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Emerging Advances in Oral and Injectable Anti-Obesity Pharmacotherapies: A Review of Current Evidence

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ABSTRACT

GLP-1–based therapies have substantially reshaped the management of type 2 diabetes and obesity, prompting rapid development of next-generation anti-obesity medications. Liraglutide, semaglutide, and the dual GLP-1/GIP agonist tirzepatide are currently approved and induce mean body-weight reductions of approximately 6–8% and up to 23%, but with attenuated effects in individuals with type 2 diabetes.

This review synthesizes progress made over the past 1–2 years in the development of anti-obesity pharmacotherapies, including mono-agonists of injectable and oral GLP-1 and injectable amylin, dual GLP-1/amylin agonists, GLP-1/GIP agonists and antagonists, as well as GLP-1/glucagon co-agonists and GLP-1/GIP/glucagon triple agonists currently in development for the treatment of type 2 diabetes, obesity, and metabolic liver disease. Looking ahead, achieving mean body weight reductions exceeding 25% now appears feasible.

The adverse-event profile of GLP-1–based therapies is characterized primarily by gastrointestinal symptoms— including nausea, vomiting, constipation, and diarrhea— which can often be mitigated by initiating treatment at lower doses and employing a more gradual dose-escalation strategy.

GLP-1–based therapies are poised to increasingly shape treatment paradigms for obesity, type 2 diabetes, cardiovascular and kidney disease, fatty liver disease, sleep apnea, and osteoarthritis. Nevertheless, long-term weight maintenance remains a major unresolved challenge, and current evidence suggests that sustained pharmacological treatment may be required to mitigate weight regain.

Keywords: GLP-1 receptor agonist, GLP-1/GIP agonist, amylin agonist, GLP-1/amylin agonist, GLP-1/Glucagon, GLP-1/GIP/glucagon triple agonist, type 2 diabetes, overweight, obesity, MASLD.

Introduction

Obesity is a chronic, relapsing disease associated with numerous comorbidities[1]. It is defined as a body mass index (BMI) greater than 30 kg/m^2 [2]. In Western countries, more than 20% of the adult population is classified as obese, and in the United States the prevalence continues to rise, currently reaching approximately 42%[3]. Comorbid conditions commonly linked to obesity include, i.e. type 2 diabetes, metabolic syndrome, cardiovascular disease, obstructive sleep apnea, pain from arthrosis, and several obesity-associated cancers as well as psychiatric diseases[4]. The conditions also impose a substantial economic burden, primarily through elevated healthcare expenditures and diminished workforce productivity[2].

Management of obesity typically involves lifestyle modifications, primarily dietary changes and increased physical activity, pharmacological therapy, and for a minority of patients, bariatric surgery[2]. Life-style interventions may induce weight loss of about 5-10 kg, but most people will regain weight after 1-2 years[5]. Until recently, the weight loss with anti-obesity medications (AOM) was in the range of 3-8 kg[6].

Tirzepatide is a dual GLP-1/GIP receptor agonist[7]. In phase 3 clinical trials, semaglutide achieved average weight reductions of approximately 15–16%, whereas tirzepatide produced reductions of about 20–23%[7]. Both medications are administered as once-weekly subcutaneous injections.

Historically, pharmacologic treatment for obesity has been limited by modest efficacy, safety concerns, and poor patient acceptance. This landscape has changed substantially over the past five years with the development of GLP-1–based therapies, which have demonstrated weight-loss outcomes approaching those achieved with metabolic and bariatric surgery. The success of semaglutide and tirzepatide has catalyzed both scientific and commercial interest in anti-obesity pharmacotherapy. Industry investment in research has intensified, and the current therapeutic pipeline includes a wide array of highly potent dual and triple agonists, as well as orally administered small-molecule non-peptide agents.

This review examines the emerging anti-obesity medications that are poised to shape the next phase of therapeutic development. As the field rapidly evolves, clinicians, researchers, and policymakers must interpret an expanding and increasingly complex body of evidence. To support this effort, the review provides a comprehensive synthesis of current data on novel oral and injectable anti-obesity therapies, emphasizing their clinical efficacy and outlining considerations for future research.

The primary focus of the review is the competitive landscape poised to introduce the next generation of effective anti-obesity medications for regulatory approval within the next 1–3 years. Early-stage agents in phases 1 and 2, as well as phase 2 and 3 clinical trials published up to September 2024, have been reviewed previously and will therefore not be discussed in detail here[7]. Instead, this review will examine the most influential pivotal obesity trials conducted over the past five years to provide essential context for interpreting future research and drug development in obesity management.

Search methodology

Search was on publications on GLP-1 receptor agonist-based pharmacotherapies with focus on the last two years. Abstract programs from Obesity Week, European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) for 2024 until November 2025 and press release from relevant pharmacological companies were reviewed. Focus was on randomized-controlled trials written in English.

Physiology of GLP-1 and GIP

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones secreted from the intestine in response to nutrient ingestion, where they potentiate glucose-dependent insulin secretion from pancreatic

β-cells[8]. GLP-1 receptor agonists (GLP-1 RAs) were initially developed for the treatment of type 2 diabetes[9–11]. These agents mimic the actions of endogenous GLP-1 by enhancing insulin secretion, suppressing glucagon release, increasing satiety and thereby promoting weight loss, and delaying gastric emptying[11]. The effect on gastric emptying is most pronounced with short-acting GLP-1 RAs, as tachyphylaxis to this effect develops after only a few days of treatment with long-acting GLP-1 RAs[9]. GLP-1 agonists have also been shown to increase heart rate and reduce postprandial triglyceride levels as well as blood pressure[12]. Their anorectic effects involve activation of both peripheral and central GLP-1 receptors[13]. GLP-1 receptor agonists have anti-inflammatory actions, which may explain some of the beneficial cardiovascular effects[12].

Although GIP was discovered earlier than GLP-1, its physiology remains less well understood[14]. Much of what is known derives from rodent studies or from acute infusions of GIP or GIP-receptor antagonists in humans[14]. In addition to potentiating postprandial insulin secretion, GIP has been reported to stimulate glucagon release under normal or low glycaemic conditions, increase heart rate, and enhance blood flow to the intestine and subcutaneous adipose tissue, while also reducing bone resorption[14]. Preclinical studies suggest that adding GIP agonism to GLP-1 agonists may attenuate the gastrointestinal adverse effects commonly associated with GLP-1, thereby enabling the administration of higher doses of GLP-1/GIP co-agonists[15]. A dual role of GIP in lipid metabolism has also been described, whereby its lipogenic or lipolytic effects appear to depend on the presence or absence of insulin, respectively[14].

Acute GIP infusions have shown that its insulinotropic effects are diminished or absent in individuals with impaired glucose tolerance or established type 2 diabetes[16]. However, interest in GIP has increased following evidence that its insulinotropic responsiveness can be restored after weight-loss or pharmacological - induced improvements in glycaemia[16]. Moreover, the clinical development of the GLP-1/GIP receptor co-agonist tirzepatide has demonstrated substantially greater reductions in HbA1c and body weight compared with the GLP-1 RA semaglutide in trials involving individuals with type 2 diabetes and obesity[7]. In contrast, isolated GIP agonism has not shown clinical meaningful effects on appetite or food intake in human studies[14]. A comprehensive review of GIP physiology has recently been published[14].

Amylin physiology and amylin analogues

Amylin is a peptide hormone co-secreted with insulin from pancreatic β-cells. It acts as a satiety signal, slows gastric emptying, and suppresses the postprandial glucagon response - an effect likely mediated indirectly through delayed gastric emptying[17]. Several amylin analogues are currently in development for the treatment of obesity. The most extensively studied is *cagrilintide*, a long-acting amylin analogue[18]. Cagrilintide has been investigated both as monotherapy and in combination with GLP-1 receptor agonist semaglutide, including in the dual-hormone formulation *cagrisema* and in the unimolecular co-agonist *amycristin* as discussed below[19,20].

Glucagon physiology and GLP-1/glucagon dual-agonism:

In the liver, glucagon stimulates β-oxidation of lipids and inhibits de novo lipogenesis and reduces liver fat content[21,22]. Glucagon has also been shown to reduce food intake, potentially through activation of receptors in the hypothalamus and brainstem[21,22]. Although the effect of glucagon on energy expenditure in humans remains uncertain, several studies suggest that glucagon may enhance energy expenditure[21,22]. Glucagon increases blood glucose concentrations by promoting hepatic glucose production, making the balance between GLP-1 receptor agonism and glucagon receptor agonism a critical determinant of overall effects on glucose tolerance[23].

Oxyntomodulin, a peptide secreted from intestinal L-cells, is a naturally occurring dual agonist of the GLP-1 and glucagon receptors, though with approximately 1/100 of the potency of the native ligands[24]. Oxyntomodulin also suppresses appetite and reduces food intake[24].

Several long-acting GLP-1/glucagon co-agonists are currently in clinical development for the treatment of obesity, metabolic dysfunction–associated steatotic liver disease (MASLD), and metabolic dysfunction–associated steatohepatitis (MASH). These agents have demonstrated varying degrees of efficacy and differing adverse-event profiles, likely reflecting differences in the relative activities of GLP-1 versus glucagon within each co-agonist[23].

GLP-1 receptor unimolecular agonists

SEMAGLUTIDE

Semaglutide 2.4 mg once weekly (OW) has been approved since 2021 for the treatment of overweight and obesity. Its efficacy was evaluated in the Semaglutide Treatment Effect in People with Obesity (STEP) clinical program, which examined its use in obesity treatment and, in STEP 2, also in type 2 diabetes (reviewed in[7]). Across STEP 1–3 and STEP 5, semaglutide 2.4 mg OW induced weight reductions of approximately -15–17%, and a reduction of about - 9% to -10% in individuals with type 2 diabetes (STEP 2)[7]. Improvements in several cardiovascular risk factors were also reported. Semaglutide has also been investigated in adolelescents (12-18 years of age), resulting in a -13.9% weight reduction[25].

The phase 3 ESSENCE trial is a 240-week, double-blind study involving 1197 adults with MASH[26]. At week 72, semaglutide 2.4 mg demonstrated superior improvement in liver fibrosis (36.8% vs. 21.3%) as well as higher rates of steatohepatitis resolution (62.9% vs. 34.3%) compared with placebo. Mean change in body weight was -10.5% and -2.0%, respectively.

The safety and efficacy of semaglutide 2.4 mg OW were further evaluated in the SELECT trial, which included 17,600 individuals with obesity but without diabetes, all of whom had established cardiovascular disease[27]. After a median follow-up of 3.8 years, semaglutide reduced the incidence of major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke by 20% compared with placebo. Semaglutide was also superior in reducing each individual component of the composite endpoint. Weight loss in the SELECT trial, achieved without structured lifestyle intervention, was approximately - 9.4% with semaglutide versus -1% with placebo. Adverse events leading to treatment discontinuation occurred in 16.6% of participants receiving semaglutide and 8.2% receiving placebo.

Additionally, semaglutide 2.4 mg OW improved symptoms in individuals with heart failure with preserved ejection fraction[28]. In Patients with type 2 diabetes and peripheral artery disease semaglutide increased walking distance, claudication pain and quality of life after 52 weeks[29].

STEP UP TRIALS - SEMAGLUTIDE 7.2 mg OW

Modelling and simulation of semaglutide 2.4 mg have suggested that doses higher than the approved 2.4 mg may yield further body-weight reduction.

Recently, results from the phase 3b *STEP UP* trial were presented[30]. This randomized, double-blind, placebo-controlled study (n = 1,407) investigated a high dose of semaglutide 7.2 mg once weekly (OW) compared with semaglutide 2.4 mg OW and placebo in adults with BMI ≥ 30 kg/m² (mean BMI 39.9 kg/m²; mean body weight 113.0 kg) without diabetes. Semaglutide was initiated at 0.25 mg OW and escalated every 4 weeks to 2.4 mg at week 16 and to 7.2 mg at week 20. A lifestyle intervention targeting a daily caloric deficit of 500 kcal and at least 150 minutes of weekly physical activity was part of the study protocol. Participants assigned to the 2.4 mg group maintained the 2.4 mg dose from week 16 onward.

After 72 weeks, mean weight loss was −18.7% with semaglutide 7.2 mg, −15.6% with semaglutide 2.4

mg, and −3.9% with placebo. Nearly one-third of participants receiving 7.2 mg achieved ≥25% body-weight reduction. Total fat mass was reduced by -25.1%, while lean body mass decreased by - 6.7% with semaglutide 7.2 mg. Among participants with prediabetes, 83.4% reverted to normoglycaemia with 7.2 mg, compared with 73.8% with 2.4 mg and 36.6% with placebo. Cardiovascular risk factors showed modestly greater improvement with semaglutide 7.2 mg compared with 2.4 mg[30].

Gastrointestinal adverse events were more common with semaglutide 7.2 mg (70.8%) than with 2.4 mg (61.2%) or placebo (42.8%), with vomiting occurring more frequently in the 7.2 mg group. The adverse event skin dysaesthesia was also more prevalent with semaglutide 7.2 mg (22.0%) versus 2.4 mg (6.0%) and placebo (0.5%)[30]. Dysaesthesia encompassed altered skin sensations such as allodynia, burning, hyperaesthesia, and skin discomfort. Permanent discontinuation of trial medication occurred in 5.4% (7.2 mg), 4.0% (2.4 mg), and 1.0% (placebo). The findings suggest that the 7.2 mg dose may provide additional benefit for patients requiring greater weight loss. Notably, the nadir of weight loss had not been reached at week 72 for the 7.2 mg group.

In the parallel phase 3a *STEP UP T2D* trial, semaglutide 7.2 mg OW was evaluated versus semaglutide 2.4 mg OW and placebo in adults with type 2 diabetes (n = 512; mean BMI 38.6 kg/m²; mean body weight 110.1 kg; mean HbA1c 8.1%; diabetes duration 8.4 years)[31]. Most participants were treated with metformin (92.4%), followed by SGLT2 inhibitors (28.9%), sulfonylureas (27.9%), thiazolidinediones (2.1%), DPP-4 inhibitors (1.6%), and α-glucosidase inhibitors (0.8%). Titration followed the same schedule as in STEP UP.

At week 72, treatment adherence remained high: 90.6% for semaglutide 7.2 mg, 91.3% for 2.4 mg, and 83.3% for placebo[31]. The maximum dose was reached by 74.8% in the 7.2 mg group, 85.1% in the 2.4 mg group, and 98.8% in the placebo group. Mean weight reductions were −13.2% (7.2 mg), −10.4% (2.4 mg), and −3.9% (placebo). HbA1c reductions were similar in both semaglutide groups (−1.5% each) compared with placebo. The proportions achieving HbA1c ≤6.5% were 72.6% (7.2 mg), 66.7% (2.4 mg), and 16.0% (placebo); corresponding values for HbA1c <5.7% were 25.0%, 17.7%, and 5.3%, respectively. Improvements in cardiovascular risk factors did not differ between semaglutide doses. Hypoglycaemia risk was low (~2%) and similar across groups, despite nearly 28% of participants receiving sulfonylureas. Gastrointestinal adverse events were reported in 53.1% (7.2 mg), 51.5% (2.4 mg), and 25.5% (placebo). Serious adverse events were comparable between groups.

Skin dysaesthesia occurred more often with semaglutide 7.2 mg (18.9%) than with 2.4 mg (4.9%) or placebo (0%). Most events resolved during treatment without dose adjustment, and only one participant discontinued semaglutide 7.2 mg due to dysaesthesia. The underlying mechanism remains unknown.

Overall, semaglutide 7.2 mg produced greater weight loss than 2.4 mg, without additional benefit in HbA1c reduction or cardiovascular risk-factor improvement[31]. The magnitudes of change in body weight and HbA1c are similar to those reported in the SURMOUNT-2 trial with tirzepatide, although comparisons between trials should be interpreted with caution[32]. Both STEP UP studies demonstrated gastrointestinal adverse event rates comparable to those of the 2.4 mg dose; however, skin dysaesthesia was more frequently observed with 7.2 mg.

Semaglutide 7.2 mg OW is submitted to the US Food and Drug Administration (FDA) for approval.

HIGH-DOSE SEMAGLUTIDE 16 mg OW

In a phase 2 trial, high-dose semaglutide up to 16 mg OW for 40 weeks was evaluated in individuals with type 2 diabetes and overweight or obesity (mean BMI 37.5 kg/m²)[33]. Doses were escalated every 4 weeks. HbA1c reductions were 1.8% (8 mg) and 2.1% (16 mg) compared with 1.85% with semaglutide 2 mg, likely reflecting a floor effect given the relatively low baseline HbA1c (8.35%). Weight loss was 9.3% (8

mg), 11.7% (16 mg), and 8.3% (2 mg). Gastrointestinal adverse events were dose-dependent, and discontinuation rates due to adverse events were 23% (8 mg), 18% (16 mg), and 7% (2 mg). Dysaesthesia occurred in 8% (8 mg), 18% (16 mg), and 0% (2 mg). The modest incremental improvements in HbA1c and weight relative to 2 mg do not appear to justify the substantially increased adverse-event burden, although dosing flexibility may mitigate this[33].

Ecnoglutide

Ecnoglutide is a novel biased GLP-1 receptor agonist developed in China. In a phase 3 study, 664 adults with overweight or obesity were randomized to receive ecnoglutide 1.2 mg, 1.8 mg, 2.4 mg, or placebo once weekly (OW)[34]. The starting dose was 0.3 mg, with escalation every 4 weeks to 0.6 mg, 1.2 mg, 1.8 mg, or 2.4 mg by week 20. The half-life of ecnoglutide is approximately 124–138 hours. At week 40, mean percentage changes in body weight were –9.1% (1.2 mg), –10.9% (1.8 mg), and –13.2% (2.4 mg) compared with 0.1% with placebo. Cardiovascular risk factors improved across all ecnoglutide groups. Serious adverse events occurred in 5.4%, 9.0%, 6.0%, and 4.9% of participants, respectively. Overall, 2% of participants discontinued treatment.

A second study evaluated ecnoglutide in adults with type 2 diabetes treated with metformin (n = 623; mean HbA1c 8.4%)[35]. Participants were randomized to ecnoglutide 0.6 mg, ecnoglutide 1.2 mg, or dulaglutide 1.5 mg for 52 weeks. At week 32, reductions in HbA1c were −1.91%, −1.89%, and −1.65%, respectively. HbA1c improvements were sustained through week 52. Weight loss was - 5.2 kg, - 5.7 kg, and - 2.8 kg, respectively, consistent with findings from a previous phase 2 study[36].

EFPEGLENATIDE

Is a long acting GLP-1 RA developed from exenatide. Efpeglenatide has completed several phase 3 studies in people with type 2 diabetes or obesity and has shown cardiovascular and renal benefits and is not yet approved for clinical use[37].

MET-097i

This GLP-1 RA from Metsera is an ultralong-acting, biased GLP-1 receptor agonist designed for once-monthly dosing. In a phase 2 study (n = 239), the placebo-subtracted weight loss reached up to 14.1% at the 1.2 mg dose after 28 weeks. Treatment was well tolerated, with risk differences versus placebo of 13% for nausea and 11% for vomiting, and a low study-discontinuation rate of 2.9% (press release, Metsera, 29. September 2025). The company, recently acquired by Pfizer after strong competitive interest from Novo Nordisk A/S is now initiating phase 3 clinical development.

ORAL SEMAGLUTIDE

Oral administration offers advantages in convenience and adherence compared with injectable formulations but challenges in relation to absorption. Oral semaglutide up to 14 mg once daily (OD) was investigated in people with type 2 diabetes in the *PIONEER* clinical program[7]. In seven PIONEER trials the 14 mg daily led to a weight reduction in HbA1c between - 0.7% to -2.6% with greater reductions seen in higher baseline HbA1c levels and -3.2 kg to -7.1 kg weight loss after 52 weeks of treatment in patients with type 2 diabetes[38]. In *PIONEER 6* after 15.9 months follow-up in patients with type 2 diabetes (n=3183) the cardiovascular risk profile with semaglutide did not differ significantly from placebo, while cardiovascular and total mortality was less with semaglutide[39]. The reduction from baseline in HbA1c (-1.0 vs -0.3%) and body weight (-4.2 kg vs -0.8 kg) decreased more with oral semaglutide than in the placebo group. In the *SOUL* cardiovascular outcomes trial (n = 9,650), oral semaglutide reduced major adverse cardiovascular events (MACE) by 14% and kidney disease progression by 9% after 4 years of follow-up[40]. Major adverse limb events were reduced by 29%[40].

In a phase 3 study *OASIS 1* evaluating oral semaglutide 50 mg in adults with overweight or obesity, 667 participants were randomized to oral semaglutide, escalated to 50 mg daily, or placebo for 68 weeks[41]. Treatment began at 3 mg and was escalated to 7

mg, 14 mg, 25 mg, and finally 50 mg at week 16. After 68 weeks, mean body-weight reduction was −15.1% with oral semaglutide versus −2.4% with placebo. Altered skin sensation was reported by 42 participants (12.5%) on semaglutide compared with 4 (1.2%) on placebo.

In the *PIONEER PLUS* trial involving adults with type 2 diabetes (mean HbA1c 9.0%, mean BMI 33.8 kg/m²), the efficacy and safety of oral semaglutide 14 mg, 25 mg, and 50 mg OD were compared[42]. After 52 weeks, weight reductions were −4.4 kg, −7.0 kg, and −8.0 kg, respectively. Corresponding HbA1c reductions were −1.5%, −1.8%, and −2.0%. Treatment completion rates were 83%, 79%, and 81%, respectively.

Recently, results from the phase 3 *OASIS 4* trial were published[43]. This 71-week, double-blind, randomized, placebo-controlled study evaluated oral semaglutide 25 mg OD in people with obesity but without diabetes (n = 205; baseline BMI 37.3–37.6 kg/m²; mean body weight 105.9 kg). Oral semaglutide was initiated at 3 mg OD and escalated to 7 mg, 14 mg, and 25 mg by week 12. In total, 81.4% of participants in the semaglutide group and 74.5% in the placebo group completed the trial; among completers, 81.4% reached the final 25 mg dose.

The mean change in body weight from baseline to week 64 was −13.6% with oral semaglutide versus −2.2% with placebo. Furthermore, 29.7% of semaglutide-treated participants achieved ≥20% weight loss compared with 3.3% receiving placebo. Improvements in quality of life and physical-function scores were also observed. Among participants with prediabetes at baseline, 71.1% reverted to normoglycaemia by week 64. Skin dysaesthesia was reported in 4.9% of semaglutide-treated participants and in none of the placebo group. Adverse events leading to permanent discontinuation occurred in 6.9% and 5.9%, respectively. Oral semaglutide 25 mg OD has been submitted for regulatory approval in the United States and the European Union.

Orforglipron

A major advance is the development of non-peptide small molecules that require no absorption enhancer and can be readily scaled for large-scale manufacturing. Orforglipron can be administered irrespective of fasting status, providing greater flexibility in treatment.

Orforglipron, a small-molecule, nonpeptide oral glucagon-like peptide-1 receptor agonist, has been investigated as a treatment for obesity in the phase 3 *ATTAIN-1* trial[44]. In this 72-week study, daily doses of 6 mg, 12 mg, or 36 mg were compared with placebo. Orforglipron was initiated at 1 mg daily and escalated every 4 weeks to the assigned dose (6 mg at week 8, 12 mg at week 12, and 36 mg at week 20). A total of 3,127 participants (mean body weight 103.2 kg, mean BMI 37.0 kg/m²), all without type 2 diabetes, were randomized. The trial was completed by 85.1% of participants, with no significant differences between groups. Overall, 25% of participants discontinued treatment in the orforglipron groups compared with 29.9% in the placebo group.

After 72 weeks, mean percentage weight changes were −7.5% (6 mg), −8.4% (12 mg), and −11.2% (36 mg) compared with −2.1% with placebo. In the 36 mg group, 36.0% of participants achieved ≥15% weight loss and 18.4% achieved ≥20% weight loss[44]. Cardiovascular risk factors improved in all orforglipron groups relative to placebo. Body composition analysis showed that 73.1% of weight reduction was due to fat-mass loss and 26.9% due to lean-mass loss. Adverse events leading to treatment discontinuation occurred in 5.3%–10.3% of orforglipron treated participants and 2.7% in the placebo group. Discontinuation due to gastrointestinal adverse events occurred in 3.5%–7.0% versus 0.4% in the placebo group. Five cases of mild pancreatitis were reported with orforglipron, and seven participants had aminotransferase elevations ≥10 times the upper limit of normal[44].

In the *ACHIEVE-1* phase 3 trial, orforglipron was evaluated in adults with type 2 diabetes at doses of

3 mg, 6 mg, and 36 mg once daily, using the same stepwise escalation schedule as in ATTAIN-1[45]. Of 559 participants (mean HbA1c 8.0%; mean body weight 90.2 kg; mean BMI 33.0 kg/m²; diabetes duration 4.4 years), all were treated with diet and exercise alone prior to randomization. A total of 94.1% completed the trial, and 90.2% continued treatment through week 40[45].

At week 40, mean HbA1c reductions were −1.24% (3 mg), −1.47% (6 mg), and −1.48% (36 mg) compared with −0.41% with placebo, resulting in end-of-study HbA1c values of 6.5–6.7%. The HbA1c target of <7.0% was achieved in 73% of participants receiving 6 mg and 33% receiving placebo. The more stringent target of HbA1c <5.7% was reached in 24% (36 mg) and 4%, respectively. Weight reductions were −4.5% (3 mg), −5.8% (6 mg), and −7.6% (36 mg) compared with −1.7% with placebo. Gastrointestinal adverse events were the most frequent, and discontinuation due to gastrointestinal events occurred in 2.2%–5.7% of orforglipron-treated participants and none in the placebo group. Serious adverse events did not differ between groups, and no cases of severe hypoglycaemia or pancreatitis were observed. Aminotransferase levels decreased during the trial. Permanent discontinuation due to adverse events occurred in 4.4%–7.8% of orforglipron-treated participants and 1.4% of placebo recipients[45].

Orforglipron has also been evaluated in the *ACHIEVE-3* trial (press release, Eli Lilly), a 52-week comparison with oral semaglutide. A total of 1,608 adults with type 2 diabetes (mean HbA1c 8.3%), all receiving metformin, were randomized to orforglipron 12 mg, orforglipron 36 mg, or oral semaglutide 7 mg or 14 mg once daily. Reductions in HbA1c from baseline were −1.7% (12 mg) and −1.9% (36 mg) with orforglipron compared with −1.2% and −1.5% with semaglutide 7 mg and 14 mg, respectively. Weight reductions were −6.1%, −8.2%, −3.9%, and −5.3%, respectively. The percentages of participants achieving HbA1c <5.7% were 21.4% (12 mg), 31.4% (36 mg), 7.4% (semaglutide 7 mg), and 11.7% (semaglutide 14 mg). Orforglipron also improved cardiovascular risk factors. Most adverse events were gastrointestinal, and treatment-discontinuation rates were 8.7%, 9.7%, 4.5%, and 4.9%, respectively. Eli Lilly has announced plans to submit orforglipron for FDA approval in Q1 2026.

Development of oral **danuglipron** is halt because of due to 50% discontinuation because of Gastrointestinal side effects including hepatotoxicity (Press release Pfizer).

Unimolecular amylin agonists

Amylin is secreted from the beta-cells in the pancreas and functions as a satiety signal, slows gastric emptying and suppresses postprandial glucagon response to a meal (although probably by slowing gastric emptying)[46]. It has been suggested that amylin attenuate metabolic adaptation after weight loss due to counteraction of the reduction in energy expenditure associated with weight loss[47].

CAGRILINTIDE

Cagrilintide is a long-acting amylin analogue. In a 26-week, dose-finding phase 2 trial, adults without diabetes and with a mean BMI of 37.8 kg/m² were randomized to once-weekly subcutaneous cagrilintide at doses of 0.3, 0.6, 1.2, 2.4, or 4.5 mg; once-daily liraglutide 3.0 mg; or placebo[18]. Approximately 10% of participants discontinued treatment, with similar rates across groups.

Mean weight loss at week 26 was −10.8% with cagrilintide 4.5 mg, compared with −9% with liraglutide 3.0 mg and −3% with placebo. For the highest cagrilintide doses, weight loss did not appear to have reached a plateau by week 26. Gastrointestinal adverse events occurred in 40–63% of participants receiving cagrilintide, compared with 32% with placebo and 60% with liraglutide, and were dose-dependent. Reductions in systolic and diastolic blood pressure were observed with cagrilintide but were not significantly different from placebo; heart rate did not differ from placebo[18].

Cagrilintide has also been further evaluated in combination with semaglutide 2.4 mg (*CagriSema*) as discussed below[19,48,49, 50].

ELORALINTIDE

Eli Lilly recently announced results for eloralintide, a selective amylin agonist administered once weekly (OW), from a phase 2 study involving 263 adults with overweight or obesity (mean BMI 39.1 kg/m²)[51]. After 48 weeks of treatment, a dose-dependent weight loss was observed, ranging from - 9.5% (1 mg OW) to - 20.1% (9 mg OW), compared with - 0.45% with placebo. Improvements in lipid profiles and C-reactive protein were also greater with eloralintide. The most common adverse events were gastrointestinal symptoms and fatigue (up to 20% vs. 0.4% with placebo), both of which were dose-dependent up to the 9 mg dose. Treatment discontinuation occurred in 21% of participants receiving 6 mg compared with 8% receiving placebo. It remains unclear whether eloralintide produces fewer side effects than GLP-1 receptor agonists or what mechanisms may underlie the reported fatigue[51].

OTHER GLP-1/AMYLIN AGONISTS

Several biotech companies also have amylin agonists in early development, including GUBAR (**Gubamy** OW), Zealand Pharma (**petrelintide** OW), and Metsera (**MET-233** for once-monthly administration).

Dual GLP-1/amylin agonists

CAGRISEMA

The phase 3a *REDEFINE 1* study evaluated the efficacy and safety of the combination of semaglutide and cagrilintide (CagriSema) in adults with overweight or obesity but without diabetes (n = 3,417; mean body weight 106.9 kg; BMI 37.9 kg/m²; 32.1% with prediabetes)[50]. Participants were randomized to once-weekly semaglutide up to 2.4 mg plus cagrilintide up to 2.4 mg, semaglutide 2.4 mg alone, cagrilintide 2.4 mg alone, or placebo. The maximal dose of each drug was reached by week 16.

At week 68, retention rates were 88.2% in the CagriSema group, 91.4% with semaglutide, 87.7% with cagrilintide, and 75.9% with placebo. Among participants still on treatment at week 68, the proportions receiving the maximal assigned dose were 54.7%, 70.9%, 82.5%, and 70.6%, respectively[50]. Dose reduction or delayed escalation was permitted in cases of intolerable side effects or if participants approached the lower end of the normal BMI range.

After 68 weeks, mean weight loss was −20.4% with CagriSema compared with −14.9% with semaglutide 2.4 mg, −11.5% with cagrilintide 2.4 mg, and −3.0% with placebo (68). With CagriSema, 67% of total weight loss was attributable to reductions in fat mass and 33% to reductions in lean soft tissue mass. Improvements in cardiovascular risk factors were observed. Among participants with prediabetes at baseline, 87.7% achieved normoglycaemia with CagriSema versus 32.2% with placebo.

The most frequently reported adverse events were gastrointestinal, occurring in 79.6%, 73.8%, 54.0%, and 39.9% of participants in the CagriSema, semaglutide, cagrilintide, and placebo groups, respectively. Discontinuation rates due to adverse events were 5.9%, 3.6%, 2.6%, and 3.5%, respectively. The safety profile was consistent with that known for GLP-1 receptor agonists[50].

Thus, the weight loss achieved with CagriSema represents one of the greatest magnitudes reported for any existing anti-obesity medication. The ability to adjust doses flexibly likely explains why not all participants reached the target dose of 2.4 mg for each component drug.

In the *REDEFINE 2* trial, 1,206 adults with overweight or obesity and type 2 diabetes (mean body weight 102.2 kg; BMI 36.2 kg/m²; mean HbA1c 8.0%) were randomized to CagriSema 2.4 mg or placebo once weekly for 68 weeks[49]. Dose escalation began at 0.25 mg OW and increased every 4 weeks to 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg. Background glucose-lowering therapy included metformin (85.9%), SGLT2 inhibitors (33.4%), and sulfonylureas (26.9%)[49].

After 68 weeks, mean weight loss was −13.7% with CagriSema versus −3.4% with placebo. A weight loss of ≥20% was achieved in 22.9% of participants receiving CagriSema compared with 0.5% receiving

placebo. HbA1c was reduced by −1.8% with CagriSema and −0.4% with placebo, and 73.5% versus 15.9% achieved HbA1c ≤6.5%.

Continuous glucose monitoring (CGM) showed an increase in time in range (3.8–10 mmol/L) from 43.6% at baseline to 86.8% at week 68 in the CagriSema group, compared with from 41.3% to 50.2% in the placebo group. CagriSema also improved cardiovascular risk factors, CRP, and physical-function scores. Serious adverse events did not differ between groups[49].

Gastrointestinal adverse events occurred in 72.5% of CagriSema-treated participants and 34.4% of the placebo group. Discontinuation due to adverse events occurred in 8.4% and 3.0%, respectively. Level 2 hypoglycaemia occurred in 3.3% of the CagriSema group and 0.2% of the placebo group, despite ~27% being treated with sulfonylureas. At week 68, 61.9% of CagriSema-treated participants and 80.5% of placebo-treated participants remained on the highest dose[49].

Thus, CagriSema produced clinically meaningful weight loss in adults with overweight or obesity and in type 2 diabetes, accompanied by near-normoglycaemic glycaemic control and substantially improved CGM time-in-range, with a low incidence of hypoglycaemia despite concomitant sulfonylurea use in 27% of participants. The weight loss achieved is comparable to or greater than those seen with tirzepatide 10 mg and 15 mg[7]. CagriSema is currently being directly compared with tirzepatide in patients with obesity (NCT06131437) and type 2 diabetes (NCT06534411).

AMYCRETIN

Amycretin is a novel, unimolecular GLP-1 and amylin receptor agonist. In a small phase 1b/2a study, 125 participants were allocated to various doses and dose-escalation regimens of once-weekly subcutaneous amycretin or placebo[20]. After 36 weeks of treatment, mean body-weight reductions were −24.3% with amycretin 60 mg (vs. −1.1% with placebo), −22.0% with 20 mg OW (vs. −1.9%), and −16.2% with 5 mg OW (vs. −2.3%). The prevalence of adverse events was high, and withdrawal rates were substantial (up to 59%), with a clear dose-dependent pattern; however, the nature of adverse events was consistent with what is typically observed for GLP-1–based therapies. Slower dose escalation and smaller dose increments are expected to improve tolerability in future trials (NCT06542874). The half-life of amycretin is approximately 4 days, with peak exposure occurring 1.0–1.5 days after injection, supporting once-weekly subcutaneous dosing[20].

In a phase 1 study of oral amycretin (administered as 2 × 50 mg in a single daily dose) in adults with overweight or obesity, the mean weight reduction after 12 weeks was -13.1%, which exceeds that reported for any other oral obesity pharmacotherapy to date[20]. The mean time to maximum amycretin concentration was approximately 0.7 hours after dosing, and the mean half-life was 92–100 hours[20]. Adverse events were consistent with the known GLP-1–based therapy class and were generally mild to moderate. Oral amycretin was administered in the fasting state.

In a phase 2 study in people with type 2 diabetes treated with metformin with or without SGLT2i with doses from 0.4 mg to 40 mg with amycretin OW the reduction in HbA1c was up to -1.8% from a baseline of 7.8% after 36 weeks. (Novo Nordisk press release 25. November 2025). The proportions of people achieving HbA1c < 7.0% and < 6.5% was 89.1% and 76.2%, respectively. Weight loss was up to -14.5% compared to -2.6% with placebo.

In participants treated with oral amycrestin 6 mg, 25 mg and 50 mg, the reduction in Hba1c was up to -1.5% from a baseline of 8.0% after 36 weeks. In total, 77.6% and 62.6% achieved a HbA1c below 7.0% and 6.5%, respectively. Weight loss was up to -10.1% compared with - 2.5% with placebo.

Amycretin is currently being evaluated in phase 3 clinical trials both as an injectable formulation and as an oral tablet.

Dual GLP-1/GIP agonists

TIRZEPATIDE

The unimolecular GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual agonist tirzepatide has been approved for the treatment of type 2 diabetes and, since 2023, for the treatment of overweight and obesity[7]. Tirzepatide is a biased GLP-1 RA[52]. In clinical trials, tirzepatide has produced weight reductions of approximately 11–14% in individuals with type 2 diabetes and around 20–23% in individuals with overweight or obesity[7]. Tirzepatide has also been shown to reduce the risk of cardiovascular diseases including heart failure, kidney disease (reported at the 2025 EASD meeting in Vienna) as well as improving MASH and sleep apnea[7].

MARIDEBART CAFRAGLUTIDE

Maridebart cafraglutide (previously known as mariTide) is a long-acting peptide–antibody conjugate that links two GLP-1 receptor agonist analogues to a single monoclonal antibody targeting the GIP receptor as an antagonist[53]. It has an extended half-life of approximately 21 days, enabling dosing every 4 weeks[53].

In a 52-week phase 2 obesity trial, 592 participants (mean BMI 37.9 kg/m²) were randomized to receive maridebart cafraglutide at doses of 140, 280, or 420 mg every 4 weeks without dose escalation; 480 mg every 8 weeks without escalation; or 420 mg every 4 weeks with either 4-week or 12-week dose escalation; or placebo[53]. Completion rates ranged from 67% to 82% in the maridebart cafraglutide groups versus 62% with placebo. Body-weight reductions ranged from −12.3% to −16.2% across active treatment groups, with no clear plateau reached by week 52, compared with −2.5% with placebo. Fat mass was reduced by −26.2% to −38.8%, and lean mass by −8.6% to −11.6%. No substantial changes in bone mineral density were observed. The most frequently reported adverse events were gastrointestinal, and discontinuation rates reached up to 27%.

In a second study of adults with obesity and type 2 diabetes (n = 127; mean BMI 36.5 kg/m²; mean HbA1c 7.8%), maridebart cafraglutide 140, 280, or 420 mg every 4 weeks (without dose escalation) was evaluated[53]. Completion rates were 59% to 81% in the maridebart cafraglutide groups versus 69% with placebo. Weight loss ranged from −8.4% to −12.3% with maridebart cafraglutide compared with −1.7% with placebo, and HbA1c reductions ranged from −1.2% to −1.6%[53].

Maridebart cafraglutide is currently in phase 3 development, with treatment initiated at 21 mg and gradually escalated to target doses of 140 mg, 210 mg, or 350 mg every 4 weeks.

Maridebart cafraglutide is as mentioned a GIP antagonist. One hypothesis explaining the effect of GIP antagonism in respect to effect on body weight and HbA1c is that GIP agonism per se also leads to desensitization of the receptor and function as an antagonist based on the concept of receptor downregulation[54,55] .

VK 2735

Is a dual GLP-1/GIP dual agonist. In a phase 2 study was the weight loss after 13 weeks up to - 14.7% and as oral formulation -12.2% after 13 weeks (press release Viking Therapeutics). Phase 3 program VANQUISH for subcutaneous dosing once weekly is initiated.

NNC0090

Is an unimolecular dual GLP1-1/GIP agonist OD, but the weight loss after 12 weeks did not differ from liraglutide 1.8 mg daily and development in phase 3 was stopped[56].

CT388

CT-388 is a once-weekly subcutaneous investigational agent that functions as a dual agonist of the GLP-1 and GIP receptors. The GLP-1 component has been engineered using a biased-signaling strategy. In a phase Ib, randomized, placebo-controlled clinical trial of CT-388 in adults with obesity the mean placebo-adjusted mean weight reduction of approximately

-18.8% at week 24[57]. CT-388 has progressed into Phase 2 clinical development.

GLP-1/glucagon dual agonists

Several long-acting GLP-1/glucagon analogues are in clinical development for the treatment of obesity, MASLD, and MASH. These compounds show varying efficacy and tolerability profiles, likely reflecting differences in the relative GLP-1 and glucagon receptor activities of each co-agonist[23,24].

SURVODUTIDE

Among GLP-1(biased)/glucagon dual agonists, the phase 2 results for survodutide (T½ about 100 Hours) in people with overweight or obesity are of interest[58]. In this 46-week trial, participants were randomized to survodutide 0.6, 2.4, 3.6, or 4.8 mg once weekly, or placebo. Treatment included a 20-week titration phase with dose increases every second week, followed by a 26-week maintenance phase. A total of 387 adults (mean BMI 37.1 kg/m²; mean body weight 105.7 kg) were enrolled. At week 46, the greatest weight loss was observed with survodutide 4.8 mg (−14.9%).

In a 16-week phase 2 study in adults with type 2 diabetes (n = 413; mean HbA1c 8.1%) treated with metformin, participants were randomized to survodutide, placebo, or semaglutide up to 1 mg once weekly[59]. Survodutide reduced HbA1c by up to −1.7% compared with −1.5% for semaglutide. Weight loss was dose-dependent, reaching −8.7% with survodutide, greater than the −5.3% with semaglutide. Gastrointestinal adverse events were reported in 77.8% of survodutide-treated participants, compared with 52.0% and 52.5% in the semaglutide and placebo groups, respectively.

In a 48-week phase 2 biopsy-confirmed MASH trial involving 393 participants with fibrosis stage 1–3, survodutide improved MASH with no worsening of fibrosis in up to 62% of participants, compared with 14% in the placebo group[60].

Survodutide is currently in phase 3 development (NCT06066528) including a CVOT (NCT06077864), with the first results expected in Q1 2026.

MAZDUTIDE

Mazdutide (also known as IBI362 or LY3305677) is a once-weekly analogue of oxyntomodulin[61]. In a phase 2 randomized trial including 248 participants (mean BMI 31.8 kg/m²; mean body weight 90 kg), 24-week weight reductions were −6.7% with 3 mg, −10.4% with 4.5 mg, −11.3% with 6 mg, and +1% with placebo[62]. Reductions in HbA1c, fasting glucose, HOMA-IR, lipids, and blood pressure were observed across all mazdutide doses. Adverse events were consistent with the known GLP-1 receptor agonist class effects. In another trial the reduction in HbA1c and body weight were greater than with dulaglutide after 20 weeks[63]. Mazdutide is currently in phase 3 development in China in adults with obesity or type 2 diabetes (NCT05607680; NCT05606913).

COTADUTIDE

Is a dual GLP-1/glucagon agonist for once weekly administration[64,65]. Its development for MASLD and chronic kidney disease was discontinued at the level of phase 2 development.

SAR425899

Is a novel dual agonist and in a phase 2 trial the postprandial glycaemic control was better than with liraglutide[66].

EFINOPEGDUTIDE

Is a dual GLP-1/glucagon agonist causing weight loss in obese individual with type 2 diabetes comparable to semaglutide, however, with no effect on HbA1c. in a phase 2 study efinopegdutide reduced liver fat more than semaglutide 1 mg (72.7% vs 42.3%) after 24 weeks in people with MAFLD. Reduction from baseline in body weight at Week 24 did not differ (efinopegdutide 8.5% vs. semaglutide 7.1%). Slightly higher incidences of adverse events and drug-related adverse events were observed in the efinopegdutide group compared with semaglutide, primarily related to an imbalance in gastrointestinal events [67] .

PEMVIDUTIDE

Is a GLP-1/glucagon dual receptor agonist. In people with MASH (n=212) pemvidutide in a phase 2b study reduces liver fat without fibrosis worsening in

58% in the 1.8 mg group compared with 24% with placebo after 24 weeks[68]. Improvement in fibrosis was observed in 36% and 28%, respectively. Pemvidutide was well-tolerated and discontinuation rate was 1% in the highest 1.8 mg dose and 2% in the placebo group[68].

In 391 subjects with obesity or overweight the weight loss was after 48 weeks -10.3%, -11.2% and -15.6% with 1.2 mg, 1.8mg and 2.4 mg, respectively, compared with -2.2% with placebo[69]. Patients in the active groups were still losing weight at week 48. Pemvidutide resulted in reductions in lipids and improvements in blood pressure. Pemvidutide is planned to start phase 3 development.

GLP-1 based triple agonists

Retatrutide is a monomolecular triple agonist targeting the GLP-1, GIP, and glucagon receptors, currently in development for the treatment of type 2 diabetes and obesity[70].

In a phase 2, double-blind, randomized, placebo-controlled trial, participants received 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), 12 mg (initial dose 2 mg), or placebo once weekly for 48 weeks. A total of 338 adults with a mean BMI of 37.3 kg/m² (mean body weight 107.7 kg) were enrolled[71]. After 48 weeks, weight loss reached −24.2% in the 12 mg group compared with −2.1% with placebo; 83% of participants receiving 12 mg lost ≥15% of baseline weight, and 26% lost ≥30%. Greater percentage reductions in body weight were observed in participants with BMI ≥35 compared with those <35 (12 mg: 26.5% vs. 22.1%), and among women compared with men (28.5% vs. 21.9%). Weight-loss trajectories suggested that a plateau had not yet been reached at week 48.

The most common adverse events were gastrointestinal, dose-related, and generally mild to moderate in severity, partly mitigated by lower starting doses. Discontinuation due to adverse events occurred in 6–16% of participants receiving retatrutide, versus none in the placebo group. Heart rate increased in a dose-dependent manner up to week 24 before declining thereafter. Cutaneous hyperesthesia and increased skin sensitivity were reported in 7% of retatrutide-treated participants. Retatrutide also improved blood pressure, fasting glucose, and lipid parameters. Among participants with prediabetes, 72% reverted to normoglycaemia (HbA1c <5.7% [38 mmol/mol]). Completion rates ranged from 74% to 88% across retatrutide groups versus 71% with placebo[71].

In a substudy of this trial, 98 participants with ≥10% liver fat content assessed by MRI were included[72]. At 48 weeks, reductions in liver fat content were −51.3%, −59.0%, −81.7%, and −86.0% with the 1, 4, 8, and 12 mg doses, respectively, compared with −4.6% with placebo. Reductions in liver fat correlated strongly with percentage weight loss, and near-maximal reductions appeared to coincide with approximately 20% weight loss.

In a 24-week phase 2 trial, adults with type 2 diabetes treated with lifestyle alone or stable-dose metformin were randomized to placebo, dulaglutide 1.5 mg, or retatrutide 0.5 mg, 4 mg, 8 mg, or 12 mg once weekly[73]. Reductions in HbA1c were −0.01% with placebo, −1.41% with dulaglutide, and up to −2.0% with retatrutide 12 mg; HbA1c ≤6.5% and <5.7% were achieved in 77% and 27% of those receiving retatrutide 12 mg, respectively. Corresponding reductions in body weight were −3.0%, −2.0%, and −16.9%. Improvements in non-HDL cholesterol (−3.9%, −0.7%, −19.6%), triglycerides (−9.9%, −4.3%, −34.4%), and systolic blood pressure (+1.5 mmHg, −1.5 mmHg, −8.8 mmHg) were greater with retatrutide than with placebo or dulaglutide.

Mild-to-moderate gastrointestinal symptoms, including nausea, diarrhoea, vomiting, and constipation were reported in 13–50% of participants receiving retatrutide, 13% with placebo, and 35% with dulaglutide, primarily during dose escalation and partly mitigated by the lower 2 mg starting dose.

The glucagon component of the triple agonist probably decreases circulating aminoacids that

potentially could decreases protein syntheses. In a sub-study in patients with type 2 diabetes the placebo subtracted weight loss was with 12 mg retatrutide 23.2%, corresponding to 14.6 kg of which 8.8 kg (18.7%) was fat mass and 5.8 kg (10.5%) lean mass evaluated by DEXA after 36 weeks[74]. Thus, lean mass comprised around 38% of the total weight loss, which seems not to differ from other GLP-1 agonists changes in body composition[75].

On December 11, 2025, Eli Lilly reported results from the phase 3 TRIUMPH-4 trial evaluating retatrutide in participants with obesity and knee osteoarthritis. The study enrolled 445 participants with a mean baseline body mass index (BMI) of 40.4 kg/m² and a mean body weight of 112.7 kg. After 68 weeks of treatment, mean weight reduction from baseline was −20.0% (−22.9 kg) in the 9-mg retatrutide group and −23.7% (−27.2 kg) in the 12-mg group, compared with −4.7% (−5.3 kg) in the placebo group.

The safety profile was consistent with that observed for GLP-1–based therapies. Dysesthesia was reported in 8.8% and 20.9% of participants receiving 9 mg and 12 mg of retatrutide, respectively, while treatment discontinuation rates were 12.2% and 18.2%, compared with 4.0% in the placebo group.

Among participants who remained on the assigned study intervention, weight loss was even greater, reaching −26.4% (−29.1 kg) and −28.7% (−32.3 kg) with retatrutide 9 mg and 12 mg, respectively, compared with −2.1% (−2.1 kg) in the placebo group.

Improvements in knee pain were substantial, with reductions in pain scores of −67.2% and −62.6% in the 9-mg and 12-mg retatrutide groups, respectively, versus −35.1% with placebo.

It remains to be established whether retatrutide will provide glycaemic control comparable to that of tirzepatide. The GLP-1 component in retatrutide is balanced. Retatrutide is currently in phase 3 development, including a cardiovascular outcomes trial in individuals with obesity and established cardiovascular disease (NCT05882045).

EFICOPEGTRUTIDE

Is a GLP-1/GIP/glucagon agonist at present in phase 2 development for treatment of MASH. After 12 weeks the reduction in liver fat was up to 81% in people with MASLD[76]

Discussion

In 2022, an estimated 830 million people worldwide were living with type 2 diabetes[4], and approximately 800 million had obesity[32]. Obesity is now recognized as a chronic, relapsing disease that remains difficult to treat effectively[12]. The development of new pharmacotherapies for overweight and obesity has therefore been one of the most dynamic research areas in recent years, progressing from mono-agonists to multi-hormone agonists and orally small-molecule GLP-1 agonists. Nearly all emerging agents are GLP-1–based developed as GLP-1 agonists alone or in combination with GIP, Amylin or glucagon agonists[7]. Currently, once-weekly semaglutide and tirzepatide are leading treatments, producing approximately weight loss of -15 to -25% after one year of treatment[7]. Both agents have demonstrated cardioprotective and renoprotective effects, including reduced progression of albuminuria and slower decline in kidney function as well as improvements in MAFLD, MASH, sleep apnea, and obesity-related musculoskeletal pain[7]. In a head-to-head trial in individuals with obesity Tirzepatide (10 or 15 mg) was superior to semaglutide (1.7 or 2.4 mg), achieving greater weight loss (20.2% vs 13.7%) after 72 weeks[77]. Cardiovascular outcome trials of the triple agonist retatrutide and the GLP-1/glucagon agonist servotrutide are ongoing.

The most common adverse events of GLP-1 based therapies are gastrointestinal, although these effects can often be minimized through flexible dosing strategies incorporating a lower starting dose and slower dose escalation[7,78]. GIP agonism in dual GLP-1/GIP agonists may further reduce the frequency or severity of gastrointestinal symptoms[14,15]. GLP-1 receptor agonists are also known to increased heart rate, however, no serious arrhythmias have been reported[12]. More recently, altered skin sensations,

including dysesthesia, hyperesthesia, skin pain, and paresthesia, have been reported with high-dose oral semaglutide (25 mg and 50 mg), subcutaneous semaglutide 7.2 mg OW, semaglutide 16 mg OW, and with the triple agonist retatrutide[7]. In addition, alopecia was more frequently reported with the 50 mg oral semaglutide formulation[41].

Among the dual and triple agonists, tirzepatide, and in development cagrisema, and retatrutide appear to be the most potent with respect to reduction in body weight and HbA1c[7]. Achieving the full therapeutic effect on body weight typically requires treatment duration of up to two years. In clinical studies, weight loss has been greater among participants with higher baseline BMI and in women, likely reflecting higher drug exposure due to lower absolute body weight and sex-related differences in body composition[7].

Most studies have shown that weight loss achieved in people with type 2 diabetes is substantially lower than that observed in individuals with obesity but without diabetes. For example in the trials with semaglutide and tirzepatide, average weight loss in participants with diabetes was only about 60 % of that achieved in non-diabetic patients[79]. The mechanisms underlying this difference are not fully understood. Concomitant use of other antidiabetic medications, such as insulin and sulfonylurea, which are associated with weight gain, may contribute in some cases. In addition, the more pronounced insulin resistance characteristic of type 2 diabetes may lead to higher peripheral insulin levels, reduced lipolysis and increased lipid uptake and storage, thereby counteracting pharmacologically induced weight loss[79].

Oral semaglutide 25 mg and small-molecule GLP-1 receptor agonists such as orforglipron are poised to provide injectable-free treatment options for obesity, administered as once-daily tablets[43, 44]. Although the weight loss efficacy of these agents has thus far been lower than that of tirzepatide, they are expected to become popular and clinically valuable options, particular for individuals with overweight or obesity who are reluctant to use injectable therapy, including many with a BMI below 40 kg/m². Orforglipron can be administered irrespective of fasting status, providing greater flexibility in treatment.

Small-molecule GLP-1 RAs, together with tirzepatide, have introduced the concept of *biased* GLP-1 receptor agonism, characterized by preferential activation of the cAMP pathway over the β-arrestin pathway, which mediates receptor internalization and signal termination[52]. This signaling bias prolongs GLP-1 activity and may enhance reductions in body weight and HbA1c. However, to establish the true clinical advantage of biased GLP-1 receptor agonists, direct comparisons with pharmacokinetically matched, non-biased (neutral) GLP-1 receptor agonists would be informative. Because small molecules may also bind to off-target receptors, they carry a potential risk of additional adverse effects. Other biased GLP-1 receptor agonists include CT-388 and orforglipron. In contrast, semaglutide is a balanced GLP-1 receptor agonist that activates both the cAMP and β-arrestin pathways.

Despite recent therapeutic advances, bariatric surgery will continue to play an important role in the management of severe obesity, given its excellent long-term durability—typically achieving 25–30% weight loss—and its lower ongoing cost compared with GLP-1–based therapies [80, 81]. However, it will be important to monitor trends in bariatric procedure rates over the next five years in light of the expanding availability of potent dual agonists such as cagrisema and triple agonists such as retatrutide, which can produce 20–30% weight loss[7]. Bariatric surgery will remain an important option for individuals who discontinue anti-obesity medications or who do not achieve adequate results with pharmacotherapy alone. Notably, the weight-loss response to GLP-1–based therapies is highly heterogeneous, and individual response cannot be reliably predicted before treatment initiation[82]. A randomized clinical trial comparing bariatric surgery with semaglutide and tirzepatide in terms of weight outcomes,

comorbidity reduction, and overall cost-effectiveness would provide valuable evidence to inform both clinical practice and health policy.

Concerns have been raised regarding sarcopenia following substantial weight loss[83, 84]. Across clinical trials, GLP-1–based therapies have produced consistent changes in body composition, with approximately 65–75% of the weight loss attributable to reductions in fat mass and about 25% attributable to decreases in lean mass—including muscle, water, solid organs, and bone—often referred to as the "one-to-four" rule[83]. Current evidence suggests that the reduction in lean mass is generally proportional (adaptive) to the degree of weight loss achieved[75]. Particular attention should be given to individuals at high risk for sarcopenia, such as older adults and those with heart failure or kidney and liver disease. To minimize muscle loss, it is important to incorporate regular physical activity, especially resistance training, and to ensure adequate protein intake (>1.2 g/kg body weight), both to preserve muscle and to achieve the many additional health benefits conferred by physical activity[85, 86]. Because the impact of GLP-1–based therapy on muscle quality and function remains unclear, future studies should assess these parameters rather than focusing solely on muscle mass.

There is considerable interest in strategies to preserve muscle mass during pharmacologically induced weight loss. Recent findings highlight the potential of antibody blockade of activin type II receptors to mitigate loss of lean mass[87]. Bimagrumab, a monoclonal antibody administered every four weeks, produced a 20% reduction in fat mass compared with 0.5% with placebo, together with a 3.6% increase in lean body mass versus a 0.8% decrease in the placebo group after 48 weeks in adults with type 2 diabetes[87].

Additional data were presented in the BELIEVE study at the American Diabetes Association Scientific Sessions in June 2025. Semaglutide monotherapy resulted in 15.7% weight loss, including a 27.8% reduction in fat mass and a 7.4% reduction in lean mass at 72 weeks. In contrast, combination therapy with bimagrumab and semaglutide produced 22.1% total weight loss, driven by a 45.7% reduction in fat mass and a smaller 2.9% reduction in lean mass. Muscle spasms and acne were noted as specific adverse events with bimagrumab, in addition to the expected gastrointestinal effects of semaglutide.

Another relevant dataset was presented at EASD 2025 from the phase 2 COURAGE trial (n = 605 adults with obesity), which evaluated the monoclonal myostatin inhibitor trevogrumab at 200 mg or 400 mg every four weeks compared with semaglutide 2.4 mg once weekly. At week 26, semaglutide alone was associated with a 6.5% reduction in lean mass, whereas the combination of semaglutide plus trevogrumab (400 mg) reduced lean mass by only 3.3%. The corresponding reductions in fat mass were 15.7% and 19.1%, and in body weight 10.6% and 11.1%, respectively. Treatment discontinuation rates were 4.6% and 10.6%, respectively.

Eli Lilly has announced discontinuation of a trial (NCT06901349) evaluating bimagrumab in combination with tirzepatide in individuals with type 2 diabetes, although development of the combination in people with obesity without diabetes is ongoing.

Discontinuation of GLP-1–based pharmacotherapy leads to weight regain in nearly all treated individuals[88, 89]. Consequently, effective strategies for maintaining weight loss are essential. Current evidence indicates that pharmacological therapy may need to be long-term or potentially life-long to prevent weight regain[1, 88]. Nevertheless, it is possible that lower maintenance doses, combined with improvement in healthier lifestyle habits, may help preserve weight loss[86]. Treatment adherence represent an additional challange: real-world one-year discontinuation rates are high, likely driven to out-of-pocket costs related to insurance barriers as well as side effects, and safety concerns[90].

Conclusion

The success of semaglutide and tirzepatide has catalyzed the development of a new generation of GLP-1–based therapeutics. Numerous agents are currently in phase 3 trials and are expected to receive approval within the next 1–3 years for indications including type 2 diabetes, overweight and obesity, cardiovascular and kidney diseases, sleep apnea, fatty liver disease, and osteoarthritis. The emergence of orally administered small-molecule GLP-1 receptor agonists is anticipated to simplify obesity treatment and further expand therapeutic options. Future head-to-head studies comparing the efficacy and safety profiles of these agents will be essential for determining optimal patient selection and clinical indications. A major limitation of existing GLP-1–based pharmacotherapies is their high cost, which restricts access for individuals with limited financial resources and contributes to treatment disparities.

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