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REVIEW

Special Issue: *Real-world evidence on the use of GLP1 receptor agonists*

Emerging concepts in obesity management: focus on glucagon receptor agonist combinations

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Abstract

The global rise in obesity and its associated health risks has driven the need for more effective pharmacological treatments. Glucagon receptor (GCGR)-based multi-agonist drugs are emerging as promising treatments for obesity, with several in advanced stages of clinical development. Agents like mazdutide, pemvidutide, survodutide and retatrutide have demonstrated the ability to trigger significant weight loss in earlier phase trials, often surpassing the amount of weight loss obtained with existing therapies. Their potential to address obesity-related comorbidities, including type 2 diabetes mellitus and cardiovascular disease, positions them as important additions to future obesity treatment guidelines. As these GCGR-based multi-agonists advance through clinical trials, their impact on obesity management may be substantial, particularly for patients who have not achieved success with current medications or lifestyle interventions. Some are also being evaluated for cardiovascular outcomes, highlighting their relevance in populations at high risk with overweight and obesity. Key considerations as these drugs move forward in development to eventual approval include cost, access and long-term safety.

This article is part of the *Real-world evidence on the use of GLP1 receptor agonists* Special Issue: https://www.drugsincontext.com/special_issues/real-world-evidence-on-the-use-of-glp1-receptor-agonists

Keywords: endocrinology, gastric inhibitory polypeptide, glucagon-like peptide-1 obesity, overweight.

Citation

Anderson SL. Emerging concepts in obesity management: focus on glucagon receptor agonist combinations. *Drugs Context*. 2025;14:2025-4-8. https://doi.org/10.7573/dic.2025-4-8

Introduction

Obesity remains a global health crisis, with its prevalence amongst adults nearly doubling since 1990 and now affecting over 650 million adults.[1] Obesity is a chronic condition associated with a host of metabolic and cardiovascular (CV) comorbidities, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, chronic kidney disease (CKD), metabolic dysfunction-associated steatotic liver disease and certain cancers.[2] Despite the widespread implementation of lifestyle interventions and the availability of several pharmacological treatments for obesity, sustained weight loss remains unachievable for many individuals. Medications like orlistat and the combination of phentermine plus topiramate have shown promise in people with overweight and obesity, yet they often cause intolerable side-effects and fall short in achieving or maintaining clinically meaningful weight reduction for a substantial portion of patients.[3–6]

Glucagon-like peptide 1 (GLP1) receptor agonists (RAs) were originally developed to treat hyperglycaemia in people with T2DM and have shown significant efficacy in producing weight loss, leading to the approval of two agents in this class for the treatment of obesity. These agents - semaglutide and liraglutide - enhance satiety and reduce appetite, contributing to substantial reductions in body weight.[7,8] Tirzepatide is a novel agent that combines GLP1 receptor agonism with gastric inhibitory polypeptide (GIP) receptor agonism that has also demonstrated efficacy in treating both T2DM and obesity.[9] Like liraglutide and semaglutide, tirzepatide is approved for the treatment of obesity in people with and without T2DM. Whilst GLP1 RAs and dual GLP1/GIP RA combinations represent a major advancement, many individuals either do not respond to

these agents or are unable to maintain optimal weight loss, prompting the development of next-generation therapies for managing overweight and obesity.[7–9]

Emerging therapeutic options for the treatment of obesity, including glucagon receptor (GCGR) agonists and their combinations (GLP1 RAs, GIP RAs or both), are showing promise in achieving weight loss for people with overweight and obesity beyond what has been accomplished with GLP1 RA monotherapy or GLP1/GIP RA dual therapy. These GCGR-based multi-agonists aim to deliver greater metabolic benefits by targeting multiple hormonal pathways. These combinations may offer improved efficacy in the treatment of obesity by leveraging complementary mechanisms in appetite regulation and energy expenditure.[10]

Recent preclinical and clinical studies have investigated various dual-agonist and triple-agonist peptides that simultaneously target GCGRs along with other receptors, including GLP1 and GIP receptors. These GCGR-based dual and triple combination therapies aim to leverage the synergistic benefits of appetite suppression, enhanced energy expenditure and improved glucose homeostasis. These developments represent a paradigm shift in pharmacotherapy for overweight and obesity, moving towards multi-receptor targeting agents that more closely mimic the complex hormonal milieu that regulates energy balance.[11]

This narrative review provides a comprehensive examination of the current landscape of GCGR-based combinations in phase III trials for the treatment of obesity. The physiological rationale behind GCGR targeting, findings from recent clinical and preclinical trials, and the benefits and limitations of these emerging therapies are analysed and discussed. Special attention is given to the safety profiles, metabolic effects and therapeutic potential of GCGR-based multi-agonists in comparison to existing pharmacological options where data exist. An English language MEDLINE search was conducted through 14 April 2025 using the search terms "glucagon receptor agonist", "GCGR", "GCGR agonist", "glucagon-like peptide 1", "GLP1", "glucose-dependent insulinotropic polypeptide", "GIP" and "obesity". A manual search of the references cited within the research manuscripts and review articles was conducted to find additional relevant sources.

Review

Mechanisms of GCGR-based multi-agonist combinations

Glucagon is a peptide hormone produced primarily in pancreatic α-cells that plays a critical role in regulating both glucose and lipid metabolism. Activation of the GCGR enhances hepatic glucose production and stimulates lipolysis, contributing to increased energy expenditure and thermogenesis. These effects are particularly beneficial in the context of obesity, where a reduction in basal metabolic rate often hinders sustained weight loss. GLP1 RAs, which improve glycaemic control and promote satiety, have shown strong efficacy in weight management; however, their use may be limited by gastrointestinal (GI) side-effects and an eventual plateau in weight loss response. To overcome these limitations, novel multi-receptor agonists, such as those targeting both GLP1 receptor and GCGR activation, and even triple agonists that add GIP receptor agonism to GLP1 RA and GCGR agonism, are under investigation. These agents synergistically enhance insulin secretion, suppress appetite and increase energy expenditure, offering a promising approach to more effective and durable obesity treatment.[12]

GCGR-based dual agonists: glucagon and GLP1 receptor co-agonism

Dual agonists targeting both the GCGR and GLP1 receptor have demonstrated enhanced efficacy in promoting weight loss and improving metabolic parameters compared to GLP1 RA monotherapy. Activation of the GLP1 and glucagon receptors is believed to mimic the complementary effects of diet and exercise on weight loss with GLP1 suppressing appetite and glucagon increasing energy expenditure.[13]

Four dual GCGR-based agonists have completed phase II clinical trials evaluating their efficacy and safety in the treatment of people with overweight or obesity - mazdutide, pemvidutide, survodutide and efinopegdutide. Of these, mazdutide has one completed phase III trial with another underway, whilst pemvidutide and survodutide each have several phase III trials underway (Table 1).

Mazdutide

Mazdutide (IBI362) is a dual GCGR-based agonist in development that has been evaluated in the phase III trial GLORY-1. In this multi-centre, randomized, double-blind, placebo-controlled trial, 610 Chinese adults with overweight or obesity were enrolled and randomized to receive low-dose (4 mg) mazdutide, high-dose (6 mg) mazdutide or placebo subcutaneously weekly for 48 weeks. At weeks 32 and 48, mazdutide 4 mg and 6 mg demonstrated superior weight loss efficacy compared to placebo, as reflected by the mean percentage change in body weight from baseline and the proportion of participants achieving weight reductions of ≥5%, ≥10% and ≥15% ($p<0.001$). At week 48, the treatment difference in mean percentage weight change between mazdutide 6 mg and placebo was –14.31% for the treatment-policy estimand and –14.37% for the efficacy estimand.[14] Also at week 48, mazdutide

Table 1. Summary of GCGR-based multi-agonists in development for the treatment of obesity.

Drug	Mechanism of action	Percent weight loss	Safety	Key obesity clinical trial programme
Mazdutide[14]	Glucagon and GLP1 receptor co-agonist	−12 (4mg) and −14.8 (6mg) *vs* −0.5 with placebo at 48 weeks (phase III trial)	GI side-effects (nausea, vomiting, diarrhoea) common	GLORY, phase III
Pemvidutide[18]	Glucagon and GLP1 receptor co-agonist	−10.3 (1.2 mg), −11.2 (1.8 mg) and −15.6% (2.4 mg) *vs* −2.2 with placebo at 48 weeks (phase II trial)	GI side-effects (nausea, vomiting) noted in phase II study in patients with MASH	VELOCITY, phase III
Survodutide[21]	Glucagon and GLP1 receptor co-agonist	−6.2 (0.6 mg), −12.5 (2.4 mg), −13.2 (3.6 mg), −14.9 (4.8 mg) *vs* −2.8 with placebo at 46 weeks (phase II trial)	GI side-effects (nausea, vomiting, diarrhoea) common	SYNCHRONIZE, phase III
Retatrutide[31]	Glucagon, GLP1 and GIP receptor co-agonist	−8.7 (1 mg), −17.1 (combined 4 mg group), −22.8 (combined 8 mg group), −24.2 (combined 12 mg group) *vs* −2.1 with placebo at 48 weeks	GI side-effects (nausea, vomiting, diarrhoea, constipation) common	TRIUMPH, phase III

GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP1, glucagon-like peptide-1; MASH, metabolic-associated steatohepatitis.

treatment led to notable reductions in waist circumference, with decreases of 9.48 cm and 10.96 cm for the 4 mg and 6 mg doses, respectively, compared to 1.48 cm with placebo. The pooled mazdutide groups also showed significant improvements in several cardiometabolic risk factors, including blood pressure, lipid levels, serum uric acid and alanine aminotransferase.

In an exploratory analysis of the GLORY-1 study, participants with elevated liver fat at baseline experienced an average of 80.2% reduction in liver fat content with mazdutide 6 mg *versus* a reduction of only 5.3% with placebo.[15] Mazdutide was well tolerated with low and comparable discontinuation rates due to adverse events across treatment and placebo groups (1.5%, 0.5% and 1% for the 4 mg, 6 mg and placebo groups, respectively). Its safety profile aligned with previous studies with no new safety signals. GI events were the most common, generally mild or moderate, and occurred during dose escalation phases. Serious adverse events were rare, and heart rate changes remained minimal, with no indication of increased CV risk over the 48-week study period.[14]

A second phase III trial in adults with obesity (GLORY-2) aims to enrol 450 Chinese participants with a high BMI (≥30 kg/m^2) to receive a higher dose of mazdutide (9 mg) or placebo. The primary endpoints are the percentage change in body weight from baseline to week 60 and the proportion of participants with 5% or greater body weight loss from baseline.[16] Another phase III trial (DREAMS-3) is evaluating mazdutide compared to semaglutide in Chinese adults with obesity and early T2DM (Table 2).[17]

Pemvidutide

Pemvidutide - another dual GCGR/GLP1 RA - was recently evaluated in the phase II clinical trial MOMENTUM. This study enrolled 391 people with overweight or obesity and randomized them 1:1:1:1 to receive pemvidutide 1.2 mg, 1.8 mg, 2.4 mg or placebo subcutaneously weekly for 48 weeks. Over 48 weeks, pemvidutide led to significant, dose-dependent weight loss, with up to 15.6% mean reduction at the highest dose compared to 2.2% with placebo. At the 2.4-mg dose, over half of participants lost ≥15% of their body weight, and 48% no longer met criteria for obesity. Participants with elevated baseline lipids saw substantial improvements, including a 55.8% drop in triglycerides. The treatment was generally well tolerated with mostly mild to moderate adverse events (these are likely GI in nature, though details not provided in publication), stable glycaemic control and minimal heart rate changes.[18]

Based on the success of phase II clinical trials, pemvidutide is being studied in a series of phase III clinical trials. The VELOCITY clinical trial programme is evaluating pemvidutide across various populations with overweight or obesity and aims to enrol approximately 5000 participants across four trials. The safety and efficacy of each of the pemvidutide doses studied in phase II trials will be evaluated with the intention of obtaining FDA approval of all three doses. VELOCITY-1 focuses on weight loss and improvements in cardiometabolic markers such as waist circumference, lipids and blood pressure. VELOCITY-2 targets patients with elevated low-density lipoprotein cholesterol, including those taking statins, to assess the potential of pemvidutide to enhance lipid lowering. VELOCITY-3 investigates effects on weight and liver fat reduction, whilst VELOCITY-4 examines impacts on body composition and functional health, particularly in older adults with sarcopenia.[19] At the time of writing, the VELOCITY clinical trials were not yet registered with ClinicalTrials.gov (Table 2).

Survodutide

Survodutide is a compound that mimics oxyntomodulin, a natural gut hormone, that activates both glucagon and GLP1.[20] A phase II randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of survodutide in 387 adults with overweight or obesity without T2DM. Participants received weekly subcutaneous injections of survodutide at doses of 0.6 mg, 2.4 mg, 3.6 mg or 4.8 mg, or placebo, over 46 weeks. The study found significant dose-dependent reductions in body weight, with the 4.8-mg dose achieving a mean weight loss of 14.9% compared to 2.8% with placebo. Additionally, 40% of participants on the highest survodutide doses achieved at least 20% weight loss. Regarding safety, 90.9% of survodutide recipients experienced treatment emergent adverse events, predominantly GI in nature (nausea, vomiting, diarrhoea), compared to 75.3% in the placebo group. Discontinuation due to adverse events occurred in 24.6% of the survodutide group, mainly during the rapid dose escalation phase. No unexpected safety concerns were identified, and the adverse event profile was consistent with that of GLP1 receptor agonist monotherapy.[21]

These findings suggested that survodutide may offer a potent treatment option for obesity, warranting further investigation in phase III trials. A phase III randomized controlled trial named SYNCHRONIZE-1 has recently been initiated, targeting the enrolment of 600 adults with overweight or obesity, with an anticipated completion date of January 2026. Participants will receive once-weekly subcutaneous injections of survodutide at doses of either 3.6 mg or 6 mg, or placebo, over a treatment period of 76 weeks. The primary endpoints of the study include the percentage change in body weight from baseline and the proportion of individuals achieving at least 5% weight loss.[22,23] SYNCHRONIZE-2 is a similarly structured phase III trial designed to evaluate survodutide efficacy and safety in adults with overweight or obesity and T2DM.[23,24] SYNCHRONIZE-JP is studying survodutide for the treatment of obesity, specifically in Japanese individuals.[25]

The SYNCHRONIZE-CVOT trial is a global, phase III, randomized, double-blind study evaluating the CV safety and efficacy of survodutide in adults with obesity and elevated CV risk. The trial compares once-weekly subcutaneous survodutide to placebo in individuals with a BMI ≥27 kg/m² and established CV disease, CKD, or ≥2 weight-related complications or CV risk factors. Randomization is stratified by heart failure status and presence of T2DM. The primary outcome is time to first occurrence of a 5-point major adverse cardiovascular event. With a target enrolment of 4935 participants, this is the first study to assess the CV impact of survodutide (Table 2).[26]

Efinopegdutide

Efinopegdutide is another dual GCGR/GLP1 receptor agonist in development. Positive phase II trial results in people with overweight or obesity have been published but there are no ongoing phase III trials of efinopegdutide for obesity. Efinopegdutide is being studied for the treatment of metabolic-associated steatotic liver disease, which is where all its phase III trials are currently focused.[27]

GCGR-based triple agonists: glucagon, GLP1 and GIP receptor co-agonism

Similar to dual GCGR-based agonists, triple agonists that combine glucagon, GLP1 and GIP receptor co-agonism may be more beneficial than GLP1 RA monotherapy or even GCGR-based dual therapy. GLP1 and GIP both enhance insulin release and reduce glucagon secretion but each has distinct additional functions. GIP, secreted from the duodenum and jejunum in response to food, plays a role in nutrient and energy metabolism. It is believed to cross the blood–brain barrier and affect areas like the hypothalamus, influencing energy balance and reducing nausea induced by GLP1. Peripherally, GIP aids lipid storage and improves metabolic control in adipose tissue. When combined with GLP1, GIP enhances lipid handling and reduces appetite, offering synergistic effects. This dual agonism improves glucose control and weight loss as seen with tirzepatide. Preclinical studies show that triple agonism (GLP1, GIP and glucagon) outperforms dual agonism, offering greater improvements in body weight, energy expenditure and metabolic control, with the potential to further enhance therapeutic outcomes in obesity and diabetes management.[28–30]

Retatrutide

Retatrutide is a once weekly, subcutaneous triple agonist of glucagon, GLP1 and GIP receptors, with the greatest potency at GIP receptors. In a phase II double-blind, randomized, placebo-controlled trial of 338 adults with obesity, participants were randomized 2:1:1:1:1:2:2 to receive subcutaneous retatrutide 1 mg, 4 mg (initial dose, 2 mg), 4 mg (initial dose, 4 mg), 8 mg (initial dose, 2 mg), 8 mg (initial dose, 4 mg) or 12 mg (initial dose, 2 mg), or placebo once weekly for 48 weeks. Treatment with retatrutide led to dose-dependent weight loss over the study period, with reductions ranging from −8.7% (1 mg) to −24.2% (12 mg), compared to −2.1% with placebo. Weight loss outcomes were similar regardless of initial dose, and the 8 mg and 12 mg doses showed overlapping efficacy. Greater weight reduction was observed in participants with BMI ≥35 kg/m² and in women. Adverse events were primarily GI in nature (nausea, vomiting, diarrhoea, constipation), dose related and generally mild to moderate; discontinuation due to side effects ranged from 6% to 16% in the retatrutide groups, with none in the placebo group. Lower starting doses (for example, 2 mg instead of 4 mg) helped improve tolerability.[31]

These positive results were the impetus for the creation of the TRIUMPH series of phase III trials of retatrutide for the treatment of overweight and obesity (Table 1). The TRIUMPH clinical trial programme is a comprehensive series of studies evaluating retatrutide targeting obesity and its comorbid conditions. Each TRIUMPH trial targets a different population, and TRIUMPH-1 through TRIUMPH-6 are all randomized, double-blind, placebo-controlled clinical trials. Based on phase II study results, the dosing scheme used in the phase III TRIUMPH programme uses a starting dose (named Dose 1) subcutaneously weekly, increasing incrementally based on individual study design. TRIUMPH-1 is enrolling adults with obesity or overweight without T2DM, measuring percentage change in body weight.[32] TRIUMPH-2 examines similar weight outcomes in adults with T2DM.[33] TRIUMPH-3 focuses on participants with obesity and established CV disease, whilst TRIUMPH-4 explores the impact of retatrutide on both weight and knee osteoarthritis symptoms using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale.[34,35]

Additional trials in the series include TRIUMPH-5, which directly compares retatrutide to tirzepatide in people with obesity, and TRIUMPH-6, a phase IIIb weight maintenance study evaluating sustained outcomes after initial weight loss. The TRIUMPH-Outcomes trial is an event-driven trial designed to assess the long-term effects of retatrutide on major adverse CV and renal outcomes in individuals with obesity and established atherosclerotic CV disease and/or CKD, with or without T2DM.[36,37] Across the TRIUMPH clinical trial programme, the trials aim to assess not only weight loss but also meaningful improvements in obesity-related comorbidities and long-term health outcomes. Initial results from the TRIUMPH clinical trial programme are expected in late 2025 (Table 2).

Limitations of available study data

Early-phase studies of mazdutide, pemvidutide, survodutide and retatrutide demonstrate promising weight loss efficacy but several limitations temper how broadly the findings can be applied in clinical practice. A common concern across trials is limited population diversity - many studies included predominantly white or East Asian participants and underrepresented older adults, those with multiple chronic conditions, and racially diverse populations. In addition, most trials excluded patients with advanced CV or kidney disease, limiting generalizability to those at the highest risk from obesity-related complications.

Trial durations in published phase II and early phase III studies were generally short (16–48 weeks), which are insufficient to assess long-term efficacy, safety, weight maintenance and durability of response given that these drugs will likely be chronic medications for the patients taking them. Key outcomes, like quality of life, functional status and comprehensive cardiometabolic effects, remain underreported. Moreover, high adherence and close monitoring in clinical trial settings do not reflect real-world conditions, where factors like cost, access and tolerability could significantly affect outcomes. Longer trials and real-world data that include more diverse individuals will be critical to defining the true clinical utility of these multi-agonists across the spectrum of patients living with obesity.

Implications for practice

The GCGR-based multi-agonists in phase III trials, including mazdutide, pemvidutide, survodutide and retatrutide, are showing significant promise for transforming obesity management. These drugs have demonstrated weight loss efficacy in phase II trials, in some cases exceeding 20% total body weight reduction, potentially offering a more effective option for patients who struggle to lose weight through lifestyle interventions alone. Their use could benefit a broader patient population, including those with obesity-related comorbidities like T2DM, CV disease and CKD. If approved, these therapies may not only improve metabolic health and reduce obesity-related complications but could also shift clinical guidelines towards earlier and more aggressive pharmacological intervention in obesity care.

However, integration into clinical practice will depend on overcoming several important barriers. Cost and insurance coverage remain amongst the most pressing

Table 2. Overview of completed or ongoing phase III clinical trials of GCGR-based multi-agonists for obesity.

Trial name and population	Inclusion criteria	Drug and dose(s)	Comparator	Primary endpoint(s)	Trial duration in weeks
Mazdutide					
GLORY-1[14] Chinese people with overweight or obesity	BMI ≥28 kg/m², or BMI ≥24 kg/m² with ≥1 BW-related comorbidity without T2DM	Mazdutide 4 mg and 6 mg SC weekly	Placebo	Percent change from baseline in body weight and weight reduction of ≥5% at week 32	48 (completed)
GLORY-2[16] Chinese people with more severe obesity NCT06164873	BMI ≥28 kg/m²	Mazdutide 9 mg SC weekly	Placebo	Percent change from baseline in body weight and weight reduction of ≥5% at week 60	60
DREAMS-3[17] Chinese people with obesity and T2DM NCT06184568	BMI ≥30 kg/m² and T2DM	Mazdutide up-titrated to 4 mg SC weekly	Semaglutide up-titrated to 1.0 mg SC weekly	Proportion who achieve composite endpoint of A1C <7.0% and ≥10% weight loss	32
Pemvidutide					
VELOCITY-1[19] People with obesity or overweight	Overweight or obesity without T2DM	Pemvidutide 1.2 mg, 1.8 mg and 2.4 mg SC weekly	Placebo	Percent change from baseline in body weight	60
VELOCITY-2[19] People with obesity or overweight and elevated LDL-C	Overweight or obesity and elevated LDL-C (with or without statin therapy)	Pemvidutide 1.2 mg, 1.8 mg and 2.4 mg SC weekly	Placebo	Percent change from baseline in body weight Changes in lipids	60
VELOCITY-3[19] People with obesity or overweight and elevated liver fat	Overweight or obesity and elevated liver fat	Pemvidutide 1.2 mg, 1.8 mg and 2.4 mg SC weekly	Placebo	Percent change from baseline in body weight Changes in liver fat	60
VELOCITY-4[19] People with obesity or overweight in older adults with sarcopenia	Overweight or obesity in older adults with sarcopenia	Pemvidutide 1.2 mg, 1.8 mg and 2.4 mg SC weekly	Placebo	Percent change from baseline in body weight Changes in lean body mass	60 weeks
Survodutide					
SYNCHRONIZE-1[22,23] People with overweight or obesity NCT060665157	BMI ≥30 kg/m², or BMI ≥27 kg/m² with ≥1 BW-related comorbidity without T2DM	Survodutide 3.6 mg or 6 mg SC weekly	Placebo	Percent change from baseline in body weight and weight reduction of ≥5% at week 76	76
SYNCHRONIZE-2[23,24] People with overweight or obesity and T2DM NCT06066528	BMI ≥27 kg/m² and T2DM	Survodutide 3.6 mg or 6 mg SC weekly	Placebo	Percent change from baseline in body weight and weight reduction of ≥5% at week 76	76
SYNCHRONIZE-JP[25] Japanese people with overweight or obesity NCT06176365	BMI ≥35 kg/m² with ≥1 BW-related health comorbidity or BMI ≥27 kg/m² and ≥2 BW-related health comorbidities	Survodutide 3.6 mg or 6 mg SC weekly	Placebo	Percent change from baseline in body weight and weight reduction of ≥5% at week 76	76

(*Continued*)

Table 2. (Continued)

Trial name and population	Inclusion criteria	Drug and dose(s)	Comparator	Primary endpoint(s)	Trial duration in weeks
SYNCHRONIZE-CVOT[26] People with obesity and ASCVD or CKD NCT06077864	BMI ≥27 kg/m², with or without T2DM, and established ASCVD and/or CKD or ≥2 BW-related health comorbidities	Survodutide 3.6 mg or 6 mg SC weekly	Placebo	Time to first occurrence of 5-point MACE	114
Retatrutide[a]					
TRIUMPH-1[32] People with obesity or overweight NCT05929066	BMI ≥30 kg/m², or BMI ≥27 kg/m² with ≥1 BW-related comorbidity without T2DM	Retatrutide dose 1, dose 2 or dose 3 SC weekly	Placebo	Percent change from baseline in body weight	80
TRIUMPH-2[33] People with T2DM and obesity or overweight NCT05929079	T2DM and BMI ≥27 kg/m²	Retatrutide dose 1, dose 2 or dose 3 SC weekly	Placebo	Percent change from baseline in body weight	80
TRIUMPH-3[34] People with obesity and CV disease NCT05882045	BMI ≥35 kg/m² and established CV disease with ≥1 of the following: prior MI, prior ischaemic or haemorrhagic stroke, or symptomatic PAD	Retatrutide dose 1 or dose 2 SC weekly	Placebo	Percent change from baseline in body weight	80
TRIUMPH-4[35] People with obesity or overweight and knee OA NCT05931367	BMI ≥27 kg/m² and index knee pain for >12 weeks prior to screening and for >15 days over previous month, knee X-ray with moderate radiographic changes, meets ACR criteria for OA	Retatrutide dose 1 or dose 2 SC weekly	Placebo	Change from baseline in WOMAC Pain Subscale Score Percent change from baseline in body weight	68
TRIUMPH-5[36] People with obesity NCT06662383	BMI ≥27.0 kg/m²	Retatrutide SC weekly	Tirzepatide SC weekly	Percent change from baseline in body weight	89
TRIUMPH-6[37] Weight maintenance in people with obesity NCT06859268	BMI ≥27.0 kg/m²	Retatrutide dose 1 or dose 2 SC weekly	Placebo	Percent change from baseline in body weight	125
TRIUMPH-Outcomes[38] People with obesity and ASCVD and/or CKD NCT06383390	BMI ≥27.0 kg/m2, with or without T2DM, and established ASCVD and/or CKD	Retatrutide SC weekly	Placebo	Time to first occurrence of composite endpoints Time to first occurrence of composite endpoint of ESKD, ≥40% sustained decline in eGFR, CV death or renal death	248

[a]Study drug dose details are not provided on ClinicalTrials.gov.

A1C, glycosylated haemoglobin A1C; ACR, American College of Rheumatology; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BW, body weight; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; OA, osteoarthritis; PAD, peripheral arterial disease; SC, subcutaneous; T2DM, type 2 diabetes mellitus; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

challenges. Given the high pricing of similar agents currently on the market, these therapies may not be accessible to many patients without a clear demonstration of long-term cost-effectiveness. Payers are likely to demand robust outcome data beyond weight loss, including reductions in CV events, healthcare utilization and T2DM incidence. Until such data are available, inconsistent insurance coverage may limit uptake, particularly in countries or systems where anti-obesity medications are not routinely reimbursed. Real-world implementation may also be hindered by factors such as patient adherence to injectable therapies, GI side-effects and the need for structured titration protocols. Addressing these challenges will require multidisciplinary care models that integrate pharmacotherapy with nutritional counselling, behavioural support and chronic disease management.

Although GI-related side-effects are the most commonly reported with these agents, several metabolic and hormonal effects, whilst not yet fully characterized, warrant close attention as clinical use expands. Ongoing clinical trials are monitoring key parameters, including muscle mass and strength, bone turnover markers, resting heart rate and rhythm, and hormone panels that include cortisol, sex hormones and thyroid function. As clinical evidence matures, combination therapies and integration with lifestyle-based approaches may enhance long-term effectiveness and improve adherence.

Ultimately, long-term data will be essential to define the therapeutic role of each agent. Whilst initial weight loss with incretin-based therapies is common, sustaining that loss remains a challenge. Extended follow-up will reveal whether weight loss is maintained, plateaus or rebounds, and whether continued treatment is necessary to prevent regain. It will also clarify if treatment interruptions (for example, 'drug holidays') or dose reductions are feasible, or if long-term use of the maximum dose is needed to sustain efficacy or risks leading to desensitization. As clinical trials continue to evaluate these questions along with key metabolic and hormonal parameters, integrating GCGR-based multi-agonists with behavioural support may enhance long-term outcomes. If efficacy, safety and access challenges can be successfully addressed, these agents could significantly advance both individual obesity care and broader clinical practice.

Conclusion

GCGR-based multi-agonists represent an exciting new treatment paradigm for people living with overweight and obesity. These emerging agents, once approved, are likely to offer more substantial and sustained weight loss to people with overweight or obesity. They also have the potential to mitigate metabolic conditions commonly associated with overweight and obesity, including T2DM and CV disease. More data are needed to fully understand the role of each in therapy and their long-term safety profiles but the future of obesity treatment is bright.

Contributions: The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, takes responsibility for the integrity of the work as a whole, and has given approval for this version to be published.

Disclosure and potential conflicts of interest: The author declares no conflicts of interest relevant to this manuscript. The author is a Senior Editor for *Drugs in Context*. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2025/07/dic.2025-4-8-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/emerging-concepts-in-obesity-management-focus-on-glucagon-receptor-agonist-combinations

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Provenance: Invited; externally peer reviewed.

Submitted: 18 April 2025; **Accepted:** 2 July 2025; **Published:** 24 July 2025.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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