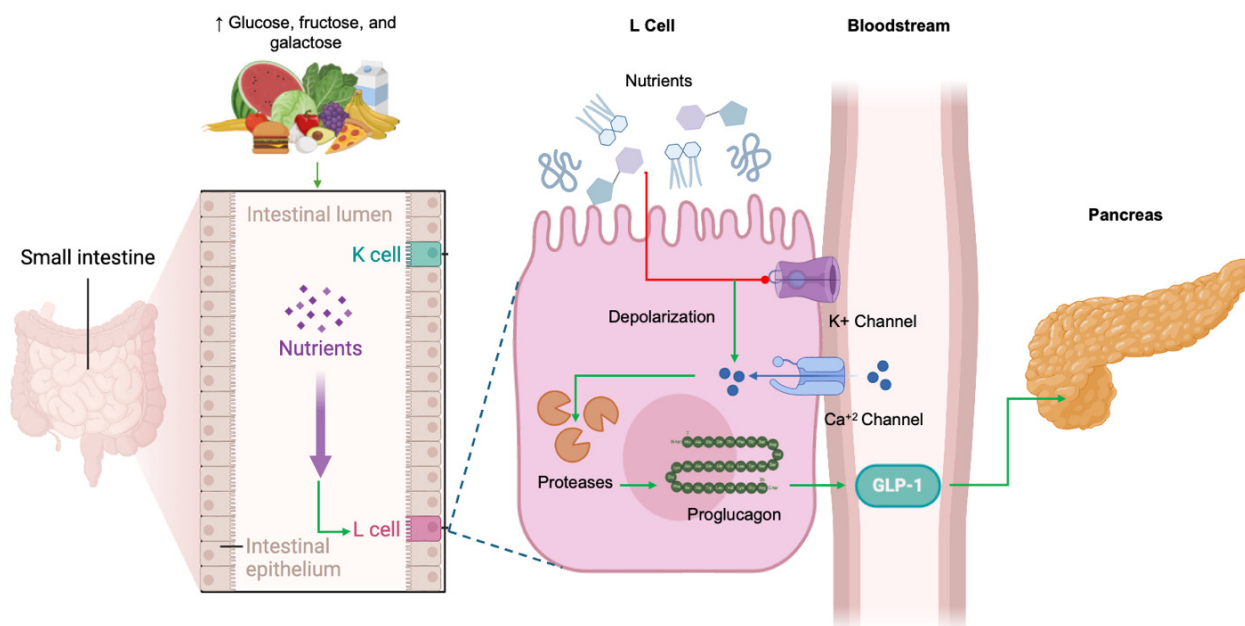


Figure 1. Mechanism of synthesis of GLP-1.

Abbreviations: K⁺: Potassium, Ca²⁺: Calcium, GLP-1: Glucagon-like peptide-1. Green arrows indicate activation, while red arrows indicate inhibition.

to form GLP-1.²⁴ In this regard, prohormone convertase enzymes cleave proglucagon into several small peptides including glicentin, glicentin-related pancreatic polypeptide, glucagon, oxyntomodulin and GLP-1.²⁷

It is well known that enteroendocrine cells produce low basal levels of GLP-1 during pre-prandial state, however after food ingestion the synthesis and secretion of GLP-1 sharply raises with a peak 30–60 min following nutrient intake.^{24,25,28} The L-cell's apical surface faces the gut lumen, allowing direct contact with nutrients. Molecules like glucose, fructose, and galactose stimulate the synthesis of GLP-1 by closing ATP-sensitive K⁺ channels. This closure causes membrane depolarization, which opens voltage-dependent calcium channels. The influx of calcium then activates proteases that cleave proglucagon peptides, ultimately boosting GLP-1 production.²⁷ Importantly, GLP-1 action is short-lived, with a half-life of just 1–2 minutes in the bloodstream under normal physiological conditions, after which it is broken down by the enzyme dipeptidyl peptidase IV (DPP-4), resulting in a loss of its biological activity.^{24,25} The mechanisms of regulation and synthesis for GLP-1 secretion are summarized in [Figure 1](#).

GLP-1R ACTIVATION AND MULTIFUNCTIONAL EFFECTS

GLP-1 has its main effects through the activation of GLP-1R which belongs to the family of G-protein coupled receptors.^{24,29} Through this receptor, GLP-1 leads to an increase of cAMP levels that thereafter activates

protein kinase A (PKA).³⁰ PKA then promotes the synthesis of insulin peptide precursor in beta-pancreatic cells and inhibits the release of glucagon by alpha pancreatic cells.³¹ Moreover, it has been demonstrated that GLP-1 promotes the activation of phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) pathway that favor the survival and function of beta-pancreatic cells.³²

GLP-1 has critical effects on alternative pathways that favor the insulin signal transduction in peripheral tissues.³³ GLP-1 also reduces hepatic production of glucose by reducing the expression of key metabolic regulators of glycogenolysis. Moreover, GLP-1R cascade also has interactions to regulatory proteins involved in the insulin receptor cascades such as the insulin receptor substrates (IRS) and the PI3K involved in the positive regulation for survival, metabolism and proliferation of beta pancreatic cells as well as apical glucose transport in peripheral tissues.³⁴ These effects are achieved by the expression and translocation of apical glucose transporter type 4 (GLUT4) thus increasing glucose uptake and by the inhibition of pro-apoptotic proteins such as Bad, Bax and FOXO family proteins, thereby improving beta cell survival.³² As previously explained, the mediator Akt is also demonstrated to activate mTOR, allowing beta cell growth through cell cycle progression and by enhancing protein synthesis.²⁴ The main cascades involved in the signal transduction of GLP-1R are summarized in [Figure 2](#).

GLP-1 exhibits several pleiotropic effects beyond their primary role in glycemic control. For example, studies involving GLP-1 RAs have been shown to reduce major

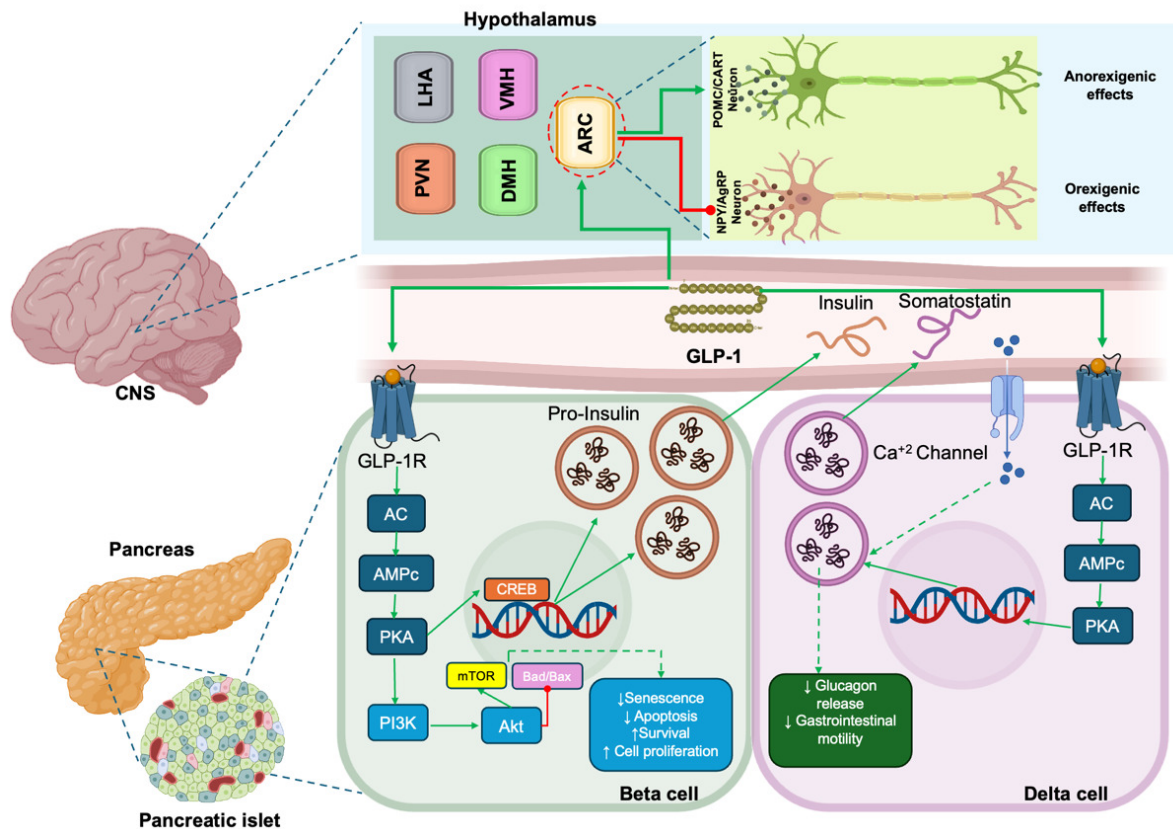


Figure 2. Principal mechanisms lead by GLP-1R activation.

Abbreviations: Ca²⁺: Calcium, GLP-1: Glucagon-like peptide-1, GLP-1R: Glucagon-like peptide-1 receptor, AC: Adenylate cyclase, AMPc: Cyclic adenosine monophosphate, PKA: protein kinase A, PI3K: Phosphoinositide 3-kinases, mTOR: mammalian target of rapamycin, AKT: Protein kinase B, Bad: BCL2 associated agonist of cell death, Bax: Bcl-2 Associated X-protein, CNS: Central nervous system, PVN: Periventricular nucleus, LHA: Lateral hypothalamus, DMH: Dorsomedial hypothalamic nucleus, VMH: Ventromedial hypothalamic nucleus, ARC: Arcuate hypothalamic nucleus, NPY: Neuropeptide Y, AgRP: Agouti-related peptide, POMC: Proopiomelanocortin, CART: Amphetamine-regulated transcript. Up arrows indicate up-regulation. Down arrows indicate downregulation. Green arrows indicate activation, while red arrows indicate inhibition. Green arrows indicate activation while red arrows indicate inhibition.

adverse cardiovascular events in patients with T2DM.³⁵ They have been shown to help lower blood pressure, reduce postprandial lipemia, and decrease inflammation.³⁶ Moreover, GLP-1 RAs improve lipid profiles by decreasing serum cholesterol and triglyceride levels and increasing high-density lipoprotein (HDL) levels contributing to cardiovascular protection.³⁷ Additionally, these agents reduce the levels of proinflammatory adipokines and the expression of inflammatory genes, which can improve overall metabolic health.^{24,37} GLP-1 RAs have been associated with improved renal outcomes, including enhanced natriuresis and reduced albuminuria, which are beneficial in diabetic kidney disease.³⁸ GLP-1RAs increase microvascular blood flow in muscle tissue, enhance myocyte metabolism, inhibit muscle atrophy, and improve muscle mass and function.³⁹ The study of these clinical properties in small molecule GLP-1RAs is an undergoing area of study.

In regard to the effects of GLP-1 in weight loss, extensive evidence demonstrates that GLP-1R agonism reduces food intake, thus promoting weight loss.⁴⁰ Pre-clinical studies have shown that these effects are mainly mediated through the effects of GLP-1R activation in the

central nervous system (CNS) by the modulation of orexigenic and anorexigenic signaling pathways.⁴¹⁻⁴⁴ It has been shown that GLP-1R is highly expressed in neurons of the arcuate (ARC) and paraventricular (PV) nuclei of the hypothalamus where these pathways are involved.⁴² The ARC contains two distinct neuron types with opposing functions. Orexigenic neurons, which stimulate appetite, produce neuropeptide Y (NPY) and agouti-related peptide (AgRP).^{45,46} In contrast, anorexigenic neurons suppress appetite by expressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) peptide.^{45,46} As shown in [Figure 2](#), GLP-1RAs penetrate the blood-brain barrier and directly activate GLP-1 receptors in the hypothalamus, especially within the ARC nucleus, a key center for appetite regulation.⁴¹⁻⁴⁴ This activation enhances the activity of POMC neurons, which induce satiety, while suppressing NPY neurons that drive hunger.⁴¹⁻⁴⁴ Moreover, it has been shown that GLP-1RAs also promote satiety through the activation of the nucleus accumbens by increasing glutamatergic signaling, thus suppressing feeding behavior.⁴⁷

DANUGLIPRON

Danuglipron, is a small molecule GLP-1 receptor agonist (GLP-1RA) recently discovered.³ Pre-clinical studies revealed increased insulin levels in primates.⁴⁸ Initial evaluation in healthy humans revealed that oral administration of Danuglipron produced a dose-dependent increase in systemic exposure bioavailability.⁴⁸ Similar results were obtained in a hGLP-1R knock-in murine model in which the administration of Danuglipron resulted in an overall improvement of glucose tolerance and food intake reduction, thus opening the possibility to use an effective oral GLP-1RA.⁴⁹

Further evaluation on a double-blind, randomized phase 1 clinical trial in 98 patients with T2DM on current management with metformin revealed that Danuglipron was generally well tolerated and associated with minimal side effects such as nausea, dyspepsia, and vomiting comparable with the ones observed with the use of injectable GLP-1RA.⁴⁹ In another phase 1 study conducted in 37 Japanese patients, the most common treatment-related side effects were nausea, vomiting, abdominal discomfort, diarrhea, and headache, mostly mild to moderate in severity.⁵⁰ Danuglipron showed a dose-proportional increase in exposure at steady state with reductions in the mean daily glucose, fasting plasma glucose, and glycated hemoglobin (HbA1c) compared to baseline and placebo.⁵⁰

Later, this medication underwent a Phase 2b clinical trial that evaluated Danuglipron in 411 adults with T2DM. The randomized, double-blind, placebo-controlled study tested various doses of Danuglipron against a placebo over 16 weeks. Participants on the highest dose (120 mg twice daily) experienced an average HbA1c reduction of 1.16 percentage points and a weight loss of 4.17 kilograms.³ All doses effectively reduced HbA1c and fasting blood glucose, with the 80 mg and 120 mg doses showing the greatest weight loss compared to placebo. The most common side effects were nausea, diarrhea, and vomiting.³ More recently, a meta-analysis integrating the available trials observed that even doses as low as 80mg twice daily were able to produce significant weight loss as well as reductions in HbA1c. However, doses of 120mg twice daily were shown to be more associated with the production of reduced appetite, dyspepsia and dizziness.⁵¹ This evidence suggest that Danuglipron demonstrates potential for glycemic control and weight reduction in T2DM with an acceptable safety profile.

Ongoing clinical trials are currently investigating a single-dose regimen of Danuglipron for managing overweight and obesity (NCT04616339). As research progresses, the initiation of a phase 3 clinical trial to further evaluate its efficacy and safety remains on the horizon, signaling the next step in its development. The most im-

portant results from the clinical studies involving danuglipron are shown in [Table 1](#).

ORFORGLIPRON

Orforglipron, another oral GLP-1RA has being studied extensively for the management of T2DM and Obesity. In initial preclinical studies, orforglipron has been shown to stimulate insulin secretion and reduce food consumption in non-human primates, and it is fully efficacious at lowering hyperglycemia in mice expressing the human GLP-1R but inactive in GLP-1R knockout animals.⁵² These results, in part, supported the development of orforglipron as an orally delivered GLP-1RA in clinical testing. A Phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study was done to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of orforglipron.⁵² Orforglipron showed to have a pharmacodynamic and safety profile similar to that of injectable GLP-1 which supported continued clinical development.⁵² In a phase 1b trial done to evaluate the safety, pharmacokinetics and pharmacodynamics of orforglipron in patients with T2DM, orforglipron resulted in significant reductions in HbA1c, fasting blood glucose and body weight, with an adverse event profile consistent with that of other GLP-1RA.⁵³ In both Phase 1a and 1b trials, it has been established that orforglipron does not have food or water administration restrictions and may provide a safe and effective oral treatment option for patients with T2D and other indications.^{52,53} In a phase 2, multi-center trial conducted at 45 centers, orforglipron at doses of 12 mg or greater showed significant reductions in HbA1c and bodyweight compared with placebo or dulaglutide.⁵⁴ This trial emphasized that orforglipron might provide an alternative to injectable GLP-1 receptor agonists and oral semaglutide, with the prospect of less burdensome administration to achieve treatment goals in diabetics.⁵⁴ In another phase 2 trial done to evaluate the efficacy of orforglipron in adults with obesity without diabetes, it was found to lead to significant weight reduction compared to placebo.⁵⁵ A systematic review and meta-analysis of 7 RCT's was done to see the efficacy and safety of orforglipron and danuglipron in the treatment of T2DM and obesity. They were found to have significant HbA1c, and weight reduction compared to placebo in patients with diabetes and obesity respectively.⁵⁶ The most common adverse events were gastrointestinal in the preclinical, phase1 and 2 trials similar to trials involving injectable GLP-1 agonists.⁵⁶ These trials demonstrate that although orforglipron is safe and efficacious more longitudinal research is warranted to provide deeper insights into their efficacy, safety and tolerability before their potential incorporation in the pharmacological arse-

Table 1. Current clinical trials favoring Danuglipron for the management of obesity and diabetes

Reference	Type of Study	Population study	Intervention	Main findings
Ono, et al. ⁵⁰	Phase 1 double-blind RCT	37 healthy Japanese individuals	Twice-daily oral doses of placebo or multiple ascending doses of danuglipron titrated to 40, 80 or 120 mg twice daily over 8 weeks	Reduction of HbA1c up to -1.41% (90% CI: -2.01% to -0.82%). Reduction of body weight p to -1.87 kg (90% CI: -3.58 to -0.17). Nausea, vomiting, abdominal discomfort, diarrhea as mild moderate side effects.
Saxena, et al. ⁴⁹	Phase 1 double-blind RCT	98 patients with T2DM on background metformin management	Twice-daily oral doses of placebo or multiple ascending doses of danuglipron titrated from 10 to 200mg for 28 days.	Significant reductions in HbA1c observed with higher doses of Danuglipron compared to placebo. Moderate but significant reductions in body weight with Danuglipron treatment. Light increase in heart rate observed, consistent with GLP-1 receptor agonism, but no clinically meaningful heart rate-related events. Steady state found after 28 days of therapy. Effects align with known actions of GLP-1 receptor agonism (e.g., glycemic lowering, weight loss).
Saxena, et al. ³	Phase 2b double-blind RCT	411 adult patients with T2DM	Twice daily doses of placebo or multiple ascending doses of Danuglipron titrated from 2.5, 10, 40, 80, or 120 mg, all orally administered with food for 16 weeks.	Reduction of HbA1c up to -1.16% (90% CI: -1.47% to -0.86%) for 120 mg twice daily vs placebo at week 16. Body weight reduction with 80 mg twice daily: -2.04 kg (90% CI: -3.01 to -1.07 kg) as well as -4.17 kg (90% CI: -5.15 to -3.18 kg) with 120mg twice daily in comparison with placebo. Excellent safety profile with mild-moderate symptoms as nausea, diarrhea, vomiting.
Fatima, et al. ⁵¹	Systematic review and meta-analysis	Four RCTs published from 2021 to 2023 were included.	Twice daily doses of placebo or multiple ascending doses of danuglipron 80 or 120 mg.	Doses of 120mg twice daily showed decreased appetite: RR = 3.46 (90% CI: 1.57 to 7.62, p = 0.01); HbA1c reduction: SMD = -1.09 (90% CI: -1.39 to -0.8, p < 0.00001); Body weight reduction: SMD = -1.08 (90% CI: -1.42 to -0.74, p < 0.00001).

RCT: Randomized clinical trial; HbA1c: Glycated hemoglobin; T2DM: Type 2 diabetes mellitus. RR: Relative risk; CI: Confidence interval, SMD: Standardized Mean Difference, HR: Heart rate, BW: body weight, HOV: Healthy Obesity Volunteer, GI: Gastrointestinal.

nal against T2DM or obesity. The most important results of these trials are summarized in [Table 2](#).

ALENIGLIPRON (GSBR-1290)

Aleniglipron (GSBR-1290) is a novel oral, non-peptide GLP-1RA used in the treatment of T2DM and obesity. It has a high affinity to GLP-1R, strongly activating the GLP-1R *G_s* cAMP pathway without inducing measurable β -arrestin recruitment signaling, which indicates it is a fully biased agonist. In studies involving nonhuman primates, GSBR-1290 showed a dose-dependent increase in insulin secretion, improved glucose control, and a decrease in both food intake and body weight.⁵⁷ Phase 1b trial of GSBR-1290 (5–90 mg) in 24 healthy volunteers over 4 weeks demonstrated no study discontinuations due to AEs. Most AEs were mild and GI-related, consistent with GLP-1RAs.⁵⁸ BW was significantly reduced (up to 4.9% placebo-adjusted, p=0.013) over 4 weeks. Phase 2a trial of GSBR-1290 (45mg and 90mg) in 54 T2DM patients over 12 weeks observed significant reduction in HbA1c (45 mg: -1.01%, p=0.008; 90 mg: -1.02%, p=0.001), BW (45 mg: -3.51%, p=0.0019; 90 mg: -3.26%, p=0.0013), and plasma glucose (45 mg: -2.70, p=0.01; 90 mg: -2.50, p=0.0008).⁵⁸ Phase 2a trial of GSBR-1290 (120mg) in 40 healthy obese volunteers over 8 weeks demonstrated a significant reduction in BW (120 mg: -4.74%; p<0.0001) compared to placebo.⁵⁸ For all phase

2a, AEs were mild-moderate and GI-related, with no SAEs related to GSBR-1290. The most important results from the clinical studies involving GSBR-1290 and other small molecule GLP-1RA are shown in [Table 3](#).

LOTIGLIPRON

The development of lotiglipron for obesity and T2DM was prematurely stopped in early-phase clinical trials due to its association with elevated transaminases and potential liver toxicity.⁵⁹

SMALL MOLECULE GLP-1RA IN PRECLINICAL TRIALS

MLX-7005

MLX-7005 is a highly potent, oral small-molecule GLP-1 receptor agonist (GLP-1RA) that robustly activates the GLP-1 receptor cAMP signaling pathway without measurable β -arrestin recruitment.⁶⁰ In a functional human beta-cell line, it demonstrated a dose-dependent increase in insulin secretion. Preclinical studies in diet-induced obesity rodent models are ongoing to evaluate its efficacy, safety, and tolerability as a potential therapy for type 2 diabetes and obesity.⁶⁰

Table 2. Current clinical trials favoring Orforglipron for the management of obesity and diabetes

Reference	Type of Study	Population study	Intervention	Main findings
Pratt, et al. ⁵²	Phase 1a double-blind RCT (Involves Part A and Part B)	92 healthy participants aged 18 to 65 years with BMI of 20 to 40 kg/m ² and HbA1c <6.5%	In Part A, participants received single dose orforglipron, with four cohorts receiving escalating doses (0.3-6 mg). In Part B, participants received 4 weeks of daily repeated oral orforglipron with doses escalating weekly to four different final target doses (2-24 mg).	Pharmacokinetics were approximately dose proportional, and the mean $t_{1/2}$ was 24.6 to 35.3 hours after a single dose (0.3-6 mg). Substantial reductions in body weight of up to 5.4 kg were observed after 4 weeks in orforglipron-treated participants, compared to a reduction of 2.4 kg with placebo ($P < 0.05$). Orforglipron decreased fasting glucose levels across Days 1 to 28, and gastric emptying was delayed on Day 28. Orforglipron's long half-life (25-68 hours) allows once-daily oral dosing, without water and food restrictions.
Pratt, et al. ⁵³	Phase 1b double-blind RCT	68 participants with T2DM aged 18 to 70 years and HbA1c levels $\geq 7.0\%$ and $\leq 10.5\%$	Evaluated 5 different dosing regimens. Participants were randomized 3:1 to daily doses of orforglipron or placebo for 12 weeks.	Reduction of HbA1c up to (90% CI:) for 120 mg twice daily vs placebo at week 12. Body weight reduction with 80 mg twice daily: -2.04 kg (90% CI: -3.01 to -1.07 kg) as well as -4.17 kg (90% CI: -5.15 to -3.18 kg) with 120mg twice daily in comparison with placebo.
Frias, et al. ⁵⁴	Phase 2b double-blind RCT, multicenter study	383 adults with type 2 diabetes treated with diet and exercise, with or without metformin, and with HbA _{1c} of 7.0-10.5%, and BMI of 23 kg/m ²	Participants were randomly assigned via an interactive web-response system to placebo, dulaglutide 1.5 mg once per week, or orforglipron	At week 26, mean change in HbA _{1c} with orforglipron was up to -2.10% (-1.67% placebo adjusted), versus -0.43% with placebo and -1.10% with dulaglutide. Change in mean bodyweight at week 26 was up to -10.1 kg (95% CI -11.5 to -8.7; 7.9 kg placebo adjusted [-9.9 to -5.9]) with orforglipron versus -2.2 kg (-3.6 to -0.7) for placebo and -3.9 kg (-5.3 to -2.4) for dulaglutide.
Wharton, et al. ⁵⁵	Phase 2, double blinded, RCT	272 adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes	Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks	At week 26, the mean change from baseline in body weight ranged from -8.6% to -12.6% across the orforglipron dose cohorts and was -2.0% in the placebo group. At week 36, the mean change ranged from -9.4% to -14.7% with orforglipron and was -2.3% with placebo. A weight reduction of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo.
Karakasis, et al. ⁵⁶	Systematic review and Meta-analysis of RCT trials investigating the efficacy and safety of orforglipron and danuglipron for the treatment of type 2 diabetes mellitus (T2DM), obesity or both.	1037 patients among seven RCTs were analyzed	Literature search was performed through Medline (via PubMed), Cochrane Library and Scopus until August 16, 2023. Double-independent study selection, data extraction and quality assessment were performed. Evidence was pooled with random effects meta-analysis.	Reduction in HbA1c in patients with T2DM compared to controls of 1.03 % (95 % CI = [-1.29, -0.77]; $P < 0.001$). A significantly greater weight reduction was also noted both in patients with T2DM or obesity compared to controls (MD = -3.26 kg; 95 % CI = [-4.79, -1.72]; $P < 0.001$ and MD = -7.52 kg; 95 % CI = [-14.63, -0.41]; $P = 0.038$, respectively; P for subgroup differences = 0.25)

RCT: Randomized clinical trial; HbA1c: Glycated hemoglobin; T2DM: Type 2 diabetes mellitus. RR: Relative risk; CI: Confidence interval, SMD: Standardized Mean Difference

ID110521156

ID110521156 is a small oral molecule that directly binds to the GLP-1 receptor, as demonstrated in a surface plasmon resonance assay.⁶¹ It exhibited a dose-dependent increase in intracellular cAMP levels in CHO cells expressing the human GLP-1 receptor. Once-daily oral administration of ID110521156 in diabetic monkeys re-

sulted in reduced plasma glucose levels, increased insulin secretion, decreased food intake, and weight loss. The compound was well tolerated with no evidence of genotoxicity, indicating its potential as a therapeutic agent for type 2 diabetes and obesity in humans.⁶¹

Table 3. Current clinical trials favoring GSK-1290 and other small molecule GLP-1RA for the management of obesity and diabetes

Reference	Type of Study	Population study	Intervention	Main findings
Blai et al. ⁵⁸	Phase 1b/2a Study	Phase 1b: 24 HOV Phase 2a: 54 T2DM and 40 HOV	Phase 1b: GSK-1290 (5-90mg) and its effects on body weight (BW) were investigated in 24 HOV over 4 weeks. Phase 2a: GSK-1290 on safety, tolerability, HbA1c, glucose, and BW were investigated in 54 participants with T2DM (45 and 90mg) over 12 weeks and in an interim 8-week analysis of 40 HOV (120mg)	BW was significantly reduced (up to 4.9% placebo-adjusted, $p=0.013$) over 4 weeks. Most AE were mild to moderate; no discontinuation due to AEs. Phase 2a T2DM: Placebo-adjusted HbA1c (45 mg: -1.01%, $p=0.008$; 90 mg: -1.02%, $p=0.001$), BW (45 mg: -3.51%, $p=0.0019$; 90 mg: -3.26%, $p=0.0013$), and plasma glucose (45 mg: -2.70, $p=0.01$; 90 mg: -2.50, $p=0.0008$) were significantly reduced at day 84 Phase 2a obesity: Placebo-adjusted BW decreased through day 56 (120 mg: -4.74%; $p<0.0001$). Well tolerated, AEs were mild-moderate and GI-related, with no SAEs
Amin et al. ⁵⁹	Phase 2 RCT	901 participants (T2DM cohort: $n=512$, obesity cohort: $n=389$)	T2DM cohort: Lotiglipron QD at one of five maintenance doses (20, 40, 80, 160 or 260 mg) or matching placebo, or semaglutide daily at one maintenance dose (14 mg) Obesity cohort: Lotiglipron QD at one of four maintenance doses, with two dose titration regimens for the 200-mg dose (80 mg, 140 mg, 200 mg five-step titration, 200 mg four-step titration and 260 mg) or matching placebo.	T2DM cohort: Reductions in HbA1c were observed across all lotiglipron doses at week 16 ($p<0.0001$), with least mean decrease up to -1.44% (90% confidence interval [CI]: -1.63, -1.26) (lotiglipron 80 mg), versus placebo, -0.07% (90% CI: -0.25, 0.11) Obesity cohort: Decreases in body weight were observed across all lotiglipron doses at week 20 ($p<0.01$), up to -7.47% (90% CI: -8.50, -6.43) (lotiglipron 200 mg, five-step titration), versus placebo, -1.84% (90% CI: -2.85, -0.83) Transaminase elevations were observed in a TDM (6.6%) and obesity cohorts (6%). Clinical development terminated due to concerns for hepatotoxicity

RCT: Randomized clinical trial; HbA1c: Glycated hemoglobin; T2DM: Type 2 diabetes mellitus. RR: Relative risk; CI: Confidence interval, SMD: Standardized Mean Difference, HR: Heart rate, BW: body weight, HOV: Healthy Obesity Volunteer, GI: Gastrointestinal.

ECC5004

The preliminary results of the investigational agent ECC5004 phase 1 trial in non-human primates revealed a reduction in HbA1c levels, accompanied by weight loss and a decreased risk of adverse cardiovascular events, achieved through the mimicry of the hormone GLP-1.⁶²

RGT075

RGT075 is a small oral GLP-1RA identified through Computer-Accelerated Rational Design (CARD) with potent G-protein-coupled cAMP signaling.⁶³ It displayed reduced activity in receptor-mediated β -arrestin recruitment and subsequent internalization. In food-induced glucose-intolerant and prediabetic cynomolgus monkeys, oral administration of RGT-075 improved glucose tolerance and reduced food intake and fasting glucose levels.⁶³

Additional small molecules, including GS-4571, OWL833, and HD-7671, have demonstrated the ability to induce insulin secretion in animal models.⁶⁴⁻⁶⁶ These agents improved glucose tolerance, reduced food intake, and promoted weight loss. These preclinical findings support the further development and advancement of these small molecules as potential therapies for type 2 diabetes and obesity.

FUTURE DIRECTIONS

The development of oral GLP-1 receptor agonists represents a significant advancement in the management of

T2DM.⁹ The current advantages, research stage and areas of opportunity of small molecule GLP-1RAs is summarized in [Figure 3](#). Overall, the newer small molecule GLP-1 RAs such as danuglipron and orforglipron have shown significant reductions in HbA1c and body weight, comparable to existing GLP-1 RAs. Injectable GLP-1 RAs like liraglutide, semaglutide, and dulaglutide have been shown to significantly lower HbA1c and body weight in patients with T2DM. Semaglutide, for example, can reduce HbA1c by up to 1.8% and weight by up to 6.5 kg.^{67,68} Dulaglutide and liraglutide also provide notable reductions, with HbA1c decreases of 1.0% to 1.5% and weight loss of 2–4% of total body weight.⁶⁹ In comparison, newer oral small-molecule GLP-1 RAs, such as danuglipron and orforglipron, have demonstrated similar efficacy. Danuglipron reduced HbA1c by 1.04% to 1.57% and weight by 1.93 kg to 5.38 kg.^{49-51,56} Orforglipron achieved even greater reductions, lowering HbA1c by up to 2.1% and weight by up to 10.1 kg.⁵⁵ In regard to their safety profile, small molecule GLP-1 RAs have also shown similar side effects, being the gastrointestinal symptoms such as nausea, vomiting, and diarrhea the most commonly presented. As in the case of the injectable GLP-1RAs, these side effects were generally mild to moderate and occurred during dose escalation and were generally transient and mitigated by gradual dose escalation.^{49,55,56,67} However, most of the clinical studies conducted up to date have focused on evaluating the effects of small molecule oral GLP-1 RAs against placebo. Further studies should now focus on non-inferiority studies comparing these new oral molecules against cur-

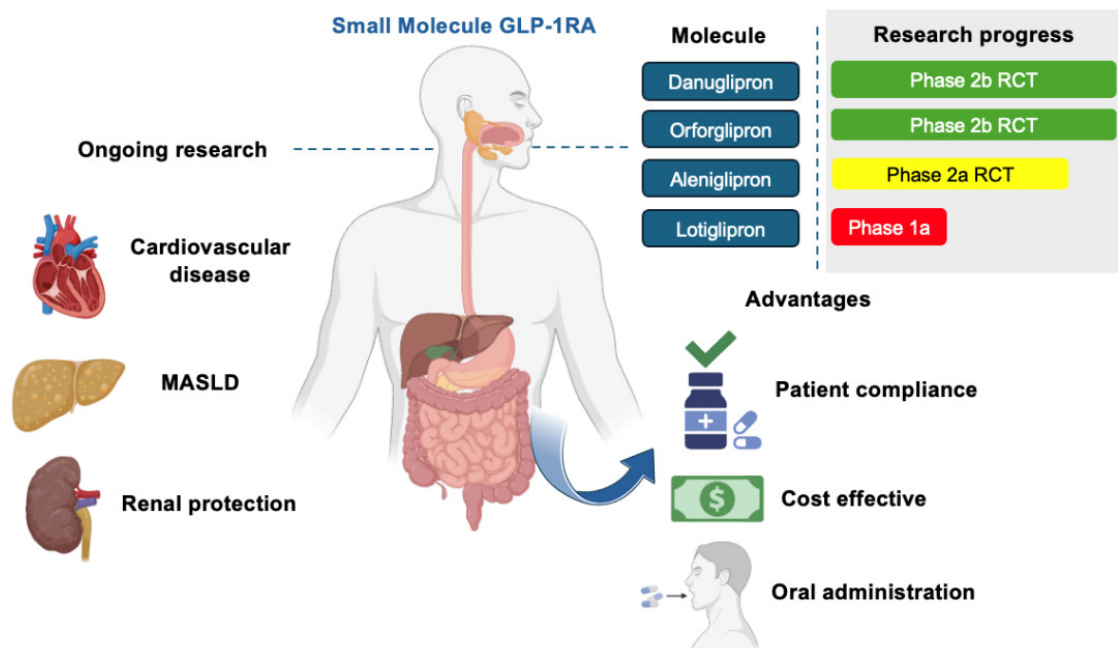


Figure 3. Current advantages, research stage and areas of opportunity of small molecule GLP-1RAs.

Abbreviations: MASLD: Metabolic dysfunction-associated steatotic liver disease. GLP-1RA: GLP-1 receptor agonist; RCT: Randomized clinical trial.

rently recommended injectable GLP-1 RAs to have a clear comparison between these families of medications.

However, several challenges need to be addressed to optimize their clinical utility. The future directions and challenges of new small-molecule GLP-1R agonists, such as danuglipron, are multifaceted.⁵¹ One significant challenge is the high rate of gastrointestinal adverse events associated with these compounds, which may be related to their pharmacokinetic properties and direct gastrointestinal irritation.⁵¹ Addressing these adverse effects is crucial for improving patient compliance and therapeutic outcomes.

Future directions include the design and synthesis of novel compounds that can mitigate these side effects while maintaining or enhancing efficacy. For instance, replacing problematic functional groups, such as the carboxylic acid group in danuglipron, with alternative structures has shown promise.⁷⁰ For example, compound 2j, a triazole-containing derivative, has demonstrated high potency and comparable efficacy to danuglipron in pre-clinical studies, suggesting it could serve as a lead compound for further development.^{70,71} Additionally, the exploration of GLP-1R positive allosteric modulators (PAMs) offers a new regulatory approach that could enhance the therapeutic profile of small-molecule GLP-1R agonists.⁷¹ These modulators can potentially provide more selective activation of the receptor, reducing adverse effects and improving efficacy.

Finally, evaluation of small molecule GLP-1R agonists beyond their effectiveness in T2DM and obesity presents a significant area of opportunity. Other GLP-1R agonists

have demonstrated extensive pleiotropic effects, including benefits in managing comorbidities such as osteoarthritis, cardiovascular disease, and neurodegenerative disorders.²⁴ This opens the door to exploring these novel compounds as potential therapeutic agents in a broader range of conditions. Future research should prioritize investigating their role in these areas, aiming to leverage their diverse mechanisms of action for improved patient outcomes across multiple diseases.

CONCLUSIONS

Small molecule GLP-1 receptor agonists represent an innovative advancement in the management of T2DM and obesity. These compounds offer distinct advantages over their peptide-based counterparts, including oral bioavailability, improved patient adherence, and the potential for broader therapeutic applications. Their smaller molecular structure also facilitates better tissue penetration and lower production costs, which could enhance accessibility to these novel medications.

Despite these promising attributes, significant challenges remain. Ensuring efficacy, safety, and durability comparable to injectable GLP-1 RAs while minimizing adverse effects, particularly gastrointestinal discomfort, is essential. Additionally, further research is needed to explore the broader therapeutic potential of these agents in managing comorbidities such as cardiovascular disease, PCOS, CKD, MASH, and osteoarthritis. Conducting rigorous studies like those that established the benefits of injectable GLP-1 RAs such as tirzepatide, semaglutide,

dulaglutide, and liraglutide on CKD, MASH, and cardiovascular outcomes will be crucial in determining the full clinical utility of these novel agents.

Small molecule GLP-RAs hold a potential to transform the landscape of metabolic and chronic disease management. Future studies will be crucial in addressing existing challenges, optimizing dosing regimens, and expanding their applications to maximize their impact on patient care.

- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures/Conflicts of interest

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest) in the subject matter or materials discussed in this article.

Corresponding Author

Eder Luna-Ceron, M.D., [M.Sc](#)
Texas Tech University Health Sciences Center,
Internal Medicine Department, El Paso, Texas 79905
Email: elunacer@ttuhsc.edu

Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-NC-4.0). View this license's legal deed at <https://creativecommons.org/licenses/by-nc/4.0> and legal code at <https://creativecommons.org/licenses/by-nc/4.0/legalcode> for more information.

REFERENCES

- Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*. 2023;402(10397):203-234. doi:[10.1016/S0140-6736\(23\)01301-6](https://doi.org/10.1016/S0140-6736(23)01301-6)
- Solis-Herrera C, Cersosimo E, Triplitt C. Antihyperglycemic Algorithms for Type 2 Diabetes: Focus on Nonglycemic Outcomes. *Diabetes Spectrum*. 2021;34(3):248-256. doi:[10.2337/ds20-0067](https://doi.org/10.2337/ds20-0067)
- Saxena A, Frias J, Brown L, et al. Efficacy and Safety of Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist Danuglipron for Glycemic Control Among Patients With Type 2 Diabetes: A Randomized Clinical Trial. *JAMA network open*. 2023;6:e2314493. doi:[10.1001/jamanetworkopen.2023.14493](https://doi.org/10.1001/jamanetworkopen.2023.14493)
- American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care*. 2024;48(Supplement_1):S181-S206. doi:[10.2337/dc25-S009](https://doi.org/10.2337/dc25-S009)
- Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update. *Endocrine Practice*. 2023;29(5):305-340. doi:[10.1016/j.eprac.2023.02.001](https://doi.org/10.1016/j.eprac.2023.02.001)
- De Boer IH, Khunti K, Sadusky T, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care*. 2022;45(12):3075-3090. doi:[10.2337/dci22-0027](https://doi.org/10.2337/dci22-0027)
- Kaul S. Mitigating Cardiovascular Risk in Type 2 Diabetes With Antidiabetes Drugs: A Review of Principal Cardiovascular Outcome Results of EMPA-REG OUTCOME, LEADER, and SUSTAIN-6 Trials. *Diabetes Care*. 2017;40(7):821-831. doi:[10.2337/dc17-0291](https://doi.org/10.2337/dc17-0291)
- Kim W, Egan JM. The Role of Incretins in Glucose Homeostasis and Diabetes Treatment. *Pharmacol Rev*. 2008;60(4):470. doi:[10.1124/pr.108.000604](https://doi.org/10.1124/pr.108.000604)
- Karagiannis T, Avgerinos I, Liakos A, et al. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. *Diabetologia*. 2022;65(8):1251-1261.
- Aspnes GE, Bagley SW, Coffey SB, et al. 6-Azaspiro [2.5] octanes as small molecule agonists of the human glucagon-like peptide-1 receptor. *Bioorganic & Medicinal Chemistry Letters*. 2023;94:129454.
- Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. *New England Journal of Medicine*. 2024;(17):1573-1583. doi:[10.1056/NEJMoa2403664](https://doi.org/10.1056/NEJMoa2403664)
- Sanyal AJ, Bedossa P, Fraessdorf M, et al. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. *New England Journal of Medicine*. 2024;(4):311-319. doi:[10.1056/NEJMoa2401755](https://doi.org/10.1056/NEJMoa2401755)
- Meissner W, Remy P, Giordana C, et al. Trial of Lixisenatide in Early Parkinson's Disease. *New England Journal of Medicine*. 2024;390(13):1176-1185. doi:[10.1056/NEJMoa2312323](https://doi.org/10.1056/NEJMoa2312323)
- Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2024;391(2):109-121. doi:[10.1056/NEJMoa2403347](https://doi.org/10.1056/NEJMoa2403347)
- Malhotra A, Grunstein R, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *New England Journal of Medicine*. 2024;(13):1193-1205. doi:[10.1056/NEJMoa2404881](https://doi.org/10.1056/NEJMoa2404881)
- Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *New England Journal of Medicine*. 2023;(24):2221-2232. doi:[10.1056/NEJMoa2307563](https://doi.org/10.1056/NEJMoa2307563)
- Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2025;375(4):311-322. doi:[10.1056/NEJMoa1603827](https://doi.org/10.1056/NEJMoa1603827)
- Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2025;375(19):1834-1844. doi:[10.1056/NEJMoa1607141](https://doi.org/10.1056/NEJMoa1607141)
- Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *The Lancet*. 2018;(10157):1519-1529. doi:[10.1016/S0140-6736\(18\)32261-X](https://doi.org/10.1016/S0140-6736(18)32261-X)
- Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis. *New England Journal of Medicine*. 2024;391(4):299-310. doi:[10.1056/NEJMoa2401943](https://doi.org/10.1056/NEJMoa2401943)
- Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *New England Journal of Medicine*. 2021;(12):1113-1124. doi:[10.1056/NEJMoa2028395](https://doi.org/10.1056/NEJMoa2028395)

22. American Diabetes Association Professional Practice Committee. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2025. *Diabetes Care*. 2024;48(Supplement_1):S59-S85. doi:[10.2337/dc25-S004](https://doi.org/10.2337/dc25-S004)
23. Michos ED, Lopez-Jimenez F, Gulati M. Role of Glucagon-Like Peptide-1 Receptor Agonists in Achieving Weight Loss and Improving Cardiovascular Outcomes in People With Overweight and Obesity. *Journal of the American Heart Association*. 2023;12(11):e029282. doi:[10.1161/JAHA.122.029282](https://doi.org/10.1161/JAHA.122.029282)
24. Zheng Z, Zong Y, Ma Y, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy*. 2024;9(1):234. doi:[10.1038/s41392-024-01931-z](https://doi.org/10.1038/s41392-024-01931-z)
25. D'Alessio D. Is GLP-1 a hormone: Whether and When? *Journal of diabetes investigation*. 2016;7:50-55.
26. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metabolism*. 2018;27(4):740-756. doi:[10.1016/j.cmet.2018.03.001](https://doi.org/10.1016/j.cmet.2018.03.001)
27. Müller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). *Molecular Metabolism*. 2019;30:72-130. doi:[10.1016/j.molmet.2019.09.010](https://doi.org/10.1016/j.molmet.2019.09.010)
28. Elliott R, Morgan L, Tredger J, Deacon S, Wright J, Marks V. Glucagon-like peptide-1 (7–36) amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. *Journal of Endocrinology*. 1993;138(1):159-166.
29. Zhang T, Perkins MH, Chang H, Han W, de Araujo IE. An inter-organ neural circuit for appetite suppression. *Cell*. 2022;185(14):2478-2494.e28. doi:[10.1016/j.cell.2022.05.007](https://doi.org/10.1016/j.cell.2022.05.007)
30. Sandoval DA, D'Alessio DA. Physiology of Proglucagon Peptides: Role of Glucagon and GLP-1 in Health and Disease. *Physiological Reviews*. 2015;95(2):513-548. doi:[10.1152/physrev.00013.2014](https://doi.org/10.1152/physrev.00013.2014)
31. Kaihara KA, Dickson LM, Ellenbroek JH, Orr CM, Layden BT, Wicksteed B. PKA enhances the acute insulin response leading to the restoration of glucose control. *Diabetes*. 2015;64(5):1688-1697. doi:[10.2337/db14-1051](https://doi.org/10.2337/db14-1051)
32. Rondas D, D'Hertog W, Overbergh L, Mathieu C. Glucagon-like peptide-1: modulator of β -cell dysfunction and death. *Diabetes, Obesity and Metabolism*. 2013;15(s3):185-192. doi:[10.1111/dom.12165](https://doi.org/10.1111/dom.12165)
33. Jun LS, Millican RL, Hawkins ED, et al. Absence of glucagon and insulin action reveals a role for the GLP-1 receptor in endogenous glucose production. *Diabetes*. 2015;64(3):819-827. doi:[10.2337/db14-1052](https://doi.org/10.2337/db14-1052)
34. Holter MM, Saikia M, Cummings BP. Alpha-cell paracrine signaling in the regulation of beta-cell insulin secretion. *Frontiers in endocrinology*. 2022;13:934775.
35. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. *Nature Reviews Cardiology*. 2023;20(7):463-474.
36. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation Am Heart Assoc*. 2017;136(9):849-870.
37. Szekeres Z, Nagy A, Jahner K, Szabados E. Impact of Selected Glucagon-like Peptide-1 Receptor Agonists on Serum Lipids, Adipose Tissue, and Muscle Metabolism—A Narrative Review. *International Journal of Molecular Sciences*. 2024;25(15):8214.
38. Kelly M, Lewis J, Rao H, Carter J, Portillo I, Beuttler R. Effects of GLP-1 receptor agonists on cardiovascular outcomes in patients with type 2 diabetes and chronic kidney disease: A systematic review and meta-analysis. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2022;42(12):921-928.
39. Mabilieu G, Pereira M, Chenu C. Novel skeletal effects of glucagon-like peptide-1 (GLP-1) receptor agonists. *Journal of endocrinology*. 2018;236(1):R29-R42. doi:[10.1530/JOE-17-0278](https://doi.org/10.1530/JOE-17-0278)
40. Campbell JE, Drucker DJ. Pharmacology, Physiology, and Mechanisms of Incretin Hormone Action. *Cell Metabolism*. 2013;17(6):819-837. doi:[10.1016/j.cmet.2013.04.008](https://doi.org/10.1016/j.cmet.2013.04.008)
41. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *The Journal of clinical investigation*. 2014;124(10):4473-4488. doi:[10.1172/JCI75276](https://doi.org/10.1172/JCI75276)
42. Burmeister MA, Ayala JE, Smouse H, et al. The hypothalamic glucagon-like peptide 1 receptor is sufficient but not necessary for the regulation of energy balance and glucose homeostasis in mice. *Diabetes*. 2017;66(2):372-384.
43. Sisley S, Gutierrez-Aguilar R, Scott M, D'Alessio DA, Sandoval DA, Seeley RJ. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. *The Journal of clinical investigation*. 2014;124(6):2456-2463. doi:[10.1172/JCI72434](https://doi.org/10.1172/JCI72434)
44. Katsurada K, Yada T. Neural effects of gut- and brain-derived glucagon-like peptide-1 and its receptor agonist. *Journal of Diabetes Investigation*. 2016;7. doi:[10.1111/jdi.12464](https://doi.org/10.1111/jdi.12464)

45. Chen XY, Chen L, Yang W, Xie AM. GLP-1 Suppresses Feeding Behaviors and Modulates Neuronal Electrophysiological Properties in Multiple Brain Regions. *Frontiers in Molecular Neuroscience*. 2021;14. doi:[10.3389/fnmol.2021.793004](https://doi.org/10.3389/fnmol.2021.793004)
46. Sohn JW. Network of hypothalamic neurons that control appetite. *BMB reports*. 2015;48(4):229. doi:[10.5483/BMBRep.2015.48.4.272](https://doi.org/10.5483/BMBRep.2015.48.4.272)
47. Mietlicki-Baase EG, Ortinski PI, Reiner DJ, et al. Glucagon-Like Peptide-1 Receptor Activation in the Nucleus Accumbens Core Suppresses Feeding by Increasing Glutamatergic AMPA/Kainate Signaling. *J Neurosci*. 2014;34(20):6985. doi:[10.1523/JNEUROSCI.0115-14.2014](https://doi.org/10.1523/JNEUROSCI.0115-14.2014)
48. Griffith DA, Edmonds DJ, Fortin JP, et al. A Small-Molecule Oral Agonist of the Human Glucagon-like Peptide-1 Receptor. *J Med Chem*. 2022;65(12):8208-8226. doi:[10.1021/acs.jmedchem.1c01856](https://doi.org/10.1021/acs.jmedchem.1c01856)
49. Saxena AR, Gorman DN, Esquejo RM, et al. Danuglipron (PF-06882961) in type 2 diabetes: a randomized, placebo-controlled, multiple ascending-dose phase 1 trial. *Nature Medicine*. 2021;27(6):1079-1087. doi:[10.1038/s41591-021-01391-w](https://doi.org/10.1038/s41591-021-01391-w)
50. Ono R, Furihata K, Ichikawa Y, et al. A phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of danuglipron (PF-06882961), an oral small-molecule glucagon-like peptide-1 receptor agonist, in Japanese adults with type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*. 2023;25(3):805-814. doi:[10.1111/dom.14928](https://doi.org/10.1111/dom.14928)
51. Fatima H, Rangwala HS, Mustafa MS, et al. Evaluating glycemic control efficacy and safety of the oral small molecule glucagon-like peptide 1 receptor agonist danuglipron in type 2 diabetes patients: a systemic review and meta-analysis. *Diabetes, Metabolic Syndrome and Obesity*. Published online 2023;3567-3578. doi:[10.2147/DMSO.S439587](https://doi.org/10.2147/DMSO.S439587)
52. Pratt E, Ma X, Liu R, et al. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: a Phase 1a, blinded, placebo-controlled, randomized, single-and multiple-ascending-dose study in healthy participants. *Diabetes, Obesity and Metabolism*. 2023;25(9):2634-2641.
53. Pratt E, Ma X, Liu R, et al. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: a Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2023;25(9):2642-2649.
54. Frias JP, Hsia S, Eyde S, et al. Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. *The Lancet*. 2023;402(10400):472-483.
55. Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *New England Journal of Medicine*. 2023;389(10):877-888.
56. Karakasis P, Patoulas D, Pamporis K, et al. Safety and efficacy of the new, oral, small-molecule, GLP-1 receptor agonists orforglipron and danuglipron for the treatment of type 2 diabetes and obesity: systematic review and meta-analysis of randomized controlled trials. *Metabolism*. 2023;155710. doi:[10.1016/j.metabol.2023.155710](https://doi.org/10.1016/j.metabol.2023.155710)
57. Mao T, Meng Q, Zhang H, et al. 760-P: Discovery of GSBR-1290, a Highly Potent, Orally Available, Novel Small Molecule GLP-1 Receptor Agonist. *Diabetes*. 2023;72(Supplement_1):760-P. doi:[10.2337/db23-760-P](https://doi.org/10.2337/db23-760-P)
58. Coll B, Zhang J, Chen L, et al. 767-P: A Phase 1b/2a Study of the Safety and Tolerability of GSBR-1290, a Novel Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA), in Healthy Overweight/Obese Volunteers (HOV) and Participants with Type 2 Diabetes Mellitus (T2DM). *Diabetes*. 2024;73(Supplement_1):767-P. doi:[10.2337/db24-767-P](https://doi.org/10.2337/db24-767-P)
59. Amin NB, Frederich R, Tsamandouras N, et al. Evaluation of an oral small-molecule glucagon-like peptide-1 receptor agonist, lotiglipron, for type 2 diabetes and obesity: A dose-ranging, phase 2, randomized, placebo-controlled study. *Diabetes Obes Metab*. 2025;27(1):215-227. doi:[10.1111/dom.16005](https://doi.org/10.1111/dom.16005)
60. Bearss DJ, Lin C, Medley K, Vankayalapati H. 1139-P: Discovery of a Potent, Orally Efficacious Small Molecule Agonist of Glucagon-Like Peptide-1 (GLP-1) Receptor. *Diabetes*. 2024;73(Supplement_1):1139-P. doi:[10.2337/db24-1139-P](https://doi.org/10.2337/db24-1139-P)
61. Je I, Im A, Lee D, et al. 93-LB: Discovery of ID110521156, a Small Molecule GLP-1 Receptor Agonist, for the Treatment of Type 2 Diabetes and Obesity. *Diabetes*. 2023;72(Supplement_1):93-LB. doi:[10.2337/db23-93-LB](https://doi.org/10.2337/db23-93-LB)
62. Haggag AZ, Xu J, Butcher L, et al. Non-clinical and first-in-human characterization of ECC5004/AZD5004, a novel once-daily, oral small-molecule GLP-1 receptor agonist. *Diabetes Obes Metab*. Published online November 4, 2024. doi:[10.1111/dom.16047](https://doi.org/10.1111/dom.16047)
63. Liu F, Sun X, Huang W, Guo W, Lin J, Zhong W. 753-P: RGT-075, an Orally Efficacious Small Molecule GLP-1R Full Agonist in Cynomolgus Monkey Models. *Diabetes*. 2022;71(Supplement_1):753-P. doi:[10.2337/db22-753-P](https://doi.org/10.2337/db22-753-P)
64. Vogel J, Seung M, Marchand B, et al. 1625-P: GS-4571, an Oral Small Molecule GLP-1R Agonist, Improves Glucose Tolerance and Suppresses Food Intake in Obese Diabetic Cynomolgus Monkeys. *Diabetes*. 2024;73(Supplement_1):1625-P. doi:[10.2337/db24-1625-P](https://doi.org/10.2337/db24-1625-P)

65. Kawai T, Tanino F, Fukazawa M, et al. OWL833, an Orally Active Nonpeptide GLP-1 Receptor Agonist, Improves Glucose Tolerance by Increasing Insulin Secretion and Reduces Food Intake of Cynomolgus Monkeys. *Diabetes*. 2018;67(Supplement_1):1118-P. doi:[10.2337/db18-1118-P](https://doi.org/10.2337/db18-1118-P)
66. Baek M, Kim D, Kim Ch, et al. 939-P: HD-7671, a Nonpeptide Small Molecule for Orally Available GLP-1 Receptor Agonist, Improves Glucose Tolerance by Increasing Insulin Secretion. *Diabetes*. 2020;69(Supplement_1):939-P. doi:[10.2337/db20-939-P](https://doi.org/10.2337/db20-939-P)
67. Huthmacher JA, Meier JJ, Nauck MA. Efficacy and Safety of Short- and Long-Acting Glucagon-Like Peptide 1 Receptor Agonists on a Background of Basal Insulin in Type 2 Diabetes: A Meta-analysis. *Diabetes Care*. 2020;43(9):2303-2312. doi:[10.2337/dc20-0498](https://doi.org/10.2337/dc20-0498)
68. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes, Obesity and Metabolism*. 2017;19(4):524-536. doi:[10.1111/dom.12849](https://doi.org/10.1111/dom.12849)
69. Das SR, Everett BM, Birtcher KK, et al. 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes: A Report of the American College of Cardiology Solution Set Oversight Committee. *Journal of the American College of Cardiology*. 2020;76(9):1117-1145. doi:[10.1016/j.jacc.2020.05.037](https://doi.org/10.1016/j.jacc.2020.05.037)
70. Wang X, Yun Y, Chen L, et al. A novel approach to exploit Small-Molecule glucagon-like Peptide-1 receptor agonists with high potency. *Bioorganic & Medicinal Chemistry*. 2024;107:117761. doi:[10.1016/j.bmc.2024.117761](https://doi.org/10.1016/j.bmc.2024.117761)
71. Zhang H, Wu T, Wu Y, et al. Binding sites and design strategies for small molecule GLP-1R agonists. *European Journal of Medicinal Chemistry*. 2024;275:116632. doi:[10.1016/j.ejmech.2024.116632](https://doi.org/10.1016/j.ejmech.2024.116632)