

REVIEW ARTICLE

Beyond GLP-1 Monotherapy: Novel Multi-Agonists, Amylin Analogues, and Combination Strategies in Obesity and Type 2 Diabetes

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ABSTRACT

Aims: To provide a clinically oriented narrative review of recently reported human trial data on emerging pharmacotherapies for obesity and type 2 diabetes beyond glucagon-like peptide-1 receptor agonist (GLP-1RA) monotherapy.

Materials and Methods: This narrative review summarizes recent clinical evidence on incretin-based and related therapeutic strategies, including dual and triple incretin- or glucagon-based agonists, long-acting amylin analogues, oral agents, and combination approaches targeting complementary satiety and metabolic pathways. The review focuses on human trial data and evaluates key outcomes including body weight reduction, glycemic control, body-composition effects, tolerability, and broader cardiometabolic changes.

Results: Incretin-based therapies have transformed the management of obesity and type 2 diabetes, with GLP-1RAs achieving levels of weight loss that begin to narrow the gap with metabolic surgery in selected populations. Recent developments have substantially expanded the field beyond GLP-1RA monotherapy. Emerging agents now include multi-agonists, amylin-based therapies, novel oral compounds, and combination strategies designed to improve not only the magnitude of weight loss, but also its quality, durability, and metabolic consequences. Across trials, these approaches have shown promising effects on body weight, glycemic control, and selected cardiometabolic parameters, although differences in tolerability, evidence maturity, and practical feasibility remain important.

Conclusions: Current data indicate a rapid shift from single-pathway interventions toward multimodal therapeutic strategies in obesity and type 2 diabetes. Future positioning of these agents within treatment algorithms will depend not only on efficacy, but also on long-term safety, durability of effect, tolerability, adherence, access, and their impact on clinically meaningful outcomes beyond body weight alone.

Abbreviations: AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; AEs, adverse events; ALT, alanine aminotransferase; BMI, body mass index; CB1R, cannabinoid receptor type 1; DPP, diabetes prevention program; DXA, dual-energy X-ray absorptiometry; FDA, U.S. Food and Drug Administration; GCG, glucagon; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; IV, intravenously; LDL, low density lipoprotein; LI, lifestyle interventions; MAE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MC4R, melanocortin-4 receptor; NPY, neuropeptide Y; ORC, obesity-related complication; PYY, peptide YY; SAEs, serious adverse events; SARM, selective androgen receptor modulator; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; TEAEs, treatment-emergent adverse events; WL, weight loss.

1 | Introduction

Obesity and type 2 diabetes (T2D) are among the most prevalent and consequential chronic diseases worldwide, driving cardiometabolic morbidity, reducing quality of life, and increasing healthcare expenditures. Lifestyle interventions (LI) remain the foundation of treatment for both conditions. According to the recommendations of major professional societies (American Association of Clinical Endocrinology—ACE [1] and American Diabetes Association—ADA [2]), long-term management begins with structured modification of dietary habits, increased physical activity, and behavioural support. Comprehensive lifestyle programs, such as the Diabetes Prevention Program (DPP [3]), have shown that sustained weight reduction of approximately 5%–7% can improve glycemic control and cardiometabolic risk; however, such effects are often difficult to achieve and maintain over time. Exercise alone generally produces only modest weight loss; however, it remains essential because of its beneficial effects on insulin sensitivity, body composition, blood pressure, lipid metabolism, physical function, and long-term weight maintenance.

Nevertheless, lifestyle measures alone are frequently insufficient for many individuals with established obesity or T2D, particularly when clinically meaningful and durable weight loss is required. In such settings, pharmacotherapy becomes an important component of treatment and is generally considered for individuals with obesity or those who are overweight and have weight-related comorbidities when weight-loss targets are not achieved with comprehensive LI alone. Among the currently available agents, glucagon-like peptide-1 receptor agonists (GLP-1RA) have reshaped the therapeutic landscape, with subcutaneous semaglutide and tirzepatide producing substantial and sustained reductions in body weight, along with broad metabolic benefits. The magnitude of weight loss (WL) observed with the most effective GLP-1-based therapies has begun to narrow the gap with bariatric surgery in selected populations, thereby redefining expectations for medical treatment.

This clinical success has catalysed a new phase of drug development in this field. The current evolution of obesity and diabetes pharmacotherapy is characterised by diversification across molecular targets, response durability, and delivery methods. Dual- and triple-agonist incretin therapies aim to extend the efficacy beyond that of GLP-1 monotherapy through the coordinated activation of glucose-dependent insulinotropic polypeptide (GIP), glucagon (GCG), and GLP-1 pathways. Amylin-based agents offer complementary mechanisms that may enhance satiety, slow gastric emptying, and improve weight loss [4]. Meanwhile, oral GLP-1RA and other non-injectable formulations aim to expand access and convenience, whereas long-acting injectables, peptide–antibody conjugates, and implantable systems are being developed to improve adherence in the management of chronic disease management [5].

In addition to classical incretin biology, new therapeutic strategies are targeting pathways such as neuropeptide Y (NPY) signaling, melanocortin receptors, myostatin/activin biology, and the endocannabinoid system. These approaches are being explored both as monotherapies and as rational combinations intended not only to increase the magnitude of weight reduction

but also to improve body composition outcomes, tolerability, and long-term durability.

In this narrative review, we provide an up-to-date overview of the most recent and rapidly evolving advances in the treatment of obesity and T2D. Because this field is dense with mechanistic terminology and trial-specific shorthand, abbreviations are used throughout for readability; all abbreviations are defined at first mention and compiled in the Abbreviations list at the beginning of the manuscript. Table 1 describes the key drug classes and their mechanisms of action. A detailed drug-by-drug summary of adverse events, serious adverse events, and discontinuation due to adverse events is provided in Table S1.

We followed a stepwise narrative. We begin with recent advances in GLP-1RA, including higher-dose, longer-acting, and reformulated agents. We then moved to multi-agonist incretin therapies, followed by amylin-based agents and combinations. Next, we summarise oral incretin options that aim to achieve injectable-level efficacy in a non-injectable format. Finally, we discuss novel delivery platforms and emerging targets beyond the incretin axis, including rational combinations designed to improve durability, body composition outcomes, and adherence. Together, these developments point to a new generation of therapies that may substantially reshape the long-term management of obesity, T2D, and their metabolic complications.

2 | Methodology

This narrative review focuses on incretin-based and related pharmacotherapies for obesity and T2D, with particular emphasis on agents for which new efficacy or safety data became publicly available in 2025 and, following peer-review revision, in the first quarter of 2026. We prioritised phase 2 and 3 randomised clinical trials (RCTs), as well as key extension and dose-finding studies, in adults with overweight, obesity, and/or T2D, in which body weight reduction and/or glycated haemoglobin (HbA_{1c}) change were reported as primary or major secondary endpoints.

Evidence was identified through structured searches of PubMed/MEDLINE, followed by manual screening of the reference lists of relevant original articles and recent review papers. We did not restrict the search to specific journals; however, particular attention was paid to reports published in major general and specialty journals covering obesity, diabetes, and endocrinology. To capture emerging data not yet fully represented in the indexed literature, we also reviewed abstracts and late-breaking presentations from major scientific meetings, including the ADA, EASD, ENDO, and ObesityWeek, as well as relevant company and regulatory press releases.

We included only human studies and excluded preclinical studies. Trials first reported before 2025 were not systematically reviewed, except where earlier data were required to provide clinical or regulatory context for agents with relevant updates in 2025 or early 2026. Our emphasis was on phase 2 and 3 randomised trials; however, we also included selected early phase studies (including phase 1 and 2a trials) when they provided first-in-human or proof-of-concept data for novel mechanisms, oral formulations, or delivery platforms that could inform

Hormones, receptors, and pathways
<p><i>GLP-1 (Glucagon-like peptide-1)</i> Gut-derived incretin hormone secreted by intestinal L-cells after meals. It enhances glucose-dependent insulin secretion, slows gastric emptying, reduces appetite, and promotes weight loss.</p>
<p><i>GIP (Glucose-dependent insulinotropic polypeptide)</i> Incretin hormone released by K-cells in the proximal small intestine. It potentiates insulin secretion in a glucose-dependent manner and may influence adipose tissue metabolism and body weight.</p>
<p><i>GCG (Glucagon)</i> Peptide hormone produced by pancreatic α-cells. It increases hepatic glucose production and, when pharmacologically coactivated with GLP-1, enhances energy expenditure and promotes weight loss.</p>
<p><i>Amylin</i> Peptide co-secreted with insulin from pancreatic β-cells. It slows gastric emptying, suppresses postprandial glucagon, and promotes satiety, thereby contributing to body weight regulation.</p>
<p><i>PYY₃₋₃₆ (Peptide YY 3-36)</i> Gut-derived peptide released from L-cells in response to food intake. The truncated form PYY₃₋₃₆ acts on neuropeptide Y₂ (Y₂) receptors in the hypothalamus to increase satiety and reduce the food intake.</p>
<p><i>NPY (Neuropeptide Y)</i> Orexigenic neuropeptide widely expressed in the hypothalamus. It promotes food intake and decreases energy expenditure.</p>
<p><i>MC4R (Melanocortin-4 receptor)</i> G-protein-coupled receptor expressed in hypothalamic nuclei. Activation reduces appetite and body weight, whereas loss-of-function variants are a common monogenic cause of obesity.</p>
<p><i>CBI (Cannabinoid receptor type 1)</i> G-protein-coupled receptor highly expressed in the central nervous system and present in peripheral tissues. Its activation promotes appetite and lipogenesis, whereas inverse agonism reduces food intake and promotes weight loss.</p>
<p><i>NPY receptor (Y-receptors)</i> Family of receptors (e.g., Y₁, Y₂) mediating the effects of NPY and PYY. Y₂-receptor activation in the hypothalamus is associated with increased satiety.</p>
<p><i>FGF21 (Fibroblast growth factor 21)</i> Hormone-like metabolic regulator produced mainly by the liver. It influences energy expenditure, glucose and lipid metabolism, and has emerged as a therapeutic target in obesity, MASLD and T2D.</p>
<p><i>Leptin</i> Adipocyte-derived hormone that signals energy sufficiency to the hypothalamus. It suppresses appetite and helps regulate body weight, although leptin resistance commonly develops in obesity.</p>
<p><i>Myostatin (GDF8)</i> Member of the transforming growth factor-β superfamily that negatively regulates skeletal muscle growth. Pharmacologic inhibition has been explored to preserve lean muscle mass during weight loss.</p>
<p><i>Activin A</i> Cytokine of the transforming growth factor-β superfamily involved in muscle, adipose tissue and inflammatory signalling. It is being targeted in combination approaches aimed at improving body composition during pharmacologic weight loss.</p>
Drug classes/mechanisms
<p><i>GLP-1 receptor agonists (GLP-1RA)</i> Synthetic peptides or small molecules that activate the GLP-1 receptor, leading to glucose-dependent insulin secretion, appetite suppression, delayed gastric emptying and weight loss.</p>
<p><i>Dual GLP-1/GIP receptor agonists (GLP-1/GIP)</i> Agents that co-activate GLP-1 and GIP receptors to enhance incretin signalling, producing robust glycemic improvement and weight loss.</p>
<p><i>Dual GLP-1/glucagon receptor agonists (GLP-1/GCG)</i> Compounds that stimulate both GLP-1 and glucagon receptors, aiming to combine appetite suppression with increased energy expenditure and improved hepatic steatosis.</p>

(Continues)

TABLE 1 | (Continued)

Drug classes/mechanisms
<p><i>Triple GLP-1/GIP/GCG receptor agonists</i> Multi-agonists, simultaneously activate GLP-1, GIP, and glucagon receptors to maximize the metabolic benefits on body weight, glycemia, and hepatic fat.</p> <p><i>Quadruple receptor agonists</i> Agents targeting four receptors (GLP-1, GIP, glucagon, and IGF-1) integrate incretin, glucagon, and anabolic growth factor pathways for large and rapid weight loss.</p> <p><i>Amylin analogues</i> Long-acting analogs of human amylin that reproduce or enhance its effects on satiety and gastric emptying often lead to preferential loss of fat mass and improved body composition.</p> <p><i>GLP-1/amylin co-agonists/combinations</i> Therapies combining GLP-1RA with amylin analogs in a single molecule or regimen can intensify appetite suppression and favour fat-predominant weight loss.</p> <p><i>Peptide-antibody conjugates/ultra-long-acting incretins</i> Engineered molecules with extended half-lives allow once-monthly or less frequent dosing while maintaining GLP-1-like efficacy.</p> <p><i>Oral GLP-1 receptor agonists/oral incretin agonists</i> Small molecules or reformulated peptides suitable for oral administration, designed to provide GLP-1-like or multi-incretin effects without the need for injections.</p> <p><i>Endocannabinoid pathway modulators (CB1 inverse agonists)</i> Peripherally biased agents that reduce CB1 signalling to decrease appetite and improve metabolic parameters while minimising central neuropsychiatric adverse effects.</p> <p><i>Melanocortin-4 receptor agonists (MC4R agonists)</i> Drugs (e.g., bremelanotide/BMT-801) that activate MC4R to reduce appetite and body weight may be useful as adjuncts to incretin therapy and in preventing weight regain.</p> <p><i>Myostatin/activin pathway inhibitors</i> Monoclonal antibodies targeting myostatin, activin A, or the activin type II receptor, used alone or with GLP-1RA to mitigate loss of lean mass during weight loss.</p> <p><i>Leptin receptor agonists</i> Agents that stimulate leptin signalling with the aim of improving weight loss and possibly counteracting adaptive weight-regain mechanisms when combined with incretin therapy.</p> <p><i>Implantable GLP-1 delivery systems</i> Long-acting devices that provide continuous subcutaneous release of GLP-1RA (exenatide or semaglutide) over months, potentially enabling annual or semi-annual dosing.</p> <p><i>Selective androgen receptor modulator (SARM)</i> Class of drugs that selectively activate androgen receptors in specific tissues (such as skeletal muscle and bone) while minimising activity in others (prostate, skin, etc.).</p> <p><i>cAMP-biased GLP-1 receptor agonists</i> GLP-1 receptor agonists engineered to preferentially activate cyclic adenosine monophosphate signalling over β-arrestin recruitment. This receptor-bias strategy aims to preserve efficacy while potentially modifying tolerability and pharmacodynamics.</p> <p><i>GIP receptor antagonists/GLP-1–GIP antagonist conjugates</i> Agents that combine GLP-1 receptor activation with antagonism of the GIP receptor. This approach is being explored to enhance weight loss while retaining incretin-based metabolic benefits.</p> <p><i>Selective amylin receptor agonists</i> Amylin-based agents designed to activate amylin receptors more selectively than older analogs. They are being developed to improve satiety, body-composition outcomes, and tolerability.</p>

(Continues)

TABLE 1 | (Continued)

Drug classes/mechanisms
<p><i>Dual GLP-1/FGF21 agonists</i> Co-agonists that combine incretin signalling with fibroblast growth factor 21 activity. They are being explored particularly for obesity complicated by MASLD and T2D because of their potential effects on liver fat, glycemia and lipid metabolism.</p> <p><i>Peripherally restricted CB1 modulators/negative allosteric modulators</i> Agents that reduce cannabinoid receptor type 1 signalling while minimising central nervous system exposure. The goal is to improve weight and metabolic outcomes without the neuropsychiatric burden associated with earlier CB1-directed drugs.</p> <p><i>Mitochondrial protonophores</i> Metabolic agents that increase mitochondrial proton leak and thereby raise energy expenditure. Newer liver-targeted compounds are being investigated as adjuncts to incretin therapy to augment fat loss while limiting systemic toxicity.</p> <p><i>NPY receptor agonists</i> Experimental agents targeting neuropeptide Y receptors to modulate appetite and energy balance. They are being explored as mechanistically distinct adjuncts to incretin-based therapy.</p>

future clinical development and help clinicians remain aware of emerging therapeutic directions. These data were considered exploratory and presented in the pipeline context rather than as practice-changing evidence. All visualisations were generated using R version 4.5.2 (R Foundation for Statistical Computing) with the ggplot2 package.

2.1 | Approved Treatment Options

Before discussing novel agents, it is important to define current therapeutic options. Among the approved anti-obesity pharmacotherapies, semaglutide and tirzepatide have set a new efficacy standard and now serve as the principal clinical comparators for emerging drugs. In clinical practice, weight loss of 5%–10% is generally regarded as a strong response to pharmacological therapy, whereas reductions exceeding 10% are considered particularly clinically meaningful because they are associated with broader metabolic, cardiovascular, and functional benefits [1]. In STEP 1 [6], once-weekly subcutaneous semaglutide 2.4 mg, combined with LI, produced a mean body weight reduction of 14.9% at 68 weeks in adults with obesity or overweight without T2D, compared with 2.4% with placebo. Beyond weight loss, semaglutide has also established outcome benefits that extend its role beyond body weight reduction alone: in the SELECT trial [7], once-weekly semaglutide reduced major adverse cardiovascular events (MACE) in adults with overweight or obesity and established cardiovascular disease but without diabetes.

A further step forward for semaglutide was the recent U.S. Food and Drug Administration (FDA) approval [8] of a higher once-weekly dose of semaglutide (7.2 mg) for chronic weight management. This approval was supported by the phase 3b STEP UP program in adults with obesity without T2D [9]. In this trial, 1407 participants (mean baseline body mass index (BMI) 39.9 kg/m²; mean body weight 113.0 kg) were randomised in a 5:1:1 ratio to semaglutide 7.2 mg, semaglutide 2.4 mg, or placebo, all in combination with LI for 72 weeks. Using the treatment-policy estimand, the mean WL at week 72 was 18.7% with semaglutide 7.2 mg, compared with 15.6% with semaglutide 2.4 mg and 3.9% with placebo. Under the efficacy estimand, the corresponding reductions were 20.7%, 17.5%, and 2.4%, respectively. Nearly half of the participants (47.7%) receiving 7.2 mg achieved

≥20% WL, and one-third (31.2%) achieved ≥25% WL, confirming that dose intensification can further extend the efficacy of GLP-1RA within an already established therapeutic class.

Improvements were also observed in other cardiometabolic parameters (triglycerides, cholesterol, and diastolic blood pressure) compared with those in the placebo group. Gastrointestinal adverse events (GI AEs) were the most frequent (70.8% vs. 61.2% for 7.2 mg vs. 2.4 mg), whereas dysesthesia-related events, an emerging AEs of incretin therapies, occurred in 22.9% of participants receiving 7.2 mg versus 6.0% with 2.4 mg and 0.5% with the placebo. Importantly, four participants permanently discontinued treatment because of these AEs in the semaglutide 7.2 mg group, whereas no such discontinuations occurred in the semaglutide 2.4 mg or placebo groups.

Taken together, these data position semaglutide 7.2 mg as an intensified approved GLP-1 option that narrows the efficacy gap between monotherapy and newer multi-agonist approaches.

Recently, Novo Nordisk extended its semaglutide program with data from the OASIS 4 trial [10], showing that oral semaglutide 25 mg provides a clinically meaningful non-injectable option for obesity management. The study enrolled adults with obesity or overweight and at least one obesity-related comorbidity (ORC). Participants were randomised (2:1) to receive oral semaglutide 25 mg or placebo once daily with LI. Treatment began at 3 mg and was titrated every four weeks. At week 64, the mean body weight reduction was –13.6% with semaglutide versus –2.2% with placebo (estimated difference –11.4%; 95% CI –13.9 to –9.0; $p < 0.001$). Among treated participants, 79.2% achieved ≥5%, 63.0% ≥10%, 50.0% ≥15% and 29.7% ≥20% WL. GI AEs were the most common, occurring in 74% of participants receiving semaglutide and 42% receiving placebo, and gastrointestinal disorders were also the most common reason for treatment discontinuation, reported in 3.4% and 2.0% of participants, respectively.

Based on these and supporting data, the FDA has approved [11] oral semaglutide 25 mg (Wegovy tablet) as the first oral GLP-1RA indicated for chronic weight management and reduction of major adverse cardiovascular events (MACE) in adults with obesity or overweight and established cardiovascular disease. This makes high-dose oral semaglutide the first approved

non-injectable incretin therapy capable of achieving weight loss at a magnitude similar to that of injectable semaglutide. In the FDA-approved label, the recommended maintenance dose is 25mg once daily, and patients should not take more than one tablet daily. This is clinically relevant because, although earlier studies such as OASIS-1 [12] and PIONEER PLUS [13] demonstrated meaningful efficacy with 50mg oral semaglutide, these regimens fall outside the currently approved dosing guidelines.

Most recently, the approved oral incretin landscape has expanded further with the FDA approval of *orforglipron* (Foundayo) [14] for chronic weight management in adults with obesity, or overweight in the presence of at least one ORC. Unlike oral semaglutide, orforglipron is a once-daily small-molecule, non-peptide GLP-1 RA that can be taken without food or water restrictions. The ATTAIn program extended the evaluation of orforglipron in patients with obesity and T2D and those who are overweight or obese over longer treatment durations. ATTAIn-1 was a Phase 3 [15], evaluating the efficacy and safety of orforglipron as an adjunct to healthy diet and LI for obesity treatment. A total of 3127 participants were randomised in a 3:3:3:4 ratio to receive orforglipron 6 mg, 12 mg, or 36 mg, or placebo for 72 weeks, and the mean BMI was 37.0 kg/m [2]. At week 72, the mean WL was 7.5%, 8.4%, and 11.2% with the 6, 12, and 36 mg doses, respectively, compared with 2.1% with placebo. The proportion of participants achieving at least 10% WL increased with dose, reaching 33.3%, 40.0%, and 54.6% with orforglipron versus 12.9% with placebo, and treatment was associated with improvements in several cardiometabolic parameters. The adverse event profile was consistent with that of the GLP-1RA class, with GI AEs being the most common and mostly mild to moderate in severity. Overall, discontinuation for any reason occurred in 21.9%–24.4% of participants across the orforglipron groups, compared with 29.9% in the placebo group; the most frequent reason was participant decision to withdraw (8.5%–8.9% vs. 13.8%, respectively), followed by AEs, which led to discontinuation in 5.1%–10.3% of participants receiving orforglipron and 2.6%–2.7% of those receiving placebo.

Further support for orforglipron as a long-term option comes from the phase 3 ATTAIn-MAINTAIN trial [16], which evaluated weight maintenance after prior injectable treatment with incretin. In this study, 376 adults with obesity who had completed 72 weeks of treatment with tirzepatide or semaglutide 2.4 mg in SURMOUNT-5 and achieved a weight plateau were re-randomised to once-daily oral orforglipron or placebo for 52 weeks, alongside LI. According to Lilly, participants who switched from tirzepatide to orforglipron maintained their WL, with only a small mean change of +0.9 kg over 52 weeks (95.0–95.9 kg), and those who switched from semaglutide to orforglipron had a mean regain of 5.0 kg (90.9–95.9 kg). A post hoc analysis at week 24 showed weight changes of 0.1 kg for those switching from semaglutide to orforglipron versus 9.4 kg for those switching from semaglutide to placebo, and 2.6 kg versus 9.1 kg, respectively, for those switching from tirzepatide.

This FDA approval of orforglipron is clinically important because it broadens the class of oral GLP-1-based therapies from peptide-based oral semaglutide to a non-peptide oral agent, potentially improving convenience and widening treatment choice.

Even with this expansion of oral options, tirzepatide remains the most effective approved incretin-based therapy for weight reduction and glycemic control. In SURMOUNT-1 [17], once-weekly tirzepatide produced a mean WL of up to 20.9% at 72 weeks in adults with obesity or overweight without diabetes, substantially exceeding that of the placebo. In patients with T2D, the SURPASS-2 trial [18] showed that tirzepatide was superior to once-weekly semaglutide 1.0 mg for both HbA_{1c} lowering and WL over 40 weeks. Regulatory indications have expanded accordingly: Zepbound is approved in the United States for chronic weight management and, more recently, for moderate-to-severe obstructive sleep apnea in adults with obesity [19]. Taken together, semaglutide and tirzepatide define the currently approved standard against which newer multi-agonists, oral agents, amylin-based therapies, and combination approaches should be interpreted.

In a practical approach, these approved agents provide efficacy and safety benchmarks against which newer investigational therapies should be judged, particularly when interpreting cross-trial differences in weight loss, glycemic control, tolerability, and treatment discontinuation.

2.2 | New Advances in the GLP-1 Field

In addition to obesity without diabetes, the high-dose semaglutide program has also been extended to patients with T2D. The STEP UP T2D trial [20] evaluated once-weekly semaglutide 7.2 mg in adults with obesity and T2D (mean BMI 38.6 kg/m²; mean HbA_{1c} 8.1%). In this 72-week, randomised trial, 512 participants were assigned in a 3:1:1 ratio to semaglutide 7.2 mg, semaglutide 2.4 mg, or placebo, all in combination with liraglutide. The mean WL reached 13.2% with semaglutide 7.2 mg, compared with 10.4% with semaglutide 2.4 mg and 3.9% with placebo, whereas HbA_{1c} reductions were similar between the two active treatment groups (–1.7% and –1.6%, respectively). The most common AEs were gastrointestinal disorders, reported in 53.1%, 51.5%, and 25.5% of participants receiving semaglutide 7.2 mg, semaglutide 2.4 mg, and placebo, respectively. Permanent discontinuation of trial treatment occurred in 5.5%, 5.8%, and 2.9% of participants, respectively, and discontinuation specifically due to GI AEs was reported in 2.9%, 4.9%, and 1.0%, respectively. Dysesthesia-related AEs, an emerging tolerability signal with higher-dose incretin therapy, were more frequent with semaglutide 7.2 mg than with semaglutide 2.4 mg (18.9% vs. 4.9%).

Whether a similar dose intensification could further extend the efficacy of tirzepatide remains unknown. An ongoing study (NCT06037252 [21]) will help determine whether higher doses of the drug can further shift the upper boundary of pharmacological WL and improve glycemic control.

Efpeglenatide (HM11260C), a long-acting GLP-1 RA developed by Hanmi, has also advanced to late-stage clinical development for obesity. According to company- and news-reported topline results [22] from a Korean phase 3 trial in 448 adults with obesity without T2D, efpeglenatide met its co-primary endpoints at 40 weeks, with a mean WL of 9.75% versus 0.95% with placebo, while 79.4% of treated participants achieved at least 5%

WL compared with 14.5% in the placebo group. GI AEs were reported as the most common TEAEs and were mostly mild to moderate. However, as full peer-reviewed results are not yet available, these findings should be interpreted with caution. In parallel, Hanmi expanded its program to T2D. In January 2026, the Korean Ministry of Food and Drug Safety approved a phase 3 trial of HM11260C as an add-on therapy to metformin and dapagliflozin in patients with inadequately controlled T2D (NCT07379333 [23]).

Metsera's ultra-long-acting, fully biased GLP-1RA *MET-097i* was acquired by Pfizer and renamed PF-3944. In the phase 2b VESPER-1 trial [24] in adults with overweight or obesity ($N=239$), once-weekly *MET-097i* produced a dose-dependent WL, reaching 14.1% at 28 weeks with the 1.2 mg regimen (placebo-subtracted) and a 2.9% discontinuation rate. Individual responses to WL were reported to be up to 26.5%. An exploratory extension to 36 weeks suggested continued WL without an early plateau effect.

VESPER-3 [25] was designed to test titration strategies that would allow an induction period with once-weekly dosing, followed by a transition to once-monthly maintenance. Participants were randomised to four active regimens or placebo, all beginning with weekly dosing for 12 weeks and then switching to monthly dosing for up to one year. The active regimens used stepwise weekly escalation from starting doses of 0.4–0.8 mg toward monthly maintenance doses of 3.2 mg or 4.8 mg. At 28 weeks, all *PF-3944* regimens achieved greater WL than placebo ($p < 0.001$ for all), according to a press release by the company. The 0.4 mg weekly to 4.8 mg monthly regimen achieved a placebo-adjusted 12.3% WL (efficacy estimand), whereas the 0.4 mg weekly to 3.2 mg monthly regimen achieved 10% WL. WL trajectories reportedly did not plateau by week 28. These two titration pathways (0.4–3.2 mg and 0.4–4.8 mg monthly) are planned for phase 3 testing.

Overall, the safety profile in the VESPER-3 study was consistent with that of the GLP-1RA class, with predominantly mild-to-moderate GI AEs and few severe adverse events (SAEs). According to Pfizer's press release, discontinuations due to AEs occurred during both the weekly induction and monthly maintenance phases, whereas no such discontinuations occurred in the placebo arm. Interim tolerability analyses suggested that gradual titration reduced GI AEs compared with fixed higher-dose weekly exposure in the VESPER-1 study. Pfizer has also announced an expanded phase 3 program, including VESPER-4 in obesity/overweight, with additional studies planned to evaluate both weekly and monthly dosing strategies in obesity and T2D.

Other developers are also exploring GLP-1RA with less frequent dosing schedules and alternative formulations. Asclepis Pharma is developing *ASC30*, a biased GLP-1RA designed for both subcutaneous (SC) depot and oral tablet delivery. In a phase 1b study (NCT06679959 [26]), the SC maintenance formulation of *ASC30* demonstrated an observed half-life of approximately 75 days, supporting the possibility of quarterly administration. In parallel, an oral formulation of *ASC30* has been clinically evaluated. According to an ADA 2025 abstract [27], first-in-human single-ascending-dose data support the development of *ASC30* as a once-daily oral GLP-1RA, while subsequent

company-presented multiple-ascending-dose results [28] suggested a placebo-adjusted WL of up to 6.5% after 28 days of treatment in participants with obesity. However, as these oral *ASC30* data are currently available only in the abstract and company-reported form, they should be interpreted as preliminary data.

Bofanglutide (GZR18), a novel biweekly GLP-1RA, demonstrated greater HbA_{1c} reduction than semaglutide 1 mg in a phase 2b trial involving 272 Chinese adults with T2D (–1.87% to –2.32% vs. –1.60%), with additional improvements in fasting plasma glucose and body weight. However, AEs were more frequent with *bofanglutide* than with *semaglutide*: TEAEs occurred in 90.6%–92.7% of *bofanglutide*-treated participants versus 72.2% with *semaglutide* and GI AEs in 79.6%–87.3% versus 44.4%, respectively. Nausea, vomiting, and diarrhoea were the most common events [29].

Taken together, these data suggest that innovation within the GLP-1 class continues to proceed in two parallel directions: dose intensification of established agents and development of next-generation long-acting molecules. However, any practical advantage from less frequent administration must be balanced against tolerability, discontinuation, and the limited peer-reviewed evidence for several of these agents.

2.3 | Dual and Triple Incretin Agonists

Multi-receptor agonists are being developed to extend the efficacy beyond single-pathway incretin therapy by engaging complementary hormonal axes relevant to appetite regulation, energy expenditure, glycemic control, and adiposity regulation.

Survodutide is a dual GCG RA and GLP-1 RA that is currently under investigation for the management of obesity and represents a strategy that combines appetite reduction with a potential increase in energy expenditure. Its phase 3 development program includes two randomised controlled trials, SYNCHRONIZE-1 (NCT06066515 [30]) and SYNCHRONIZE-2 (NCT06066528 [31]), designed to evaluate its efficacy and safety in obesity, with or without T2D. Participants received once-weekly SC injections of *survodutide* or placebo, in addition to standardised LI. The dosing regimen included gradual titration up to 3.6 mg or 6.0 mg weekly. SYNCHRONIZE-1 enrolled 726 adults with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one ORC without T2D, whereas SYNCHRONIZE-2 enrolled 755 adults with T2D. The primary endpoints for both studies included percentage WL and the proportion of participants who achieved at least 5% weight reduction by week 76. A dedicated MRI sub-study in SYNCHRONIZE-1 will further investigate changes in body composition and liver fat, providing insights relevant to metabolic dysfunction-associated steatotic liver disease (MASLD) [32].

Among dual agonists, *HRS9531*, a once-weekly GLP-1/GIP RA developed by Hengrui Pharma, has emerged as a notable candidate for obesity treatment. According to company-reported phase 3 topline data and an ObesityWeek 2025 presentation [33], 567 Chinese adults with overweight or obesity without T2D were randomised to receive once-weekly SC *HRS9531* 2 mg, 4 mg, or 6 mg or placebo for 48 weeks. The mean WL reached

10.7%, 16.4%, and 17.7% across the three dose groups, respectively, versus 1.4% with placebo, and 44.4% of participants in the 6 mg group achieved at least 20% WL. Cardiometabolic improvements have also been reported. Safety was broadly consistent with the incretin class, with mainly mild-to-moderate GI AEs and low rates of permanent discontinuation due to TEAEs (0.7%, 0.7%, and 1.4% across dose groups vs. none with placebo). Taken together, HRS9531 appears to be highly active; however, caution should be exercised in interpretation because the strongest evidence is based on conference and company-reported sources rather than full peer-reviewed publications.

Similarly, *HS-20094*, another dual GLP-1/GIP RA, is undergoing a Phase 3 program (NCT07156539 [34]) to assess its efficacy and safety over 52 weeks in adults with obesity and those who are overweight. A global licensing collaboration with Regeneron [35] has expanded its development beyond China.

BGM0504, another dual GLP-1/GIP RA, demonstrated metabolic efficacy in a phase 2b placebo and semaglutide RCT [36] conducted in 64 Chinese adults with T2D who were assigned to five groups: BGM0504 5 mg ($n=12$), 10 mg ($n=12$), 15 mg ($n=12$), placebo ($n=12$), and semaglutide 1.0 mg ($n=16$). At week 12, placebo-adjusted HbA_{1c} reductions were -1.82% , -2.05% , and -2.56% for the 5, 10, and 15 mg doses, respectively, compared with -1.86% for semaglutide 1 mg weekly. The 15 mg dose also demonstrated superior glycemic control ($p=0.0327$) and higher WL than semaglutide ($p<0.001$). However, this efficacy was accompanied by a higher number of AEs than semaglutide: TEAEs occurred in 90.6%–92.7% of BGM0504-treated participants versus 72.2% with semaglutide, and drug-related GI AEs in 79.6%–87.3% versus 44.4%, respectively. Nausea, vomiting, and diarrhoea were the most common AEs.

In parallel with these developments, *CT-868*, a biased dual GLP-1/GIP RA, was designed to preferentially activate cAMP signalling with reduced β -arrestin recruitment, thereby prolonging receptor engagement and potentially improving its tolerability. A phase 2 RCT [37] of the drug enrolled 103 overweight (BMI ≥ 27 kg/m) adults with T2D and inadequately controlled glycemia (HbA_{1c} 7.0%–10.0%) treated with metformin or physical activity only. After 26 weeks, *CT-868* (doses from 1.75 to 4.0 mg) reduced HbA_{1c} by 1.18% to 1.81% and body weight by 5.4% at 4.0 mg, outperforming the placebo and improving lipid and hepatic marker levels. Additionally, 51.7% of participants treated with 4.0 mg *CT-868* achieved a WL of $\geq 5\%$ ($p=0.036$). Importantly, TEAEs were mostly mild to moderate; no participants in the *CT-868* group discontinued treatment because of AEs, and no hypoglycemia-related AEs were reported.

CT-388, Roche's [38] dual GLP-1/GIP RA, is another prominent drug in this class. In a recent phase 2 randomised, double-blind, placebo-controlled trial, 469 adults with obesity or overweight with at least one ORC and without T2D were assigned to one of five *CT-388* dose cohorts or placebo for 48 weeks, and the highest-dose cohort was titrated to 24 mg. According to topline company-reported results, *CT-388* at 24 mg achieved a placebo-adjusted mean WL of 22.5% at week 48 using the efficacy estimand and 18.3% using the treatment regimen estimand. In the 24 mg group, 95.7% of the participants achieved at least 5% WL, 87.0% achieved at least 10%, 47.8% achieved at least 20%, and

26.1% achieved at least 30% WL by week 48. Among participants with prediabetes at baseline who received 24 mg *CT-388*, 73% reverted to normoglycemia at week 48, compared with 7.5% in the placebo group (company reported). *CT-388* was generally well-tolerated, with mostly mild-to-moderate GI AEs consistent with the incretin class. Discontinuation due to AEs occurred in 5.9% of *CT-388*-treated participants versus 1.3% of placebo-treated participants. A phase 3 program on obesity (Enith1, NCT07351045 [39]; Enith2, NCT07351058 [40]) is expected to be initiated in 2026.

Mazdutide, a dual GLP-1 and GCG RA, has demonstrated consistent dose-dependent weight-lowering efficacy in both early and late stages of development. In company-reported phase 2 data presented at ObesityWeek 2025 [41], 179 adults with obesity or overweight were randomised (177 dosed) in a 3:2:3:3 ratio to receive placebo or once-weekly mazdutide 3/6 mg, 10 mg, or 16 mg for 48 weeks, according to prespecified dose-escalation schedules. The primary endpoint was the percentage change in body weight at week 32, with the week 48 body weight change as a key secondary endpoint. By week 48, the mean WL ranged from 10.5% in the 3/6 mg group to 22.3% in the 16 mg group. Moreover, 52% of participants receiving 16 mg achieved $\geq 20\%$ weight loss, while $\geq 25\%$ WL was observed in 35% and 29% of those treated with 16 and 10 mg, respectively, versus 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively). TEAEs were predominantly gastrointestinal and mostly mild to moderate, with higher rates in the 16 mg group. Treatment discontinuation due to AEs occurred in 3.1%, 10.6%, and 19.6% of participants in the 3/6, 10, and 16 mg groups, respectively, versus 0% in the placebo group. Because these findings are currently available from a company-sponsored conference presentation rather than a full peer-reviewed publication, they should be interpreted as preliminary results.

However, these findings are supported by phase 3 evidence from the *GLORY-1*, a double-blind, placebo-controlled trial conducted in China that enrolled 610 adults with obesity or overweight and at least one ORC. At baseline, the participants had a mean age of 34.2 years and a mean BMI of 31.1 kg/m². Once-weekly mazdutide was administered with dose escalation to 4 or 6 mg over 48 weeks and produced clinically meaningful, dose-dependent WL. At week 32, the mean body weight change was -10.09% with mazdutide 4 mg and -12.55% with mazdutide 6 mg, compared with $+0.45\%$ with placebo; 73.9% and 82.0% of participants in the two active treatment groups, respectively, achieved at least 5% WL versus 10.5% with placebo. By week 48, weight loss was sustained at -11.00% and -14.01% with mazdutide 4 and 6 mg, respectively, compared with $+0.30\%$ with placebo, while 35.7% and 49.5% of participants achieved at least 15% WL versus 2.0% with placebo. In addition to WL, mazdutide improved multiple prespecified cardiometabolic measures, including waist circumference, systolic blood pressure, triglyceride concentrations, total and low-density lipoprotein (LDL) cholesterol concentrations, serum uric acid levels, and alanine aminotransferase (ALT) concentrations. The safety profile was dominated by GI AEs, primarily nausea, diarrhoea, and vomiting, which were mostly mild to moderate in severity and occurred mainly during dose escalation; discontinuation due to AEs was infrequent, occurring in 1.5% of participants receiving 4 mg, 0.5% receiving 6 mg, and 1.0% receiving placebo [42].

A subsequent phase 3 study, GLORY-2 [43], extended these findings to a higher dose regimen. According to company-reported topline results, 462 Chinese adults with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), including 16% with T2D, were randomised in a 2:1 ratio to once-weekly mazdutide 9 mg or placebo for 60 weeks. At week 60, the mean WL reached 18.55% with mazdutide versus 3.02% with placebo, and 44.0% of participants on mazdutide achieved at least 20% weight loss compared with 2.6% on placebo. In the subgroup without T2D, the mean WL was 20.08% versus 2.81% with placebo, with 48.7% versus 3.1% achieving at least 20% weight loss. All key cardiometabolic secondary endpoints were reported as met, and discontinuation due to AEs was 2.9% with mazdutide versus 0% with placebo. However, these findings should be interpreted cautiously because full peer-reviewed phase 3 results are not yet available.

In addition to obesity, mazdutide has been evaluated as a monotherapy for T2D. According to company-reported topline results from the head-to-head phase 3 DREAMS-3 trial [44], mazdutide 6 mg produced greater reductions in both HbA_{1c} and body weight than semaglutide 1 mg, with 48% of participants achieving the composite endpoint of $\text{HbA}_{1c} < 7.0\%$ and $\geq 10\%$ weight loss versus 21% with semaglutide (mean HbA_{1c} changes of -2.03% vs. -1.84% and weight changes of -10.29% vs. -6.0% , respectively). Phase 3 evidence was further extended by DREAMS-1 [45], which enrolled patients with T2D inadequately controlled by diet and exercise alone. In this placebo-controlled trial, 320 Chinese adults (mean HbA_{1c} 8.24%, BMI 28.2 kg/m^2 , diabetes duration 1.9 years) were randomised in a 1:1:1 ratio to receive once-weekly mazdutide 4 mg, mazdutide 6 mg, or placebo for 24 weeks, followed by a 24-week extended treatment period. At week 24, HbA_{1c} fell by 1.57% and 2.15% with mazdutide 4 and 6 mg, respectively, compared with 0.14% with placebo, while body weight decreased by 5.61% and 7.81% versus 1.26% with placebo. Mazdutide also increased the proportion of participants achieving $\text{HbA}_{1c} < 7.0\%$, $\geq 5\%$ WL, and the composite endpoint of $\text{HbA}_{1c} < 7.0\%$ plus $\geq 5\%$ weight loss. GI AEs, particularly diarrhoea, decreased appetite, and nausea, were the most common and consistent with the GLP-1RA class. TEAEs leading to discontinuation were reported in one participant (0.9%) receiving mazdutide 4 mg and in six participants (5.7%) receiving mazdutide 6 mg during the 24-week treatment period, while SAEs occurred in 5.7%, 2.8%, and 0.9% of participants in the 4 mg, 6 mg, and placebo groups, respectively. Mazdutide also produced a modest dose-related increase in pulse rate, which peaked during dose escalation and declined thereafter.

Mazdutide has recently received first-in-class regulatory approval from the China National Medical Products Administration (NMPA) for long-term weight management and T2D treatment. In China, it is approved for chronic weight management in adults with a $\text{BMI} \geq 28 \text{ kg/m}^2$ or a $\text{BMI} \geq 24 \text{ kg/m}^2$ with at least one ORC. While this milestone is supported by the accumulating efficacy and safety evidence from the Chinese phase 3 program, a broader evaluation is warranted to establish generalizability beyond the Chinese population and across more diverse metabolic phenotypes.

Pemvidutide, a dual GLP-1 and GCG RA, has shown promising activity in MASH. A total of 212 participants (mean BMI 38.7 kg/

m^2) were assigned to receive pemvidutide 1.2 mg ($n=41$), pemvidutide 1.8 mg ($n=85$), or placebo ($n=86$) in a randomised, double-blind, placebo-controlled phase 2b trial (IMPACT). Of the 193 (91%) participants, 188 (89%) completed 24 weeks of treatment and had interpretable paired biopsy [46]. At week 24, the primary endpoint (metabolic dysfunction-associated steatohepatitis (MASH) resolution without worsening of fibrosis) was significantly more frequent with pemvidutide than with placebo, achieved by 58% in the 1.2 mg group and 52% in the 1.8 mg group versus 20% with placebo (both $p < 0.0001$). In contrast, fibrosis improvement without worsening of MASH did not differ significantly from that of the placebo at week 24 (33% and 36% with pemvidutide 1.2 and 1.8 mg, respectively, vs. 28% with placebo). Beyond MASH, pemvidutide produced modest but clinically relevant WL at 24 weeks (-4.8% with 1.2 mg and -5.8% with 1.8 mg vs. -0.5% with placebo), with trajectories suggesting ongoing WL through the end of treatment. Pemvidutide was generally well tolerated for 24 weeks. AEs occurred in 78% and 81% of participants receiving pemvidutide 1.2 and 1.8 mg, respectively, compared with 67% receiving placebo, with GI AEs being the most common. Discontinuation due to AEs was infrequent (1% with pemvidutide and 2% with placebo).

Beyond dual-agonist strategies, *UBT251*, a once-weekly administered triple GLP-1/GIP/GCG RA, has generated early proof-of-concept data. In a phase 1b randomised, placebo-controlled study involving 36 adults with overweight or obesity, *UBT251* produced dose-dependent reductions in body weight and HbA_{1c} over 12 weeks. Based on these findings, a phase 2 study was initiated in adults with overweight or obesity in China (NCT07134335 [47]).

Among the triple agonists, *retatrutide*, which combines GIP, GLP-1, and GCG receptor agonism, has attracted particular attention because of its marked effects on both glycemic control and body composition. In a phase 2 trial [48], adults with T2D ($n=281$) were assigned to receive SC placebo, dulaglutide 1.5 mg, or retatrutide at different doses. Changes in body composition, measured using dual-energy X-ray absorptiometry (DXA), were assessed in 189 participants after 36 weeks. Retatrutide produced dose-dependent reductions in total fat mass, with the largest effect observed in the pooled 8 mg group (-26.1%) and a similarly pronounced reduction at 12 mg (-23.2%), compared with -4.5% in the placebo group and -2.6% in the dulaglutide 1.5 mg group. Although the lean mass also declined, the relative composition of WL remained within the range reported for other obesity pharmacotherapies, suggesting that retatrutide did not produce disproportionate lean-tissue loss despite its marked overall effect. Retatrutide also reduced visceral adiposity and improved fat distribution markers, such as the trunk-to-leg and android-to-gynoid fat ratios. The safety profile in the sub-study was consistent with that of the main phase 2 program: GI AEs were the most frequently reported, SAEs were uncommon across groups, and no deaths were reported.

Additional evidence for its anti-obesity potential comes from the phase 3 TRIUMPH-4 trial, the results of which are currently available as company-reported topline data rather than a peer-reviewed publication. According to Lilly's December 2025 press release [49], 445 adults with overweight or obesity and knee osteoarthritis were randomised to receive once-weekly

retatrutide 9 mg, 12 mg, or placebo for 68 weeks. In the efficacy estimand, the mean WL was 26.4% and 28.7% with 9 and 12 mg retatrutide, respectively, versus 2.1% with placebo. $A \geq 25\%$ WL was achieved in 47.7% and 58.6% of participants in the 9 and 12 mg groups, respectively, compared with 1.3% in the placebo group. Additionally, $\geq 35\%$ WL occurred in 18.2% and 23.7% versus 0% with 9 and 12 mg of retatrutide, respectively. Treatment also improved non-high-density lipoprotein (HDL) cholesterol, triglyceride, and high-sensitivity C-reactive protein concentrations. AEs were predominantly GI and consistent with incretin-based therapies, while dysesthesia was reported in 8.8% and 20.9% of participants in the 9 and 12 mg groups, respectively, versus 0.7% with placebo. Discontinuation rates due to AEs were 12.2% and 18.2% with retatrutide 9 and 12 mg, respectively, compared with 4.0% with placebo, and were often related to high baseline BMI or perceived excessive WL.

A new phase 3 trial of retatrutide has also emerged in T2D. According to Lilly's March 2026 press release [50] reporting topline results from TRANSCEND-T2D-1, 537 adults with T2D inadequately controlled with diet and exercise alone (baseline HbA_{1c} 7.9%; BMI 35.8 kg/m²) were randomised in a 1:1:1:1 ratio to once-weekly retatrutide 4 mg, 9 mg, 12 mg, or placebo for 40 weeks, with all active treatment groups starting at 2 mg and escalating every 4 weeks to the target dose. Retatrutide met the primary endpoint, reducing HbA_{1c} by 1.7%, 2.0%, and 1.9% in the 4, 9, and 12 mg groups, respectively, versus 0.8% with placebo (efficacy estimand). WL was also substantial, reaching 11.5%, 15.5%, and 16.8% versus 2.5% with placebo, with no plateau reportedly observed by week 40. Additional improvements were observed in non-HDL cholesterol, triglyceride, and systolic blood pressure levels. The most common AEs were GI, which occurred primarily during dose escalation. Nausea, diarrhoea, and vomiting were more frequent with retatrutide than with placebo, whereas dysesthesia was reported in 2.3%–4.5% of retatrutide-treated participants. Discontinuation due to AEs occurred in 2.2%, 4.5%, and 5.1% of participants receiving 4, 9, and 12 mg retatrutide, respectively, compared with 0% in the placebo group. Because these results are currently available from a company press release rather than a peer-reviewed publication, they should be interpreted as preliminary results. Taken together, these data position retatrutide as one of the most effective emerging incretin-based therapies and justify ongoing clinical development, including at least 13 active trials registered in Eli Lilly's clinical program.

HM15275 is a long-acting GLP-1/GIP/GCG triple co-agonist under early clinical evaluation. In the first-in-human randomised, double-blind, placebo-controlled phase 1 study [51], multiple ascending-dose cohorts enrolled adults with obesity without T2D (mean BMI 31.9–35.1 kg/m²), using an 8:2 allocation (active: placebo) and a 4-week treatment period followed by a follow-up. Across the MAD cohorts, placebo-adjusted weight change at day 29 showed a dose–response signal, reaching a mean reduction of –4.81% in the highest titration cohort (0.5/2/4/8 mg). In the safety dataset, TEAEs were common and largely GI, and no SEA was reported. Two discontinuations occurred in the active arms and were not considered treatment-related. The pharmacokinetics of HM15275 support once-weekly dosing, and a phase 2 obesity study (NCT07205900 [52]) is currently in the recruitment phase.

Once-monthly SC *maridebart cafraglutide* (MariTide) [53], a long-acting peptide-antibody conjugate developed by Amgen, which combines GLP-1 RA with GIP receptor antagonism, was evaluated in a multinational, double-blind, placebo-controlled phase 2 dose-ranging trial that enrolled 592 participants across two cohorts: an obesity cohort ($n=465$; mean BMI 37.9 kg/m²) and an obesity-diabetes cohort ($n=127$; mean BMI 36.5 kg/m²; mean HbA_{1c} 7.9%). In the obesity cohort, participants were randomised to receive monthly doses of 140, 280, or 420 mg every 4 weeks; 420 mg every 8 weeks; 420 mg every 4 weeks with a 4-week dose escalation; 420 mg every 4 weeks with a 12-week dose escalation; or placebo. In the obesity-diabetes cohort, participants received 140, 280, or 420 mg every 4 weeks or placebo. At week 52, the treatment-policy estimand showed a mean WL ranging from 12.3% to 16.2% in participants without diabetes versus 2.5% with placebo and from 8.4% to 12.3% in those with obesity and T2D versus 1.7% with placebo. Under the efficacy estimand, the WL reached 19.9% and 17.0%, respectively. In the obesity-diabetes cohort, HbA_{1c} decreased by 1.2% to 1.6% with the treatment-policy estimand and by up to 2.2% with the efficacy estimand. The safety profile was largely GI and dose dependent. In the obesity cohort, 90%–99% of MariTide-treated participants reported at least one AEs versus 68% with placebo; in the obesity-diabetes cohort, the corresponding rates were 91%–97% versus 81%. GI AEs, particularly nausea and vomiting, were the most common and were clearly less frequent with lower starting doses and dose-escalation regimens. In the obesity cohort, discontinuation of the trial regimen due to GI AEs occurred in 8% of participants in the dose-escalation groups, compared with 12%–27% in the non-escalation groups. In the obesity-diabetes cohort, the corresponding range was 6%–16%. These findings support MariTide as a promising once-monthly therapy; although, its tolerability appears to depend substantially on lower starting doses and gradual dose escalation.

Kailera [54] is also advancing an early stage research portfolio, including *KAI-4729*, a next-generation injectable GLP-1/GIP/GCG receptor agonist intended for the treatment of obesity and metabolic diseases.

Efinopegdutide (MK-6024), a GLP-1/GCG co-agonist, remains in clinical development with ongoing trials; however, no major peer-reviewed outcomes in obesity/T2D have been identified in 2025, and earlier trials reported tolerability limitations at higher doses.

Overall, this group of dual and triple agonists illustrates the widening mechanistic scope of obesity pharmacotherapy: some agents may offer differentiated effects on liver disease or body composition, whereas others are being developed primarily to increase the upper boundary of WL. Simultaneously, differences in phase, population, and evidence maturity remain important when making cross-trial comparisons.

2.4 | Amylin Analogues and Related Peptides

Amylin analogues represent a complementary strategy to incretin-based therapy. *Cagrilintide*, a long-acting human amylin analogue, was evaluated in combination with semaglutide in the phase 3a REDEFINE 1 trial [55], a 68-week,

multicenter, double-blind, placebo- and active-controlled study in adults without T2D who were obese or overweight with at least one ORC. Participants were randomised in a 21:3:3:7 ratio to once-weekly fixed-dose *cagrilintide-semaglutide* (2.4 mg/2.4 mg), semaglutide 2.4 mg, cagrilintide 2.4 mg, or placebo, all combined with LI. Treatment was initiated at 0.25 mg of each component and escalated every 4 weeks to the target dose by week 16, with protocol-permitted dose delays or reductions for tolerance. In the full trial population ($n = 3417$; mean age 47.0 years, mean BMI 37.9 kg/m²), CagriSema achieved a mean WL of 20.4% at week 68 under the treatment-policy estimand, compared with 14.9% with semaglutide, 11.5% with cagrilintide, and 3.0% with placebo; under the trial-product estimand, WL reached -22.7% with CagriSema. WL target attainment was also substantially greater with CagriSema, with 91.9% of participants achieving at least 5% WL, 53.6% at least 20%, 34.7% at least 25%, and 19.3% at least 30%, whereas the corresponding 25% and 30% thresholds were reached by 14.8% and 8.7% with semaglutide alone, respectively. Beyond WL, CagriSema significantly improved waist circumference, systolic blood pressure, and physical function scores; among participants with prediabetes at baseline, 87.7% attained normoglycemia versus 32.2% with placebo. The safety profile was dominated by GI AEs, which occurred in 79.6% of participants receiving CagriSema versus 73.8% with semaglutide, 54.0% with cagrilintide, and 39.9% with placebo. Permanent discontinuation due to AEs occurred in 5.9% of patients treated with CagriSema, including 3.6% due to GI AEs; SEA were reported in 9.8% of patients, and two deaths occurred in the CagriSema group, adjudicated as suicide and cancer. Notably, only 57.4% of participants in the CagriSema group were receiving the maximum dose at week 68, although 74.7% had reached it at some point, suggesting that substantial efficacy was maintained despite flexible dose adjustment under routine-like conditions. A subsequent post hoc analysis further focused on cardiometabolic effects: clinically relevant reductions in blood pressure were observed across BMI subgroups, irrespective of whether the baseline BMI was above or below 35 kg/m². At week 68, reductions in blood pressure with CagriSema were greater than those reported for either monotherapy, and systolic blood pressure decreased by 10.9 mmHg despite a substantial proportion of participants reducing their concomitant antihypertensive treatment use [56].

REDEFINE 2 [57] extended CagriSema to adults with T2D. This phase 3a, double-blind, placebo-controlled trial randomised 1206 adults in a 3:1 ratio to once-weekly fixed-dose *cagrilintide-semaglutide* 2.4 mg/2.4 mg ($n = 904$) or placebo ($n = 302$), both combined with LI, for 68 weeks. At baseline, the mean BMI was 36.2 kg/m², the mean HbA_{1c} level was 8.0%, and the mean diabetes duration was 8.5 years. Dose escalation was similar to that used in the REDEFINE 1 study. Notably, 61.9% of the participants in the CagriSema group received the full 2.4 mg dose at week 68, although 75.9% had reached it at some point during the trial.

Using the treatment-policy estimand, the mean WL at week 68 was 13.7% with CagriSema versus 3.4% with placebo, with 83.6% versus 30.8% of participants achieving at least 5% WL. Higher responder thresholds also favoured CagriSema: 65.6%

versus 10.3% achieved at least 10% WL, 43.8% versus 2.4% achieved at least 15% WL, and 22.9% versus 0.5% achieved at least 20% WL. In parallel, glycemic control improved substantially, with a decrease in HbA_{1c} of 1.8% with CagriSema versus 0.4% with placebo; 73.5% of treated participants achieved HbA_{1c} $\leq 6.5\%$ compared with 15.9% in the placebo group. Additional benefits included greater reductions in waist circumference and systolic blood pressure, and improvements in physical function scores. In the continuous glucose monitoring subgroup, the mean time in range increased from 43.6% at baseline to 86.8% at week 68 with CagriSema, compared with 41.3% to 50.2% with placebo.

GI AEs were common and were reported in 72.5% of participants receiving CagriSema versus 34.4% with placebo; however, they were mostly transient and mild to moderate in severity. Permanent discontinuation due to any AEs occurred in 8.4% versus 3.0%, and discontinuation specifically due to GI AEs occurred in 4.8% versus 0.7%, respectively. SAEs were reported in 10.4% of participants in the CagriSema group and 12.9% in the placebo group. Level 2 hypoglycemia occurred in 6.0% versus 3.3%, whereas level 3 events were rare (0.2% with CagriSema and none with placebo) and occurred only in participants receiving concomitant sulfonylureas. Overall, REDEFINE 2 showed that CagriSema can deliver clinically meaningful WL together with near-normoglycemic control in patients with T2D, albeit with the expected tolerability burden of a potent incretin-amylin combination.

According to Novo Nordisk, CagriSema is now being advanced in head-to-head programs against established therapies, including semaglutide and tirzepatide. In a press release [58] reporting topline results from the phase 3 REIMAGINE 2 trial (68 weeks), Novo Nordisk stated that CagriSema 2.4 mg/2.4 mg was superior to semaglutide 2.4 mg for both glycemic control and WL in 2728 adults with T2D inadequately controlled on metformin, with or without a sodium-glucose cotransporter-2 inhibitor [SGLT2i] (approximately 40% on SGLT2i; mean baseline HbA_{1c} was 8.2%). Using the efficacy estimand, HbA_{1c} decreased by 1.91% with CagriSema 2.4/2.4 mg versus 1.76% with semaglutide 2.4 mg and increased by 0.09% with placebo; concomitant WL was 14.2% versus 10.2% (semaglutide 2.4 mg) and 1.5% (placebo), with no plateau reported at week 68. Using the treatment regimen estimand, Novo Nordisk reported HbA_{1c} reductions of 1.80% versus 1.68% and WL of 12.9% versus 9.2% for CagriSema 2.4/2.4 mg versus semaglutide 2.4 mg, respectively. Safety was consistent with that of incretin- and amylin-based therapies, with predominantly mild-to-moderate GI AEs diminishing over time. Separately, Novo Nordisk disclosed [59] topline results from REDEFINE 4 (open-label, 84 weeks), a phase 3 head-to-head trial in 809 adults with obesity and at least one comorbidity (mean body weight was 114.2 kg) comparing once-weekly CagriSema 2.4/2.4 mg with tirzepatide 15 mg. The company reported that the trial did not meet its primary non-inferiority endpoint for WL versus tirzepatide: under the efficacy estimand, WL was 23.0% with CagriSema versus 25.5% with tirzepatide at week 84; under the treatment-regimen estimand, WL was 20.2% versus 23.6%, respectively. In the same press release, Novo described a class-consistent tolerability profile with GI AEs that were largely mild-to-moderate and diminished over time

and noted that additional trials, including higher-dose combinations, are planned to further explore the full weight-loss potential of CagriSema.

Taken together, the peer-reviewed REDEFINE 1 and REDEFINE 2 trials established CagriSema as one of the most effective incretin-amylin combinations currently in development, whereas the more recent head-to-head data from REIMAGINE 2 and REDEFINE 4 remain company-reported and should be interpreted as preliminary until full peer-reviewed results become available.

Petrelintide (ZP8396), a once-weekly amylin analog, has also shown encouraging antiobesity activity during early clinical development. According to topline company-reported results [60] from the phase 2 ZUPREME-1 trial, 493 adults with obesity or overweight and at least one ORC (mean BMI 37 kg/m²; mean age 48 years; 53% women) were randomised to one of five once-weekly petrelintide regimens or a placebo for 42 weeks. The study included a dose-escalation period of up to 16 weeks, with dose increases every 4 weeks, and the primary endpoint was the change in body weight from baseline to week 28. All petrelintide groups achieved greater WL than placebo at week 28, and under the efficacy estimand, the highest-performing regimen produced WL of up to 10.7% at week 42 versus 1.7% with placebo. Notably, 98% of the participants in the group with the greatest WL reached the planned maintenance dose during the trial. Roche described petrelintide as having placebo-like tolerability, with discontinuation due to AEs occurring in 4.8% of petrelintide-treated participants and 4.9% of those receiving placebo; withdrawal for any reason was less frequent with petrelintide than with placebo (8.4% vs. 13.6%, respectively). Based on these findings, Roche announced the further development of petrelintide as a monotherapy and in combination with the dual GLP-1/GIP receptor agonist CT-388.

AZD6234, a selective amylin RA developed by AstraZeneca, is being evaluated as a monotherapy and in combination-based strategies. A phase 1 randomised, single-blind, placebo-controlled repeat-dose study (NCT06132841 [61]) in participants with overweight or obesity has been completed, and AstraZeneca's current pipeline materials also list a phase 2 monotherapy program (APRICUS, NCT06595238 [62]) in obesity or overweight individuals with comorbidities. In parallel, the phase 2b ASCEND trial (NCT06862791 [63]) is evaluating AZD6234 in combination with *AZD9550*, a GLP-1/GCG RA, in adults with obesity or who are overweight and have at least one ORC. However, no mature peer-reviewed efficacy data are available for AZD6234, and its positioning remains investigational.

Additional amylin-based candidates have emerged. *GUBamy* [64], a once-weekly SC amylin analog evaluated in healthy lean and overweight participants, produced an early WL possibility in first-in-human testing, supporting its continued exploratory development.

MET-233 is a very long-acting amylin analog being developed by Metsera for SC administration, with the stated goal of enabling once-monthly dosing and potential use as monotherapy

or in combination with the company's ultra-long-acting GLP-1RA *MET-097i* (PF-3944). Early clinical evidence comes from a phase 1 program in 40 adults with overweight or obesity, in which once-weekly SC *MET-233* at 1.2 mg was associated with a placebo-subtracted 8.4% reduction in body weight over 5 weeks (company-reported) [65]. In the multiple ascending dose portion, GI AEs were mild, dose-dependent, and largely confined to the first week of dosing, suggesting rapid development of tolerance despite pharmacokinetic accumulation over the 5-week period. Lower anticipated starting doses (0.15 and 0.3 mg) were reported to have tolerability comparable to that of the placebo across both single- and multiple-dose cohorts, with no safety concerns or severe or serious adverse events reported to date (company-reported). Further evaluation is ongoing in phase 1/2 trials assessing once-weekly SC *MET-233* as monotherapy (NCT07022977 [66]) and in combination with *MET-097* (NCT06924320 [67]) in adults with overweight or obesity, with and without T2D.

A recent phase 2 study reported the efficacy and safety of *eloralintide*, a novel, selective, long-acting amylin RA that activates the human amylin 1 receptor (AMY1R) approximately 12 times more potently than the human calcitonin receptor. A total of 263 adults with BMI ≥ 30 kg/m² or ≥ 27 kg/m² without T2D were enrolled in this RCT. All participants were assigned to a placebo or one of six eloralintide regimens (1, 3, 6, 9, 6–9, and 3–6–9 mg) for 48 weeks. Under the efficacy estimand, the mean WL at week 48 was 9.5%, 12.4%, 17.6%, 20.1%, 19.9%, and 16.4% for the 1, 3, 6, 9, 6–9 and 3–6–9 mg groups, respectively, compared with 0.4% in the placebo group ($p < 0.001$ for all). A DXA substudy demonstrated that most WL reflected a reduction in fat mass rather than lean tissue. WL $\geq 20\%$ was achieved in 57% of participants receiving 9 mg and 50% of those treated with 6–9 mg, while $\geq 30\%$ reductions occurred in 19% and 21%, respectively. Eloralintide also produced favourable cardiometabolic effects (significant reductions in fasting plasma glucose and triglycerides) versus placebo, particularly in the 9 mg and dose-escalation groups. TEAEs were reported in 81% of the eloralintide-treated participants and 71% of the placebo recipients. The incidence of GI AEs was higher with eloralintide (8%–33%) than with placebo (0%–13%); however, it was lowest in the 3–6–9 mg escalation group (2%–25%), indicating improved tolerability with gradual titration. Overall, 10% (21 of 208) of participants discontinued treatment due to AEs in the eloralintide group compared with 8% (4 of 52) in the placebo group. Interestingly, treatment was also associated with modest reductions in heart rate, suggesting possible improvements in autonomic nervous system balance [68].

Amycretin, a single-molecule GLP-1 and amylin RA developed by Novo Nordisk, has also shown promise in phase 2 trials in adults with T2D and excess body weight. In a recent phase 2 trial [69], 448 adults with overweight or obesity and T2D were randomised to receive once-weekly SC amycretin (0.4–40 mg), once-daily oral amycretin (6, 25, or 50 mg), or placebo for up to 36 weeks. Subcutaneous amycretin produced dose-dependent HbA_{1c} reductions of up to 1.8%, and oral amycretin achieved HbA_{1c} reductions of up to 1.5%. All comparisons with placebo were statistically significant. Weight loss reached –14.5% with the highest SC dose (vs. –2.6% with placebo) and –10.1% with the highest oral dose (vs. –2.5% with the placebo). No plateau in WL was observed at 36 weeks in the higher-dose cohort. These

preliminary findings support amycretin as a potentially important bridge between amylin-based therapy and multi-target incretin pharmacology, although long-term efficacy and tolerability data are still needed.

Taken together, this subgroup of amylin-based agents illustrates two parallel development paths: direct anti-obesity monotherapy with newer amylin analogs and combination strategies intended to complement incretin-based efficacy. However, apart from CagriSema, most of these programs are still in the early stages of development, and their ultimate clinical value will depend on whether gains in convenience or body composition profiles can be achieved without significantly worsening tolerability.

2.5 | Oral GLP-1 Receptor Agonists

In addition to the two currently approved oral GLP-1 RAs, oral semaglutide and orforglipron, parallel efforts have focused on developing additional oral incretin-based agents capable of approaching the efficacy of weekly injectable therapies. These agents may broaden access, improve adherence, and expand first-line pharmacological options for obesity and T2D.

ACHIEVE-1 [70], a phase 3 RCT, evaluated orforglipron, a once-daily oral non-peptide GLP-1RA, in 559 adults with T2D inadequately controlled by diet and exercise alone. Participants had a mean diabetes duration of 4.4 years and a mean baseline HbA_{1c} of 8.0%, and were randomised to receive orforglipron 3, 12, or 36 mg or placebo for 40 weeks. At week 40, HbA_{1c}, the primary endpoint, decreased by 1.24% to 1.48% with orforglipron versus 0.41% with placebo, and 68%–73% of participants achieved an HbA_{1c} below 7.0%. Body weight, a key secondary endpoint, decreased by 4.5%–7.6% with orforglipron compared with 1.7% with placebo. The proportions of participants achieving at least 5%, 10%, and 15% WL were 43%–61%, 15%–30% and 4%–10%, respectively, compared to 17%, 6%, and 1% with placebo. AEs were predominantly GI, dose-dependent, and mild-to-moderate in severity. Hypoglycemia was infrequent (0%–1.4%), with no cases of severe stages, while discontinuation due to GI AEs occurred in 2.2%–5.7% of participants receiving orforglipron and in none receiving placebo.

Additional phase 3 studies [71] have extended the evidence base for orforglipron in different treatment settings. In ACHIEVE-2, orforglipron was reported to be superior to dapagliflozin for glycemic control, whereas in ACHIEVE-5, it remained superior to placebo across the tested doses. Taken together, the ACHIEVE program suggests that oral GLP-1 receptor agonism with orforglipron can deliver clinically meaningful reductions in both HbA_{1c} and body weight across a range of baseline treatment scenarios.

ACHIEVE-3 [72] provided the first randomised phase 3 head-to-head comparison between orforglipron and oral semaglutide in adults with T2D inadequately controlled with metformin (≥ 1500 mg/day; HbA_{1c} 7.0%–10.5%; BMI ≥ 25 kg/m²). Participants ($n = 1698$; mean HbA_{1c} 8.3%, weight 97.0 kg, BMI 35.1 kg/m²) were randomised 1:1:1 to receive orforglipron 12 mg or 36 mg (escalated from 1 mg with 4-weekly up-titration) or semaglutide 7 mg or 14 mg (escalated from 3 mg

with the standard fasting/water and pre-meal administration requirements). The primary endpoint (HbA_{1c} change at week 52; treatment-regimen estimand) showed that both orforglipron doses were not only non-inferior but also statistically superior to both semaglutide doses: mean HbA_{1c} reductions were -1.71% (12 mg) and -1.91% (36 mg) versus -1.23% (7 mg) and -1.47% (14 mg), with treatment differences ranging from -0.24% to -0.68% . These glycemic advantages translated into higher target attainment (HbA_{1c} $< 7.0\%$: 72%–76% with orforglipron vs. 54%–64% with semaglutide; HbA_{1c} $\leq 6.5\%$: 63%–68% vs. 38%–48%; HbA_{1c} $< 5.7\%$: 21%–31% vs. 7%–12%). WL was also greater with orforglipron (treatment regimen: -6.1% and -8.2%) than semaglutide (-3.9% and -5.3%), with significantly more participants reaching clinically meaningful WL thresholds ($\geq 10\%$: 28%–44% with orforglipron vs. 13%–21% with semaglutide; $\geq 15\%$: 12%–23% vs. 5%–6%). Importantly for clinical practice, fewer participants required rescue therapy for severe persistent hyperglycemia with orforglipron (2%–3%) than with semaglutide (6%–12%). Safety was broadly class-consistent but with clear tolerability trade-offs: GI AEs were more frequent with orforglipron (58%–59%) than semaglutide (37%–45%), discontinuations due to AEs were higher (9%–10% vs. 4%–5%), and mean pulse-rate increases were larger (3.7–4.7 bpm vs. 1.0–1.5 bpm). The rates of adjudication-confirmed pancreatitis, gallbladder events, diabetic retinopathy events (including category worsening), and hepatic AEs were similar across the groups.

The ATTAIn-2 trial [73] evaluated the efficacy and safety of orforglipron in adults with T2D who were overweight or obese. In this phase 3, randomised, double-blind trial, 1613 participants (mean age 56.8 years; 46.9% women) with baseline HbA_{1c} 7.0%–10.0% were assigned in a 1:1:1:2 ratio to once-daily orforglipron 6 mg, 12 mg, or 36 mg or placebo, for 72 weeks, in addition to stable antihyperglycemic therapy or LI. At week 72, the mean WL under the efficacy estimand reached 5.5%, 7.8%, and 10.5% with the 6, 12, and 36 mg doses, respectively, compared with 2.2% with placebo ($p < 0.001$ for all comparisons). The corresponding HbA_{1c} reductions were 1.29%, 1.60%, and 1.79% versus 0.14% with placebo. More than half (66.6%) of the participants receiving orforglipron achieved HbA_{1c} $\leq 6.5\%$, and 23.7% of those treated with 36 mg reached HbA_{1c} $< 5.7\%$. The adverse event profile was consistent with that of the GLP-1RA class, with GI AEs occurring most commonly during the dose-escalation phase in the first 24 weeks. Clinically significant hypoglycemia was reported in 20 participants, and severe hypoglycemia was reported in only one participant. The rates of diabetic retinopathy and hepatic events were similar across the treatment and placebo groups. Discontinuation due to AEs occurred in 6.1%, 9.6%, and 9.9% of participants receiving orforglipron 6, 12, and 36 mg, respectively, compared with 4.1% in the placebo group.

Taken together, the ACHIEVE and ATTAIn programs suggest that orforglipron can be considered the most advanced oral GLP-1RA, with efficacy that can approach lower-range injectable GLP-1RA regimens. At the same time, GI tolerability and discontinuation remain important practical constraints, particularly at higher doses and over longer durations of treatment.

AZD5004/ECC5004 (*elecoglipron*), jointly developed by Eccogene and AstraZeneca, is an orally administered small-molecule GLP-1RA in clinical development for obesity and T2D.

According to company-reported topline results from a phase 1b trial [74] in China, once-daily evecoglipron was administered for 16 weeks to 45 adults with overweight or obesity, with or without T2D, primarily to assess safety, tolerability, and pharmacokinetics/pharmacodynamics. Evecoglipron was described as generally well tolerated, with a class-consistent adverse-event profile that was predominantly mild to moderate and GI, with no TEAEs leading to discontinuation and no reported liver safety signals.

AstraZeneca subsequently completed two global phase 2b studies: VISTA (NCT06579092 [75]; $n=310$), a 36-week placebo-controlled trial in adults with obesity or overweight and at least one ORC, and SOLSTICE (NCT06579105 [76]; $n=406$), a 26-week trial in T2D designed to evaluate glyemic efficacy versus placebo with oral semaglutide as an open-label active comparator. Both studies are listed as complete in trial registries and AstraZeneca trial materials; however, detailed efficacy and safety results have not yet been reported in peer-reviewed journals.

VCT220 is another oral, small-molecule, once-daily GLP-1RA developed for weight management. In a phase 2 trial presented at ADA 2025 [77], 250 Chinese adults without T2D (mean BMI 32.03 kg/m²) with BMI ≥ 28 kg/m² or BMI 24–28 kg/m² plus at least one ORC were randomised within dose cohorts (80 mg, 120 mg, or 160 mg) to VCT220 or placebo (3:1), and the 160 mg cohort was further split 1:1 into fast- and slow-titration regimens. At week 16, the mean WL ranged from -5.8% to -9.7% across the VCT220 cohorts versus -1.6% with placebo, with the largest reductions reported in the 160 mg titration arms (-9.7% fast titration and -9.4% slow titration; both $p \leq 0.001$ versus placebo, company-reported). In addition, 55.4%–90.3% of participants receiving VCT220 achieved at least 5% weight loss by week 16 compared with 13% on placebo, and treatment was associated with improvements in cardiometabolic measures, including blood pressure and liver enzymes. VCT220 was generally well tolerated, most AEs were GI and mild-to-moderate in severity, and no TEAEs were reported.

HRS-7535 is an orally administered small-molecule GLP-1RA that is under development for T2D, obesity, and ORC. In a 16-week phase 2 trial in Chinese adults with T2D inadequately controlled on metformin monotherapy ($n=194$; baseline HbA_{1c} 8.5%, BMI 26.7 kg/m²), participants were assigned in a 1:1:1:1:1 ratio to once-daily HRS-7535 at 15 mg, 30 mg, 60 mg, or 90 mg, or placebo; the 60 and 90 mg regimens were reached via titration [78]. At week 16, the placebo-adjusted least-squares mean HbA_{1c} reductions were -0.94% , -1.34% , -1.57% , and -1.39% across the 15–90 mg doses (all $p < 0.001$ vs. placebo). Body-weight effects were modest over this short treatment window, with a least-squares mean percentage change of -2.63% at 90 mg versus -1.30% with placebo treatment. TEAEs were common and largely GI (dose-dependent nausea, diarrhoea, and vomiting), generally mild-to-moderate; hypoglycemia was infrequent and not clinically significant. A trend toward higher amylase/lipase concentrations was observed in the absence of pancreatitis.

In a separate phase 2 study in adults with obesity without T2D ($n=235$; baseline BMI 32.5 kg/m²), participants were assigned in a 1:1:1:1:1 ratio to target once-daily doses of 30, 60, 120, and 180 mg of the drug or placebo for 36 weeks (26-week trial with

a 10-week extension) [79]. At week 26, the least-squares mean percentage WL was -2.99% (30 mg), -7.17% (60 mg), -6.17% (120 mg), and -9.36% (180 mg) versus -2.50% with placebo, with statistical separation versus placebo at 60, 120, and 180 mg. (GI) AEs (nausea, diarrhoea, and vomiting) were the most frequent, occurring often during titration and were mostly mild-to-moderate in severity; no trend toward liver enzyme elevations was reported. Early treatment discontinuation occurred in 13.2% of patients overall, including 2.1% of discontinuations due to AEs in the HRS-7535 group.

Aleniglipton is another investigational oral, once-daily, non-peptide small-molecule GLP-1RA in phase 2 development for the treatment of obesity. According to company-reported topline results [80] from ACCESS II, a randomised, double-blind, placebo-controlled 44-week study in 85 adults with obesity or overweight plus at least one ORC, participants started at 5 mg and were titrated every 4 weeks to target doses of 120, 180, or 240 mg. At week 44, the mean body weight change from baseline was -13.6% , -15.3% , and -15.0% in the 120, 180, and 240 mg groups, respectively, with no apparent WL plateau compared with $+1.1\%$ in the placebo group.

Interim data from the ongoing [81] body-composition study and ACCESS open-label extension suggest that WL continues beyond 36 weeks and that slower titration from a 2.5 mg starting dose may improve tolerability. In the open-label extension, participants previously treated with aleniglipton and transitioned to a maximum dose of 120 mg achieved up to 16.2% WL from baseline at 56 weeks, without evidence of a plateau. The safety profile described by the company was consistent with that of the drug class, with GI AEs, particularly nausea and vomiting during titration, being the most common. In ACCESS II, only one participant (3.7%) among those who received doses of 120 mg or higher between weeks 28 and 44 discontinued treatment because of AEs. Across more than 625 exposed participants, the company reported no cases of drug-induced liver injury, persistent liver enzyme elevation, or QTc prolongation.

VK-2735, an oral GLP-1/GIP RA developed by Viking Therapeutics, has emerged as a competitor in oral incretin-based weight-loss therapy. In the phase 2 VENTURE-Oral Dosing trial [82], oral VK-2735 achieved a significant mean WL of up to 12.2% from baseline after 13 weeks of treatment. However, tolerability remained an important constraint: discontinuation reached 38% in the highest-dose (120 mg) group, primarily because of GI AEs. Exploratory maintenance data suggest that lower-dose continuation after higher-dose induction may help limit weight regain; however, these findings remain preliminary. Importantly, Viking's current phase 3 program [83] is focused on the SC, not the oral, formulation of VK-2735.

NA-931 (*bioglutide*) is an oral multi-receptor agonist that targets GLP-1, GIP, GCG, and IGF-1-related pathways. According to company-reported phase 2 data [84] presented in 2025, once-daily oral NA-931 produced dose-dependent WL over 13 weeks, reaching 13.8% at 150 mg versus 1.9% with placebo, with statistical separation from placebo at 120 and 150 mg doses. Because these data currently rely on company and conference reports rather than peer-reviewed publications, the magnitude of the effect and tolerability profile should be interpreted cautiously.

Another GLP-1 RA, *danuglipron* [85], was under development; however, following a review of trial data, including a case of potential drug-induced liver injury and regulatory feedback, Pfizer decided to discontinue its clinical development.

TERN-601, developed by Terns Pharmaceuticals, was evaluated in the FALCON Phase 2 trial in adults with obesity. Unfortunately, it does not meet the prespecified efficacy threshold, and its metabolic disease development has been discontinued [86].

Several additional oral GLP-1-based drugs are in the early or uncertain stages of development. *KAI-7535* [87] is being developed by Kailera; however, globally mature phase 3 efficacy data are not yet available. *RGT-075*, another oral GLP-1RA, has shown a placebo-adjusted phase 2a signal over 12 weeks in company-reported results [88].

Taken together, the oral GLP-1 RA field is now broad enough to include one late-stage front-runner, several emerging small-molecule candidates, and several programs that remain exploratory or commercially vulnerable. This heterogeneity is important because, although oral delivery may improve convenience and scalability, clinically meaningful use will still depend on balancing efficacy against GI tolerability, discontinuation, and long-term safety.

2.6 | Novel Combination Strategies and Targets, Delivery Platforms

Combinations and novel mechanisms beyond classical incretin signalling are increasingly being explored to maximise WL while improving the quality of weight loss by preserving lean mass.

The phase 2 BELIEVE trial [89] provides peer-reviewed evidence that targeting the activin-myostatin pathway can modify both the magnitude and composition of pharmacologic WL. In this double-blind, placebo-controlled study, 507 adults with obesity or overweight and at least one ORC were randomised to placebo, *bimagrumab* (10 or 30 mg/kg intravenously (IV) every 12 weeks), semaglutide (1.0 or 2.4 mg once weekly), or combinations of both agents for 48 weeks, followed by an open-label extension to week 72. At baseline, the mean age was 47.5 years and the mean BMI was 37.3 kg/m². At week 48, the high-dose combination of *bimagrumab* 30 mg/kg plus semaglutide 2.4 mg produced greater absolute WL than semaglutide 2.4 mg alone (−17.8 kg vs. −14.2 kg), and by week 72, the efficacy estimand showed a 22.1% WL with the high-dose combination versus 15.7% with semaglutide 2.4 mg and 10.8% with *bimagrumab* 30 mg/kg alone. Importantly, the combination produced a markedly greater reduction in total body fat mass than semaglutide alone (−45.7% vs. −27.8% at week 72), while limiting lean-mass loss (−2.9% vs. −7.4%); *bimagrumab* monotherapy increased lean mass by 2.5% despite a 10.8% reduction in body weight. These findings support the concept that combination therapy can enhance both the magnitude and composition of weight loss.

Treatment discontinuations owing to AEs were more common in the *bimagrumab*-only groups (14.0%–21.4%) than in the

semaglutide (3.6%–8.8%), combination (5.3%–12.5%), or placebo (3.6%) groups. Muscle spasms, diarrhoea, and acne were more common with *bimagrumab*-containing regimens, whereas nausea, constipation, and fatigue were mostly related to semaglutide. All discontinuations due to nausea occurred in the combination groups ($N=6$), whereas those due to muscle spasms occurred in the *bimagrumab* monotherapy groups ($N=5$). Four cases of basal or squamous cell skin carcinoma were reported in the *bimagrumab*-only and semaglutide-only groups, with no other malignancies reported. Overall, BELIEVE suggests that anabolic-antiadiposity combinations may improve body composition outcomes; however, the IV dosing strategy, open-label semaglutide administration, and uncertainty regarding long-term safety mean that this approach remains investigational rather than practical.

The COURAGE phase 2 trial (NCT06299098 [90]) is evaluating the combination of *semaglutide* with *trevogrumab* (anti-myostatin [GDF8] antibody) and *garetosmab* (anti-activin A antibody) to enhance the quality of weight loss by preserving lean mass. Interim analyses [91] demonstrated that semaglutide monotherapy was associated with 6.5% lean mass loss, whereas the addition of *trevogrumab* preserved nearly 50% (−3.3% to 3.8%) of lean tissue, and the triplet regimen achieved up to 80.9% (−2.0%) preservation of lean mass, alongside superior total WL (−13.4% vs. −10.6% with semaglutide alone). These findings suggest that selective blockade of the activin-myostatin signalling axis may counteract GLP-1-mediated muscle loss. The combination was generally well tolerated, although the triplet arm exhibited higher discontinuation and AEs rates (30.9%), warranting further evaluation in ongoing studies. Together, the BELIEVE and COURAGE trials highlight the growing interest in approaches that not only amplify fat loss but also preserve metabolically active lean tissue, marking a conceptual shift in obesity pharmacotherapy toward body-composition-focused treatment.

Palatin's *bremelanotide* (BMT-801), a melanocortin-4 receptor (MC4R) agonist, showed [92] synergistic effects when combined with *tirzepatide* in a 4-week phase 2 study. The combination led to a mean WL of 4.4% compared with 1.6% in the placebo group ($p<0.0001$). Moreover, more participants achieved clinically relevant thresholds: 40% achieved $\geq 5\%$, 27% achieved $\geq 6\%$, and 19% achieved $\geq 7\%$ weight loss versus 27%, 13%, and 0%, respectively, with *tirzepatide* alone. More than half of the WL was regained within two weeks after treatment cessation; in contrast, the *bremelanotide*-only group maintained weight stability, suggesting a potential role for MC4R agonists in preventing weight regain. Co-administration was well tolerated, with no new safety concerns. Although these findings are preliminary, they support MC4R activation as a potentially complementary adjunct to incretin therapy.

Peptide YY (PYY), co-secreted with GLP-1 from intestinal L-cells, has been explored as a complementary satiety pathway to incretin therapy via Y2 receptor agonism. However, recent clinical data have tempered the enthusiasm for this approach. In a series of phase 1 and 2 studies, the long-acting PYY3-36 analog PYY1875 (NNC0165-1875) was evaluated alone and in combination with semaglutide 2.4 mg in adults with obesity. In the phase 2 program [93], after a 32-week semaglutide treatment that produced a mean WL of 14.3%, additional treatment with PYY1875

TABLE 2 | Characteristics of novel drugs and their combinations in the treatment of diabetes and obesity.

Substance 1	Substance 2 (co-administration)	Pharmaceutical company	Mechanism (Substance 1)	Mechanism (Substance 2)	Clinical trials/development stage
Semaglutide 7.2 mg	—	Novo Nordisk	GLP-1 RA (high-dose, once-weekly)	—	Approved in US; Phase 3: STEP UP, STEP UP T2D
Efpeglenatide (HM11260C)	—	Hanmi Pharmaceutical	Long-acting GLP-1 RA	—	Phase 3 (obesity); Phase 3 T2D initiated
PF-3944 (formerly MET-097i)	—	Pfizer/Metsera	Ultra-long-acting, fully biased GLP-1 RA	—	Phase 2b: VESPER-1, VESPER-3; Phase 3 planned
ASC30	—	Asclepis Pharma	Long-acting GLP-1 RA (quarterly dosing potential)	—	Phase 1b
Bofaglutide (GZR18)	—	Gan & Lee Pharmaceuticals	Long-acting GLP-1 RA	—	Phase 2b (T2D); Phase 3 obesity ongoing
Survodutide	—	Boehringer Ingelheim/ Zealand Pharma	Dual GLP-1/ GCG RA	—	Phase 3: SYNCHRONIZE-1, SYNCHRONIZE-2
HRS9531	—	Jiangsu Hengrui Pharmaceuticals/ Kailera Therapeutics	Dual GLP-1/GIP RA	—	Phase 3
HS-20094	—	Hansoh Pharma/ Regeneron	Dual GLP-1/GIP RA	—	Phase 3 in China; global development underway
BGM0504	—	BrightGene Health	Dual GLP-1/GIP RA	—	Phase 2
CT-868	—	Carmot Therapeutics/ Roche	Biased dual GLP-1/GIP RA	—	Phase 2
CT-388	—	Roche	Dual GLP-1/GIP RA	—	Phase 2
Mazdutide	—	Innovent Biologics/ Eli Lilly	Dual GLP-1/ GCG RA	—	Approved in China; Phase 3: GLORY and DREAMS programmes
UBT251	—	United Bio-Technology/ Novo Nordisk	Triple GLP-1/ GIP/GCG RA	—	Phase 2; global Phase 1b/2a ongoing

(Continues)

TABLE 2 | (Continued)

Substance 1	Substance 2 (co-administration)	Pharmaceutical company	Mechanism (Substance 1)	Mechanism (Substance 2)	Clinical trials/development stage
Retatrutide	—	Eli Lilly	Triple GLP-1/GIP/GCG RA	—	Phase 3: TRIUMPH and TRANSCEND programs
MariTide (maridebart cafraglutide)	—	Amgen	GLP-1 RA/GIP receptor antagonist peptide-antibody conjugate	—	Phase 2 completed; Phase 3 MARITIME initiated
KAI-4729	—	Kailera Therapeutics	Triple GLP-1/GIP/GCG RA	—	Clinical development
Cagrilintide	Semaglutide	Novo Nordisk	Amylin RA	GLP-1 RA	Phase 3: REDEFINE 1-3; REIMAGINE 1-4
Petrelintide (ZP8396)	—	Zealand Pharma	Amylin RA	—	Phase 2: ZUPREME-1
AZD6234	—	AstraZeneca	Long-acting amylin RA	—	Phase 1 completed; Phase 2: APRICUS
AZD9550	—	AstraZeneca	Dual GLP-1/GCG RA	—	Phase 2: CONTEMPO
AZD6234	AZD9550	AstraZeneca	Long-acting amylin RA	Dual GLP-1 RA/GCG RA	Phase 2b: ASCEND
GUBamy	—	Gubra	Long-acting amylin RA	—	Phase 1
Eloralintide (LY3841136)	—	Eli Lilly	Long-acting amylin RA	—	Phase 2
Amycretin	—	Novo Nordisk	Dual GLP-1 RA/amylin receptor agonist	—	Phase 2
Orforglipron (oral)	—	Eli Lilly	Oral small-molecule GLP-1 RA	—	Phase 3: ACHIEVE and ATTAIn programs
VK2735 (oral)	—	Viking Therapeutics	GLP-1 RA/GIP RA	—	Phase 2: VENTURE-Oral Dosing

(Continues)

TABLE 2 | (Continued)

Substance 1	Substance 2 (co-administration)	Pharmaceutical company	Mechanism (Substance 1)	Mechanism (Substance 2)	Clinical trials/development stage
NA-931 (bioglutide)	—	Biomed Industries	Oral quadruple agonist (GLP-1/GIP/GCG/IGF-1 RA)	—	Phase 2
Danuglipron (oral) ^a	—	Pfizer	GLP-1 RA	—	Phase 2; discontinued
KAI-7535 (oral)	—	Kailera Therapeutics	GLP-1 RA	—	Phase 2
CT-996 (oral)	—	Carnot Therapeutics	GLP-1 RA	—	Phase 1
AZD5004/ECC5004 (oral)	—	Eccogene/AstraZeneca	GLP-1 RA	—	Phase 1b; global Phase 2b completed (VISTA, SOLSTICE)
RGT-075 (oral)	—	Regor Pharmaceuticals	GLP-1 RA	—	Phase 2a
TERN-601 (oral) ^a	—	Terns Pharmaceuticals	GLP-1 RA	—	Phase 2: FALCON; discontinued
Semaglutide (oral)	—	Novo Nordisk	GLP-1 RA	—	Approved in US; Phase 3: OASIS 4
Bimagrumab	Semaglutide	Versanis Bio/Eli Lilly	Activin type II receptor–blocking mAb (myostatin/activin pathway)	GLP-1 RA	Phase 2: BELIEVE
Trevogrumab	Garetosmab + Semaglutide	Regeneron	Anti-myostatin (GDF8) mAb	Anti-activin A mAb; GLP-1 RA	Phase 2: COURAGE (interim data reported)
Bremelanotide (BMT-801)	Tirzepatide	Palatin Technologies	MC4R agonist	Dual GLP-1/GIP RA	Phase 2
NNC0165-1875	—	Novo Nordisk	PYY3-36 analog	—	Phase 2
Ecnoglutide	—	Sciwind Biosciences	Selective cAMP-biased GLP-1 RA	—	Phase 3: SLIMMER, EECOH-1, EECOH-2
Nisotirostide (LY3457263)	—	Eli Lilly	Neuropeptide Y Receptor Agonist	—	Phase I
Macupatide (LY3532226)	—	Eli Lilly	GIP RA	—	Phase 2

(Continues)

TABLE 2 | (Continued)

Substance 1	Substance 2 (co-administration)	Pharmaceutical company	Mechanism (Substance 1)	Mechanism (Substance 2)	Clinical trials/development stage
Tirzepatide	Mibavademab	Eli Lilly/Regeneron	Dual GLP-1 RA/GIP RA	Leptin receptor agonist	Phase 2
Enobosarm	Semaglutide	Veru Inc.	SARM	GLP-1 RA	Phase 2b: QUALITY; Phase 2b: PLATEAU initiated
Monlunabant	—	Novo Nordisk	CB1 receptor inverse agonist	—	Phase 2a
Nimacimab	Semaglutide	Skye Bioscience	CB1-inhibiting monoclonal antibody	GLP-1 RA	Phase 2a: C Beyond (+ extension interim)
HEC88473	—	Sunshine Lake Pharma/ Apollo Therapeutics	Dual GLP-1/FGF21 RA	—	Phase Ib/IIa; Phase 2 in T2D
TLC-6740	Tirzepatide	OrsoBio	Oral liver-targeted mitochondrial protonophore	Dual GLP-1/GIP RA	Phase 1b/2a
NPM-115	—	Vivanti Medical	Exenatide GLP-1 RA implant (NanoPortal)	—	Phase 1: LIBERATE-1

Abbreviations: CB1 R1A, cannabinoid receptor 1 inverse agonist; GCG RA, glucagon receptor agonist; GIP RA, glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IGF-1 RA, insulin-like growth factor-1 receptor agonist; MC4 RA, melanocortin-4 receptor agonist; PYY3-36, Peptide YY analog; RA, receptor agonist; SARM, selective androgen receptor modulator.
^aDiscontinued.

TABLE 3 | Route of administration, dosing schedule, and maximal therapeutic weight- and HbA_{1c}-lowering effects of selected emerging drugs for obesity and type 2 diabetes treatment.

Drug/regimen	Route	Dosing schedule	Key dose(s) in main trials	Max body-weight reduction (vs. baseline)	Max HbA _{1c} reduction (absolute % points)	Duration of therapy	Add on strategies	Mean BMI	Mean HbA _{1c}	Mean duration of diabetes
Semaglutide 7.2 mg (STEP UP)	SC	OW	Up-titrated to 7.2 mg vs. 2.4 mg vs. placebo; 72 weeks	-20.7% at 72 weeks (efficacy estimand) vs. -17.5% with 2.4 mg and -2.4% with placebo	NR	72 weeks	Yes	39.9 kg/m ²	No T2D	No T2D
Semaglutide 25 mg (OASIS-4)	Oral	OD	25 mg (titrated from 3 mg); 64 weeks	-13.6% vs. -2.2% with placebo	NR	64 weeks	Yes	37.6 kg/m ²	No T2D	No T2D
Semaglutide 7.2 mg (STEP UP T2D)	SC	OW	7.2 mg vs. 2.4 mg vs. placebo; 72 weeks	-13.2% vs. -10.4% with 2.4 mg and -3.9% with placebo	-1.7% vs. -1.6% with 2.4 mg	72 weeks	Yes	38.6 kg/m ²	8.1%	NR
Efpeglenatide (HM11260C)	SC	OW	Long-acting GLP-1RA vs. placebo; 40 weeks	-9.75% vs. -0.95% with placebo	NR	40 weeks	NR	NR	No T2D	No T2D
MET-097i	SC	OW	0.4, 0.6, 0.9, 1.2 mg; 28 weeks (VESPER-1)	Up to -12.5% placebo-subtracted at 28 weeks (1.2 mg; company-reported)	NR	28 weeks	NR	NR	No T2D	No T2D
Bofanglutide (GZR18)	SC	Q2W and OW	8, 16, 24 mg Q2W; 24 mg QW vs. semaglutide 1 mg; 24 weeks	Up to -6.52 kg (24 mg QW) vs. -3.25 kg with semaglutide 1 mg	-1.87% to -2.32% vs. -1.60% with semaglutide 1 mg	24 weeks	NR	28.13-28.52 kg/m ²	8.28-8.56	NR
Survodutide	SC	OW	0.6, 2.4, 3.6, 4.8 mg vs. placebo; 46 weeks	Up to -18.7% vs. -2.3% with placebo	NR	46 weeks	Yes	37.1 kg/m ²	No T2D	No T2D
HRS9531	SC	OW	2, 4, 6 mg vs. placebo; 48 weeks	Up to -19.2% at 48 weeks (17.7% placebo-adjusted; company-reported)	NR	48 weeks	Yes	33.3 kg/m ²	No T2D	No T2D
BGM0504	SC	OW	5, 10, 15 mg vs. semaglutide 1.0 mg and placebo; 12 weeks	Greater weight loss than semaglutide 1.0 mg (exact % NR)	Up to -2.56% (15 mg) vs. -1.86% with semaglutide 1.0 mg	12 weeks	NR	NR	NR	NR
CT-868	SC	OW	Titrated to 1.75-4.0 mg; 26 weeks	-5.4% at 26 weeks with 4.0 mg vs. -2.5% with placebo	Up to -1.81% vs. +0.43% with placebo	26 weeks	Diet/exercise or metformin	NR	7.0%-10.0% eligible	NR
CT-388	SC	OW	Up to 24 mg; 48 weeks	22.5% placebo-adjusted at 48 weeks (efficacy estimand; company-reported)	NR	48 weeks	NR	NR	No T2D	No T2D

(Continues)

TABLE 3 | (Continued)

Drug/regimen	Route	Dosing schedule	Key dose(s) in main trials	Max body-weight reduction (vs. baseline)	Max HbA _{1c} reduction (absolute % points)	Duration of therapy	Add on strategies	Mean BMI	Mean HbA _{1c}	Mean duration of diabetes
Mazdutide (dose-finding trial)	SC	OW	6 mg, 10 mg, 16 mg vs. placebo; 48 weeks	Up to -22.3% (16 mg) vs. -0.9% with placebo at 48 weeks	NR	48 weeks	NR	37.3-39.9 kg/m ²	5.49%-5.53%	No T2D
Mazdutide (GLORY-1)	SC	OW	4 mg, 6 mg vs. placebo; 48 weeks	Up to -14.01% (6 mg) vs. +0.30% with placebo at 48 weeks	NR	48 weeks	Yes	31.1 kg/m ²	No T2D	No T2D
Mazdutide (GLORY-2)	SC	OW	9 mg vs. placebo; 60 weeks	-18.55% vs. -3.02% with placebo	NR	60 weeks	NR	> 32.5 kg/m ²	NR	NR
Mazdutide (DREAMS-3)	SC	OW	Mazdutide 6 mg vs. semaglutide 1.0 mg; 32 weeks	-10.29% vs. -6.0% with semaglutide 1.0 mg (company-reported)	-2.03% vs. -1.84% with semaglutide 1.0 mg (company-reported)	32 weeks	Diet/exercise or metformin	32.98 kg/m ²	8.02%	NR
Mazdutide (DREAMS-1)	SC	OW	Mazdutide 4 mg, 6 mg vs. placebo; 24 weeks	-5.61% (4 mg) and -7.81% (6 mg) vs. -1.26% with placebo	-1.57% (4 mg) and -2.15% (6 mg) vs. -0.14% with placebo	24 weeks	Diet and exercise	28.2 kg/m ²	8.24%	1.9 y
Pemvidutide (IMPACT)	SC	OW	Pemvidutide 1.2 mg, 1.8 mg vs. placebo; 24 weeks	-4.8% (1.2 mg) and -5.8% (1.8 mg) vs. -0.5% with placebo	NR	24 weeks	NR	38.7 kg/m ²	6.4%	NR
Retatrutide (Phase 2 study)	SC	OW	Up to 12 mg; 36 weeks in T2D	Up to -16.00% at 36 weeks (12 mg) vs. -2.4% with placebo	NR	36 weeks	NR	35.2 kg/m ²	8.3%	NR
Retatrutide (TRIUMPH-4)	SC	OW	Retatrutide 9 mg, 12 mg vs. placebo; 68 weeks	Up to -28.7% (12 mg) vs. -2.1% with placebo (company-reported)	NR	68 weeks	NR	NR	No T2D	No T2D
Retatrutide (TRANSCEND-T2D-1)	SC	OW	Retatrutide 4 mg, 9 mg, 12 mg vs. placebo; 40 weeks	-11.5% (4 mg), -15.5% (9 mg) and -16.8% (12 mg) vs. -2.5% with placebo	-1.7% (4 mg), -2.0% (9 mg), -1.9% (12 mg) vs. -0.8% with placebo (company-reported)	40 weeks	Diet and exercise	NR	NR	NR
MariTide (maridebart cafraglutide)	SC	OM	140, 280, 420 mg; 52 weeks, non-T2D and T2D cohorts	-12.3% to -16.2% (non-T2D); -8.4% to -12.3% (T2D)	Up to -1.6% vs. +0.1% with placebo	52 weeks	NR	37.9/36.5 kg/m ²	7.9% (T2D cohort)	NR

(Continues)

TABLE 3 | (Continued)

Drug/regimen	Route	Dosing schedule	Key dose(s) in main trials	Max body-weight reduction (vs. baseline)	Max HbA _{1c} reduction (absolute % points)	Duration of therapy	Add on strategies	Mean BMI	Mean HbA _{1c}	Mean duration of diabetes
CagriSema (cagrilintide + semaglutide) REDEFINE 1 and 2	SC	OW	Cagrilintide 2.4 mg + semaglutide 2.4 mg vs. placebo	-20.4% at 68 weeks (without T2D); -13.7% in T2D	-1.8% in T2D vs. -0.4% with placebo	68 weeks	Yes	37.9/36.2 kg/m ²	8.0% (T2D study)	8.5 y (T2D study)
CagriSema (cagrilintide + semaglutide) REIMAGINE 2	SC	OW	Cagrilintide 2.4 mg + semaglutide 2.4 mg (or 1 mg/1 mg) vs. semaglutide (2.4 mg or 1.0 mg) vs. placebo	14.2% vs. 10.2% (semaglutide 2.4 mg) vs. 1.5% with placebo (company-reported)	-1.91% vs. -1.76% (semaglutide 2.4 mg) vs. +0.09% with placebo (company-reported)	68 weeks	Metformin and ± SGLT-2i	NR	8.2%	NR
CagriSema (cagrilintide + semaglutide) REDEFINE 4	SC	OW	CagriSema 2.4/2.4 mg vs. tirzepatide 15 mg	-23.0% vs. -25.5% with tirzepatide (15 mg)	NR	84 weeks	NR	NR	NR	NR
Petrelintide (ZP8396)	SC	OW	Five once-weekly regimens vs. placebo; 42 weeks	Up to -10.7% at 42 weeks vs. -1.7% with placebo (company-reported)	NR	42 weeks	NR	37.0 kg/m ²	No T2D	No T2D
GUBamy	SC	OW	1 and 2 mg for 6 weeks	-7.77% at day 43 with 2 mg vs. +1.99% with placebo (company-reported)	NR	6 weeks	NR	NR	No T2D	No T2D
Eloralintide (LY3841136)	SC	OW	1, 3, 6, 9 mg; 6-9 mg; 3-6-9 mg for 48 weeks	Up to -20.1% at 48 weeks (9 mg); -19.9% (6-9 mg) vs. -0.4% with placebo	NR	48 weeks	NR	37.9-40.6 kg/m ²	5.41%-5.54%	No T2D
Amycretin 40 mg	SC	OW	0.4-40 mg once weekly; up to 36 weeks	-14.5% vs. -2.6% with placebo (company-reported)	-1.8% vs. -0.2% with placebo (company-reported)	36 weeks	Metformin and ± SGLT-2i	NR	7.8%	NR
Amycretin 50 mg	Oral	OD	6, 25, 50 mg once daily; up to 36 weeks	-10.1% vs. -2.5% with placebo (company-reported)	-1.5% vs. -0.4% with placebo (company-reported)	36 weeks	Metformin and ± SGLT-2i	NR	8.0%	NR
Orforglipron (ACHIEVE-1)	Oral	OD	3, 12, 36 mg; 40 weeks	-4.5% (3 mg), -5.8% (12 mg), -7.6% (36 mg) vs. -1.7% with placebo	-1.24% (3 mg), -1.47% (12 mg), -1.48% (36 mg) vs. -0.41% with placebo	40 weeks	Diet and exercise	33.0 kg/m ²	7.99%	4.4 y

(Continues)

TABLE 3 | (Continued)

Drug/regimen	Route	Dosing schedule	Key dose(s) in main trials	Max body-weight reduction (vs. baseline)	Max HbA _{1c} reduction (absolute % points)	Duration of therapy	Add on strategies	Mean BMI	Mean HbA _{1c}	Mean duration of diabetes
Orforglipron vs. dapagliflozin (ACHIEVE-2)	Oral	OD	Orforglipron 3, 12, 36 mg vs. dapagliflozin 10 mg	NR	-1.3% (3 mg), -1.7% (12 mg), -1.7% (36 mg) vs. -0.8% with dapagliflozin (company-reported)	NR	Stable background therapy with metformin	NR	NR	NR
Orforglipron vs. placebo (ACHIEVE-5)	Oral	OD	Orforglipron 3, 12, 36 mg vs. placebo	NR	-1.5% (3 mg), -2.1% (12 mg), -1.9% (36 mg) vs. -0.8% with placebo	NR	Stable background therapy	NR	NR	NR
Orforglipron vs. oral semaglutide (ACHIEVE-3)	Oral	OD	Orforglipron 12 and 36 mg vs. oral semaglutide 7 and 14 mg; 52 weeks	-6.1% and -8.2% vs. -3.9% and -5.3% with oral semaglutide	-1.71% and -1.91% vs. -1.23% and -1.47% with oral semaglutide	52 weeks	Metformin background	35.1 kg/m ²	8.3%	NR
Orforglipron (ATTAIN-1)	Oral	OD	6, 12, 36 mg; 72 weeks	-7.5% (6 mg), -8.4% (12 mg), -11.2% (36 mg) vs. -2.1% with placebo	NR	72 weeks	Diet and lifestyle	37.0 kg/m ²	No T2D	No T2D
Orforglipron (ATTAIN-2)	Oral	OD	6, 12, 36 mg; 72 weeks	-5.5% (6 mg), -7.8% (12 mg), -10.5% (36 mg) vs. -2.2% with placebo	-1.29% (6 mg), -1.60% (12 mg), -1.79% (36 mg) vs. -0.14% with placebo	72 weeks	Stable therapy or lifestyle	35.6 kg/m ²	8.05%	6.9 y
VCT220	Oral	OD	80, 120, 160 mg; 16 weeks	Up to -9.7% (160 mg fast titration) and -9.4% (160 mg slow titration) vs. -1.6% with placebo (company-reported)	NR	16 weeks	NR	32.03 kg/m ²	No T2D	No T2D
HRS-7535 (T2D)	Oral	OD	15, 30, 60, 90 mg vs. placebo; 16 weeks	-2.63% (90 mg) vs. -1.30% with placebo	Up to -1.57% vs. -0.25% placebo	16 weeks	Metformin	26.7 kg/m ²	8.5%	NR
HRS-7535 (obesity)	Oral	OD	30, 60, 120, 180 mg vs. placebo; 26 weeks (+10-week extension)	Up to -9.36% at 26 weeks vs. -2.50% with placebo	NR	26 weeks	NR	32.5 kg/m ²	No T2D	No T2D

(Continues)

TABLE 3 | (Continued)

Drug/regimen	Route	Dosing schedule	Key dose(s) in main trials	Max body-weight reduction (vs. baseline)	Max HbA _{1c} reduction (absolute % points)	Duration of therapy	Add on strategies	Mean BMI	Mean HbA _{1c}	Mean duration of diabetes
Aleniglipron	Oral	OD	120, 180, 240 mg; 44 weeks	-13.6%, -15.3%, and -15.0% vs. +1.1% with placebo (company-reported)	NR	44 weeks	NR	NR	No T2D	No T2D
VK2735 (oral; VENTURE)	Oral	OD	15, 30, 60, 90, 120 mg; 13 weeks	-2.3%, -7.0%, -8.7%, -11.1%, and -12.2%	NR	13 weeks	NR	NR	No T2D	No T2D
NA-931 (bioglutide)	Oral	OD	60, 90, 120, 150 mg; 13 weeks	-5.5%, -8.7%, -11.3%, and -13.8% vs. -1.9% with placebo (company-reported)	NR	13 weeks	NR	NR	No T2D	No T2D
Bimagrumab + semaglutide (BELIEVE)	IV + SC	Q12W IV + OW SC	High-dose combination vs. monotherapy; 72 weeks	-22.1% at high-dose combination vs. -15.7% with semaglutide alone	NR	72 weeks	NR	37.3 kg/m ²	No T2D	No T2D
Bimagrumab alone (BELIEVE)	IV	Q12W IV	Bimagrumab monotherapy arm; 72 weeks	-10.8% (30 mg/kg) at week 72	NR	72 weeks	NR	37.3 kg/m ²	No T2D	No T2D
Semaglutide + trevogrumab ± garetosmab (COURAGE phase 2 trial)	SC+IV	OW semaglutide + periodic antibodies	Semaglutide alone vs. + anti-myostatin vs. + anti-myostatin + anti-activin A	Up to -13.4% with triplet combination vs. -10.6% with semaglutide alone (company-reported)	NR	26 weeks	NR	NR	NR	NR
Bremelanotide (BMT-801) + tirzepatide	SC	OD + OW	Bremelanotide 1.25 mg daily + tirzepatide 2.5 mg weekly; 8-week study	-4.4% vs. -1.6% with placebo at 8 weeks (company-reported)	NR	8 weeks	NR	NR	No T2D	No T2D
Ecnoglutide (SLIMMER)	SC	OW	1.2, 1.8, 2.4 mg; 48 weeks	-9.9% (1.2 mg), -13.3% (1.8 mg), -15.4% (2.4 mg) vs. -0.3% with placebo	NR	48 weeks	Yes	32.5 kg/m ²	5.3%–5.4%	No T2D
Ecnoglutide (EECOH-1)	SC	OW	0.6, 1.2 mg; 24 weeks	-4.51% (0.6 mg) and -4.74% (1.2 mg) vs. -2.02% with placebo	-1.96% (0.6 mg) and -2.43% (1.2 mg) vs. -0.87% with placebo	24 weeks	Diet and exercise	26.93 kg/m ²	8.52%	3.58 y
Ecnoglutide (EECOH-2)	SC	OW	0.6, 1.2 mg vs. 1.5 mg dulaglutide	-1.91% (0.6 mg), -1.89% (1.2 mg) vs. -1.65% with 1.5 mg dulaglutide at week 32	-5.23% (0.6 mg), -5.74% (1.2 mg) vs. -2.79% with 1.5 mg dulaglutide at week 52	32 weeks with extension to week 52	Metformin and diet, exercise	26.9 kg/m ²	8.4%	5.3–6.35 y

(Continues)

TABLE 3 | (Continued)

Drug/regimen	Route	Dosing schedule	Key dose(s) in main trials	Max body-weight reduction (vs. baseline)	Max HbA _{1c} reduction (absolute % points)	Duration of therapy	Add on strategies	Mean BMI	Mean HbA _{1c}	Mean duration of diabetes
Enobosarm	Oral + SC	OD + OW	Enobosarm 3 mg or 6 mg + semaglutide 2.4 mg; 16 weeks + 12-week maintenance	NR (company-reported program focused on lean-mass preservation and reduced regain)	NR	28 weeks	NR	Older adults with overweight/obesity	No T2D	No T2D
Monlunabant	Oral	OD	10, 20, 50 mg vs. placebo; 16 weeks	-6.5%, -6.9%, and -8.0% vs. -0.6% with placebo	Small HbA _{1c} reductions: -0.15%, -0.15%, and -0.16% vs. -0.01% with placebo	16 weeks	NR	NR	5.9%	No T2D
Nimacimab	SC + SC	OW + OW	200 mg weekly + semaglutide 2.4 mg; 26 weeks with 26-week extension	-22.3% at 52 weeks with nimacimab + semaglutide vs. -19.7% with placebo + semaglutide (company-reported)	NR	52 weeks (+13-week off-therapy follow-up)	NR	NR	No T2D	No T2D
HEC88473	SC	OW	5.1, 15.3, 30.6, 45.9, 68.0 mg vs. placebo; 5 weeks	NR	Up to -1.10% vs. -0.31% with placebo	5 weeks	NR	26.6 kg/m ²	8.4%	NR
TLC-6740 + tirzepatide	Oral + SC	OD + OW	TLC-6740 180 mg + tirzepatide 2.5–5.0 mg; 24 weeks	-13.3% vs. -8.8% with tirzepatide alone (company-reported)	NR	24 weeks	NR	NR	No T2D	No T2D

Abbreviations: IV, intravenous; NR, not reported; OD, once daily; OM, once monthly; OW, once weekly; SC, subcutaneous.

1.0 mg for further 16 weeks resulted in only a modest additional effect versus placebo plus semaglutide (−5.3% vs. −3.1%), which the authors judged not to be clinically meaningful. Tolerability was a major limitation: GI AEs with combination therapy were more common, which led to premature treatment discontinuation in 21.3% versus 10.7% in the placebo plus semaglutide group. Moreover, the 2.0 mg dose-escalation regimen of PYY1875 was poorly tolerated. Overall, these data suggest that, at least with the dosing strategy tested, Y2 receptor agonism with PYY1875 had limited incremental efficacy while increasing the AEs burden.

Another line of development has focused on receptor engineering within the GLP-1 class. The phase 3 SLIMMER trial [94] evaluated *ecnoglutide*, a cAMP-biased GLP-1 RA, in 664 Chinese adults with overweight or obesity. Participants were randomised to receive once-weekly *ecnoglutide* 1.2 mg, 1.8 mg, or 2.4 mg, or placebo, with escalation from 0.3 mg and concurrent LI. At baseline, the mean age was 34.2 years and the mean BMI was 32.5 kg/m². *Ecnoglutide* met both coprimary endpoints at week 40, producing dose-dependent WL of 9.1%, 10.9%, and 13.2% versus a 0.1% increase with placebo; 77%, 84%, and 87% of participants, respectively, achieved at least 5% WL versus 16% with placebo. WL continued through week 48, reaching 9.9%, 13.3%, and 15.4% across the dose groups versus 0.3% with placebo. At the 2.4 mg dose, 93% achieved at least 5% WL, 80% at least 10% WL, 64% at least 15% WL, and 28% at least 20% WL. *Ecnoglutide* also improved waist circumference, blood pressure, triglyceride concentrations, HDL-cholesterol concentrations, fasting glucose concentrations, insulin resistance, liver enzymes, uric acid concentrations, and liver fat content in participants with baseline steatosis. The safety profile was broadly consistent with that of the GLP-1RA class: TEAEs occurred in 93% of *ecnoglutide*-treated participants versus 84% with placebo; these were predominantly mild to moderate and declined over time. SEA occurred in 5%–9% of active treatment groups versus 5% with placebo, while AEs-related discontinuation was infrequent (1%–3% across dose groups vs. 0% with placebo).

Beyond obesity, *ecnoglutide* has now also phase 3 data in T2D. In EECO-1 [95], a RCT in 211 Chinese adults with T2D inadequately controlled with diet and exercise alone or with a single oral hypoglycemic agent, once-weekly *ecnoglutide* 0.6 and 1.2 mg reduced HbA_{1c} by −1.96% and −2.43% at week 24, respectively, compared with −0.87% with placebo. Body-weight reduction was more modest than in the SLIMMER trial but remained significant, reaching −4.51% and −4.74% with *ecnoglutide* versus −2.02% with placebo, and 39.1%–43.7% of *ecnoglutide*-treated participants achieved at least 5% WL compared with 11.3% in the placebo group. Glycemic target attainment also favoured treatment, with HbA_{1c} < 7.0% achieved in 68.1% and 80.3% of participants receiving 0.6 and 1.2 mg, respectively, versus 21.1% with placebo. The safety profile was broadly similar to that of other GLP-1-based therapies: TEAEs occurred in 77.5%–78.3% of *ecnoglutide*-treated participants versus 63.4% with placebo, serious TEAEs in 2.9%–4.2% versus 5.6%, and discontinuation due to TEAEs was rare (1.4% in each treatment group). GI AEs were the most frequent and were mostly transient and mild to moderate; no severe hypoglycemia, pancreatitis, or gallbladder-related disorders were reported.

These findings were extended in EECO-2 [96], a 52-week, phase 3 RCT conducted in China in 623 adults with T2D inadequately controlled with metformin monotherapy. At baseline, the mean age was 53.9 years, mean HbA_{1c} was 8.40%, and BMI was 26.9 kg/m². At week 32, the mean HbA_{1c} reductions were 1.91% with *ecnoglutide* 0.6 mg, 1.89% with *ecnoglutide* 1.2 mg, and 1.65% with *dulaglutide* 1.5 mg. Both *ecnoglutide* doses met the criterion for non-inferiority versus *dulaglutide*, and the 1.2 mg dose also showed statistical superiority, although the between-group difference was not considered clinically meaningful. Glycemic effects were sustained to week 52, when HbA_{1c} reductions remained greater with *ecnoglutide* than with *dulaglutide* (−1.72% and −1.76% vs. −1.50%, respectively). *Ecnoglutide* also produced greater weight loss than *dulaglutide*, with least-squares mean percentage body-weight reductions at week 52 of −5.23% with 0.6 mg and −5.74% with 1.2 mg versus −2.79% with *dulaglutide*, and a higher proportion of participants achieved clinically meaningful weight-loss thresholds. AEs occurred in 85% of participants receiving *ecnoglutide* 0.6 mg, 93% receiving *ecnoglutide* 1.2 mg, and 87% receiving *dulaglutide*, and were mostly mild or moderate. GI AEs were the most common and occurred predominantly during dose escalation, with diarrhoea, nausea, and vomiting reported more frequently with *ecnoglutide* than with *dulaglutide*. Discontinuation due to adverse events was uncommon and similar across groups (3%, 4%, and 3%, respectively). Taken together, SLIMMER, EECO-1, and EECO-2 suggest that the cAMP-biased mechanism of *ecnoglutide* is now supported not only in obesity but also in T2D development programs.

Eli Lilly's LY3457263 (*nisotiostide*), a neuropeptide Y (NPY) receptor agonist, was evaluated in a phase 1 study (NCT06897475 [97]) to assess its safety, tolerability, and pharmacokinetics when administered alone or in combination with tirzepatide or semaglutide in adults with T2D. Targeting the NPY pathway represents a novel mechanistic approach that could potentially complement incretin signalling to enhance glycemic and weight outcomes.

Another Lilly investigational agent, LY3532226 (*macupatide*), a GIP RA, is also under clinical development (NCT07215559 [98]) as part of the company's expanding incretin platform as a monotherapy or in combination with eloralintide.

In collaboration with Regeneron, Eli Lilly is also evaluating a combination strategy that pairs tirzepatide with *mibavademab*, a leptin receptor agonist, in a phase 2 randomised, double-blind, placebo-controlled study in adults with obesity (NCT06373146 [99]). This proof-of-concept trial reflects the growing interest in combining incretin-based therapy with agents that target complementary energy-balance pathways; however, efficacy and safety results have not yet been reported.

Enobosarm, an oral selective androgen receptor modulator (SARM), has been evaluated as an adjunct to semaglutide to improve WL composition in older adults. According to company-reported topline results from the phase 2b QUALITY program [100], *enobosarm* plus semaglutide significantly reduced lean-mass loss compared with placebo plus semaglutide (mean change −1.2% vs. −4.1%; $p=0.002$) and reduced the proportion of participants with at least a 10% decline in stair-climb power

(19.4% vs. 42.6%). In the subsequent 12-week maintenance extension, after semaglutide discontinuation, placebo-treated participants regained 43% of their previously lost body weight, whereas enobosarm 3 mg reduced weight regain by 46%; both enobosarm dose groups were reported to prevent fat regain and preserve lean mass. Because these findings are currently based on company-reported analyses rather than full peer-reviewed publications, they should be interpreted cautiously. A confirmatory next-step study has now begun: Veru recently initiated a phase 2b PLATEAU trial [101] of enobosarm plus semaglutide in older adults with obesity.

Monlunabant, a second-generation cannabinoid receptor 1 (CB1R) inverse agonist designed to reduce central penetrance, represents another non-incretin approach to obesity pharmacotherapy in patients with obesity. In a 16-week, randomised, double-blind, placebo-controlled phase 2a proof-of-concept trial conducted in 242 treated adults with obesity and metabolic syndrome [102], once-daily oral monlunabant 10, 20, and 50 mg produced statistically significant weight loss versus placebo, with least-squares mean WL changes of -7.1 kg, -7.7 kg and -8.8 kg, respectively, compared with -0.7 kg with placebo. Percentage WL ranged from 6.5% to 8.0% with monlunabant versus 0.6% with placebo. Small reductions in HbA_{1c} and triglyceride concentrations were also observed; however, these effects were modest and showed no clear dose-response pattern.

However, tolerability was a major limitation of this study. AEs were dose-dependent and consisted mainly of GI and psychiatric disorders, occurring in 69%, 78%, and 92% of participants in the 10, 20, and 50 mg groups, respectively, compared to 69% in the placebo group. Psychiatric AEs were reported in 28%, 33%, and 42% of participants receiving monlunabant, compared with 2% in the placebo group, and withdrawals due to AEs increased sharply with dose, occurring in 13%, 27%, and 42% of participants in the monlunabant groups versus none in the placebo group. The most common drivers of discontinuation were nausea, anxiety, diarrhoea, irritability, and sleep disturbance. No deaths or severe suicidal ideation were reported; however, the authors emphasised that the high rate of early discontinuation, especially at 50 mg, complicates the interpretation of efficacy and safety and suggests that any future development would need to focus on identifying a lower, more tolerable therapeutic approach.

Nimacimab, a peripherally restricted negative allosteric CB1 modulator with minimal central nervous system penetration, was evaluated in the phase 2a CBeyond trial [103] in adults with overweight or obesity without T2D. In the initial 26-week study, subcutaneous nimacimab 200 mg combined with semaglutide 2.4 mg produced greater WL than semaglutide alone (-13.2% vs. -10.25% ; $p=0.0372$). More recent interim company-reported extension data [104] suggest that this effect may persist over longer treatment periods: among the small subset of participants who continued blinded therapy to week 52, the mean WL reached 22.3% with nimacimab plus semaglutide versus 19.7% with placebo plus semaglutide, with no plateau reported. In the off-therapy follow-up subset, weight regain was lower with nimacimab plus semaglutide than with semaglutide alone (17.8% vs. 37.3% of prior WL), suggesting a possible durability advantage. During the extension period, no SAEs or AEs of

special interest were reported. However, these updated findings are based on a small extension cohort and remain company-reported; therefore, they should be interpreted cautiously until full peer-reviewed results become available.

HEC88473 is an emerging dual GLP-1/FGF21 agonist that is being developed for the treatment of MASLD with T2D. In a randomised, double-blind, placebo-controlled phase Ib/IIa multiple-ascending-dose trial [105], 60 patients with MASLD and T2D (mean HbA_{1c} 8.4%) were randomised in a 10:2 ratio to weekly SC HEC88473 at doses of 5.1, 15.3, 30.6, 45.9 or 68.0 mg, or placebo, for 5 weeks. HEC88473 produced dose-proportional reductions in liver fat assessed by MRI-PDFF, with the largest relative mean reduction observed in the 30.6 mg cohort (-47.2% vs. -15.1% with placebo), and also improved glycemic control, with the greatest HbA_{1c} reduction reaching -1.10% in the 68.0 mg cohort compared with -0.31% with placebo. Improvements in fasting and postprandial glucose and lipid parameters have also been reported. Overall, HEC88473 was generally safe and well tolerated over the 5-week treatment period: most AEs were mild to moderate, GI disorders were the most frequent (48.3%), and no drug-related SAEs or deaths were reported. These findings provide early proof of concept for GLP-1/FGF21 co-agonism in patients with coexisting MASLD and T2D, although the very short treatment duration and small sample size warrant cautious interpretation of the results.

TLC-6740, an oral liver-targeted mitochondrial protonophore developed by OrsoBio, represents a distinct add-on strategy intended to complement incretin therapy by increasing energy expenditure. According to company-reported topline results [106] from a 24-week phase 1b/2a randomised, double-blind, placebo-controlled study, 55 adults with obesity without T2D were assigned to tirzepatide plus either TLC-6740 180 mg once daily or placebo; tirzepatide was administered at 2.5 mg weekly for 4 weeks, followed by 5 mg weekly for 20 weeks. At week 24, the combination achieved a mean WL of 13.3% compared with 8.8% for tirzepatide alone ($p=0.018$, intention-to-treat), with no apparent plateau in the combination arm. The company further reported similar AEs rates between the groups, no grade 3 or SAEs, no treatment discontinuations, and improvements in insulin sensitivity, liver-related biomarkers, and MRI-based measures of liver fat and adipose tissue, without an adverse effect on lean mass. However, these findings were derived from a small early-phase trial, are currently available only through a company press release, and were obtained using a relatively low tirzepatide comparator dose.

Taken together, these post-incretin combination and non-incretin strategies illustrate several distinct approaches to improve current pharmacotherapy: preserving lean mass, reducing weight regain, minimising central psychiatric liability, and broadening efficacy toward hepatic and metabolic complications. However, most remain in the early stage, attractive, and clinically unproven, with tolerability and durability likely determining whether any of these approaches can move beyond the proof-of-concept stage.

Novel delivery systems are being developed to address one of the main practical limitations of current obesity pharmacotherapy: the need for frequent dosing over a long period. Vivani

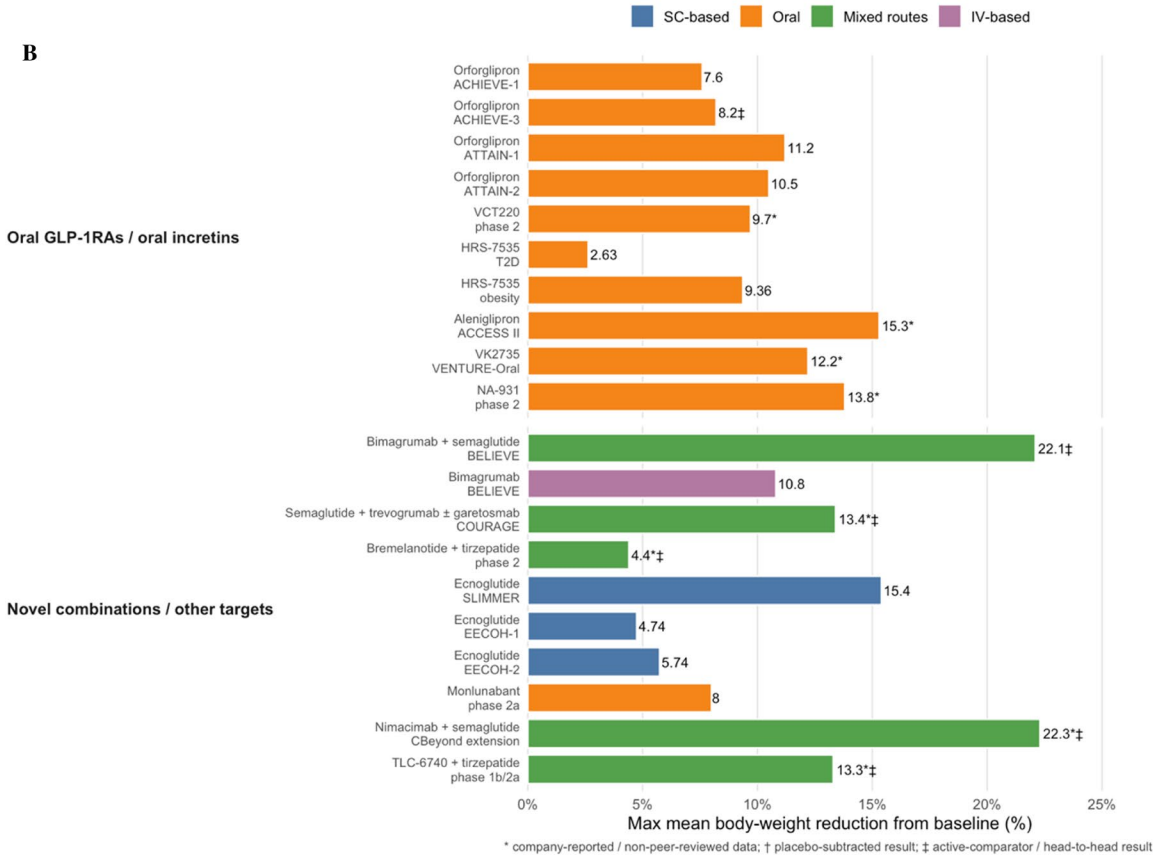
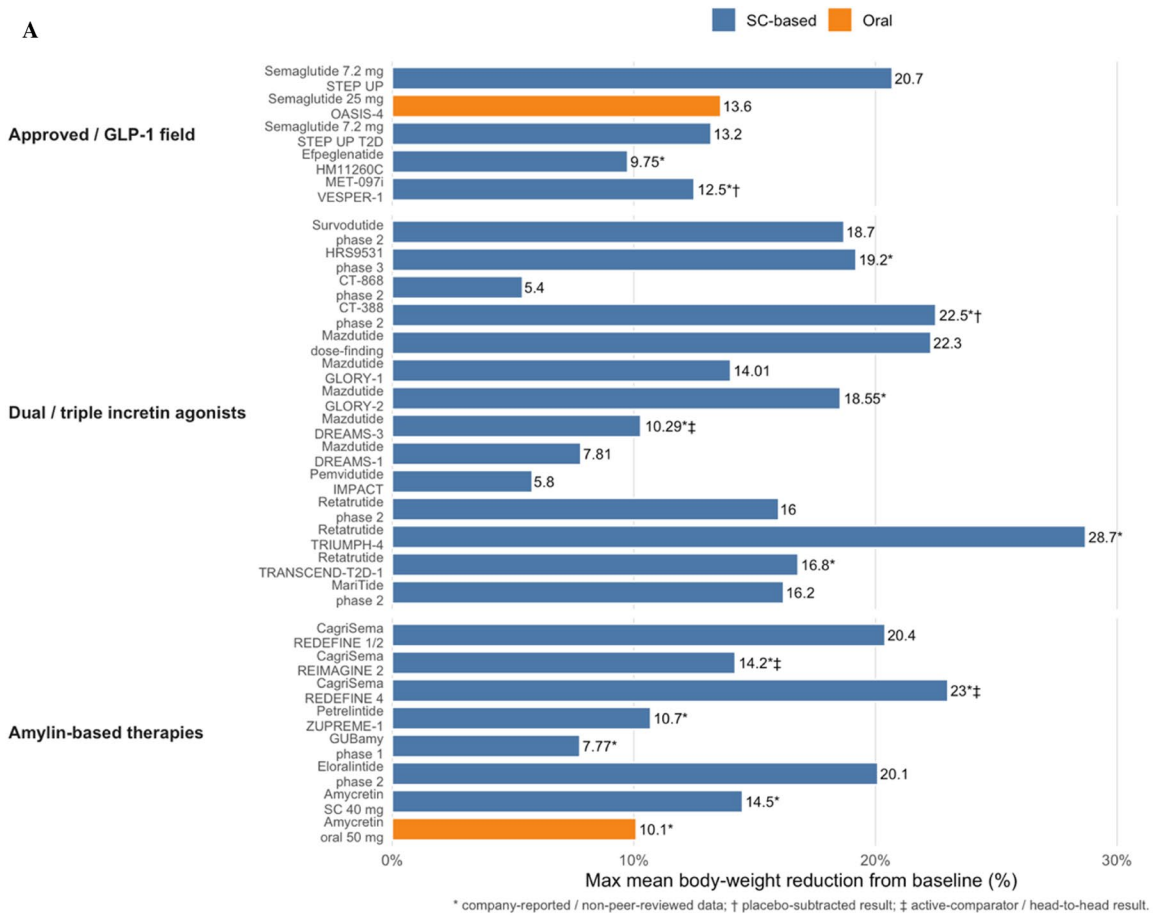


FIGURE 1 | Legend on next page.

FIGURE 1 | (A, B) Maximal %-weight reduction with emerging anti-obesity drugs according to the route of administration. Horizontal bars show the maximal percentage of body weight reduction from baseline reported for each agent or regimen in its pivotal or most advanced published/announced trial (typically the highest tested dose). Treatments are ordered from largest to smallest weight loss, with values plotted on the x-axis to indicate weight reduction. The entries included high-dose GLP-1 RA, dual and triple incretin agonists, amylin analogs, oral small-molecule incretin mimetics, and combination strategies. This comparative view highlights that several next-generation agents and combination regimens approach or exceed 20%–25% body-weight loss, with substantial heterogeneity in efficacy across both injectable and oral modalities. GLP-1 RA, glucagon-like peptide-1 receptor agonist; IV, intravenous; SC, subcutaneous. * company-reported/non-peer-reviewed data; † placebo-subtracted result; ‡ active-comparator/head-to-head result.

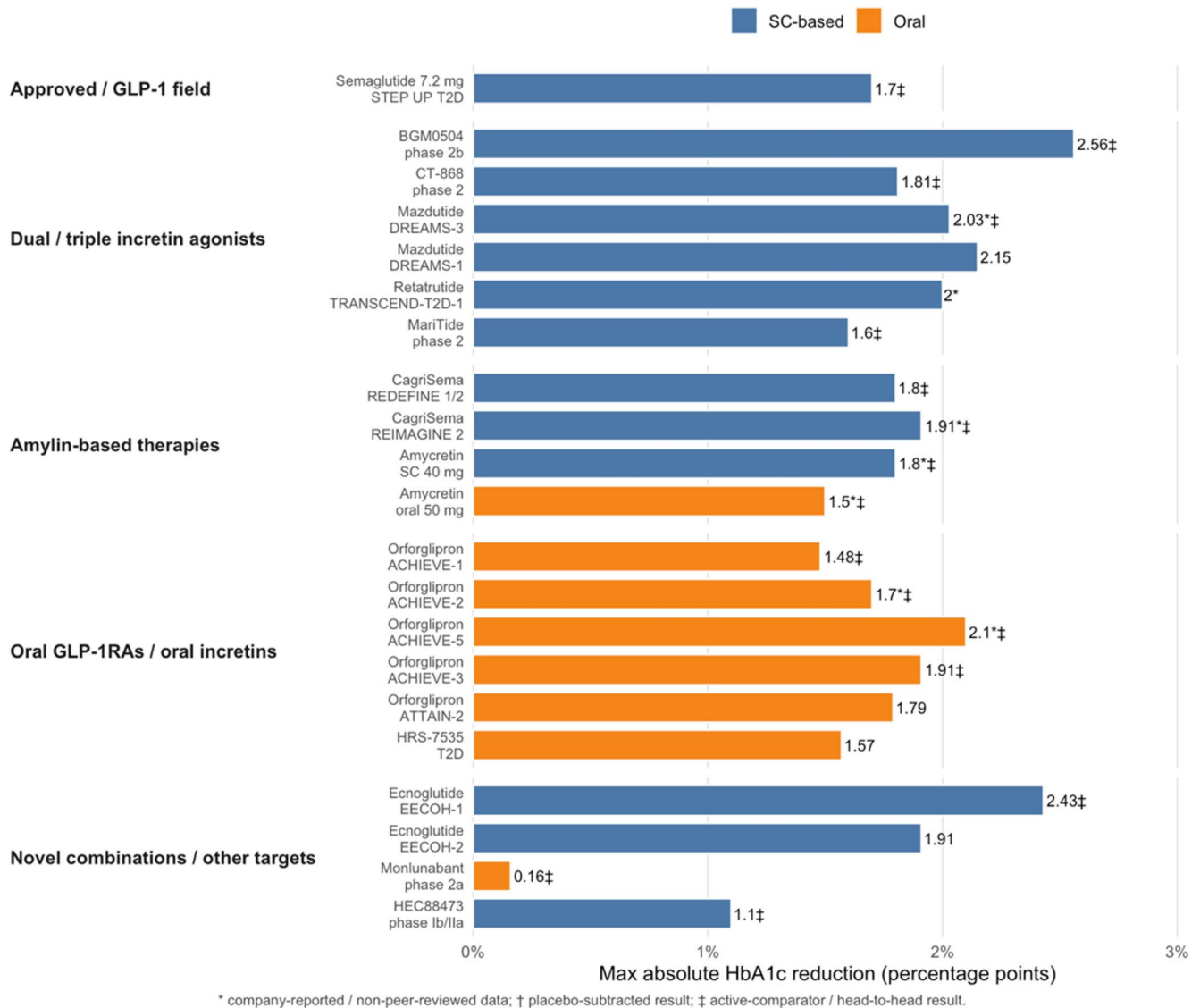


FIGURE 2 | Maximal HbA_{1c} reduction with emerging anti-obesity and glucose-lowering drugs according to the route of administration (oral agents and subcutaneous injectables). Horizontal bars depict the maximal reduction in glycated haemoglobin (HbA_{1c}, percentage points) reported for each treatment at the highest evaluated or clinically relevant dose in key studies. The figure includes high-dose GLP-1 receptor agonists, dual and triple incretin agonists (GLP-1/GIP, GLP-1/GCG, and GLP-1/GIP/GCG), amylin/incretin combinations, and oral small-molecule incretin mimetics. This comparison highlights that several next-generation injectable and oral drugs achieve HbA_{1c} reductions of approximately 1.5%–3.0%, approaching or exceeding the glucose-lowering efficacy of current standard injectable incretin regimens. GLP-1 RA, glucagon-like peptide-1 receptor agonist; SC, subcutaneous. * company-reported/non-peer-reviewed data; † placebo-subtracted result; ‡ active-comparator/head-to-head results.

Medical’s LIBERATE-1 Phase 1 trial [107] evaluated *NPM-115*, an implantable exenatide GLP-1 RA, using NanoPortal technology. Over 9 weeks, the implant showed excellent safety and tolerability, with no serious or gastrointestinal adverse events,

and a steady pharmacokinetic profile confirming controlled drug release without an initial burst. As preclinical studies were outside the scope of this review, subsequent preclinical implant programs are not discussed in detail. Nevertheless, these early

clinical data support implantable GLP-1 delivery as a plausible future strategy for reducing the treatment burden and improving adherence.

3 | Limitations

This review has some limitations. First, it is a narrative review rather than a systematic review or meta-analysis; therefore, no formal risk of bias assessment or quantitative evidence synthesis was performed. Second, the review intentionally focused on data reported in 2025 and, following the revision, through the first quarter of 2026 (Table 2).

Consequently, earlier pivotal studies were not systematically reviewed and were cited only when necessary to provide clinical or regulatory information. Third, the evidence base is heterogeneous across trial phases, populations, background therapies, dose-escalation strategies, treatment durations, estimands, and comparator selections (Table 3). Therefore, direct cross-trial comparisons of body weight (Figure 1A,B) and HbA1c outcomes (Figure 2) should be interpreted with caution. In several instances, graphical comparisons are intended to provide orientation rather than head-to-head rankings. Fourth, not all programs discussed have full peer-reviewed publications. For several agents, especially early-phase compounds, the available data were derived from conference abstracts, trial registries, or company and regulatory press releases. These data were included to provide a timely overview of a rapidly evolving field; however, they should be regarded as preliminary and may differ from subsequent peer-reviewed reports. In addition, selected early-phase studies were included if they provided first-in-human or proof-of-concept evidence for novel mechanisms, oral formulations, delivery platforms, or adjunctive strategies. Such data are useful for horizon scanning but should not be interpreted as practice-changing evidence.

Another limitation is that this review covers both obesity and T2D, which are two overlapping but not identical diseases. The clinical relevance of body weight, glycemic control (Figure 2), and body composition outcomes may differ according to baseline metabolic status, background treatment, and therapeutic goals, which further limits the strength of indirect comparisons across studies.

Long-term durability, cardiovascular and renal outcomes, body composition effects, discontinuation patterns, and post-treatment weight regain remain insufficiently characterised for many of the agents reviewed. These uncertainties are especially relevant when considering future positioning against established therapies, such as semaglutide and tirzepatide. Accordingly, the present review should be understood as a structured and time-sensitive overview of an evolving field rather than a definitive comparative assessment of efficacy or safety across agents.

4 | Conclusions

The therapeutic landscape of obesity and metabolic disease is evolving rapidly, shifting beyond GLP-1RA monotherapy

toward a broader framework that includes oral agents, longer-acting formulations, multi-receptor agonists, amylin-based therapies, and rational combination strategies. The most effective investigational programs now report levels of weight loss that narrow the gap with metabolic surgery in selected populations; although these findings vary substantially according to the mechanism, population, treatment duration, and evidence maturity. Across the field, a consistent theme is the shift from focusing solely on the magnitude of WL toward a broader assessment of treatment quality, including body composition, durability, tolerability, and feasibility of long-term use of the treatment.

Meanwhile, the evidence base remains inconclusive: some agents are now supported by peer-reviewed phase 3 data, whereas others remain at the level of conference abstracts, trial registries, or company-reported topline results. Therefore, enthusiasm about the innovations should be balanced by caution in comparing agents across studies, inferring relative superiority, or projecting clinical roles before full efficacy and safety data become available.

Overall, the data reviewed here suggest that obesity pharmacotherapy is entering a more diverse and clinically ambitious phase. Whether this progress translates into genuinely more personalised and durable treatment will depend not only on efficacy but also on long-term safety, discontinuation rates, accessibility and the ability to match specific therapeutic strategies to appropriate patients in both obesity and T2D.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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Peer Review

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References

1. K. Nadolsky, W. T. Garvey, M. Agarwal, et al., "American Association of Clinical Endocrinology Consensus Statement: Algorithm for the Evaluation and Treatment of Adults With Obesity/Adiposity-Based Chronic Disease – 2025 Update," *Endocrine Practice* 31 (2025): 1351–1394.
2. American Diabetes Association Professional Practice Committee for Diabetes, "5. Facilitating Positive Health Behaviors and Well-Being to Improve Health Outcomes: Standards of Care in Diabetes—2026," *Diabetes Care* 49, no. Suppl 1 (2026): S89–S131.
3. J. P. Crandall, D. Dabelea, W. C. Knowler, D. M. Nathan, M. Temprosa, and DPP Research Group, "The Diabetes Prevention Program and Its Outcomes Study: NIDDK'S Journey Into the Prevention of Type 2 Diabetes and Its Public Health Impact," *Diabetes Care* 48 (2025): 1101–1111.

4. C. S. Walker, J. F. Aitken, G. Vazhoor Amarsingh, S. Zhang, and G. J. S. Cooper, "Amylin: Emergent Therapeutic Opportunities in Overweight, Obesity and Diabetes Mellitus," *Nature Reviews. Endocrinology* 21 (2025): 482–494.
5. E. Melson, U. Ashraf, D. Papamargaritis, and M. J. Davies, "What Is the Pipeline for Future Medications for Obesity?," *International Journal of Obesity* 49 (2025): 433–451.
6. J. P. H. Wilding, R. L. Batterham, S. Calanna, et al., "Once-Weekly Semaglutide in Adults With Overweight or Obesity," *New England Journal of Medicine* 384 (2021): 989–1002.
7. A. M. Lincoff, K. Brown-Frandsen, H. M. Colhoun, et al., "Semaglutide and Cardiovascular Outcomes in Obesity Without Diabetes," *New England Journal of Medicine* 389 (2023): 2221–2232.
8. US Food and Drug Administration, "FDA approves fourth product under National Priority Voucher Program, higher dose semaglutide," accessed April 17, 2026, <https://www.fda.gov/news-events/press-announcements/fda-approves-fourth-product-under-national-priority-voucher-program-higher-dose-semaglutide>.
9. S. Wharton, P. Freitas, J. Hjelmæsæth, et al., "Once-Weekly Semaglutide 7.2 Mg in Adults With Obesity (STEP UP): A Randomised, Controlled, Phase 3b Trial," *Lancet Diabetes and Endocrinology* 13 (2025): 949–963.
10. S. Wharton, I. Lingvay, P. Bogdanski, et al., "Oral Semaglutide at a Dose of 25 Mg in Adults With Overweight or Obesity," *New England Journal of Medicine* 393 (2025): 1077–1087.
11. K. Schweitzer, "What to Know About the New Semaglutide Pill for Obesity," *JAMA* 335 (2026): 478–479.
12. "OASIS 1 Investigators. Oral Semaglutide 50 Mg Taken Once Per Day in Adults With Overweight or Obesity (OASIS 1): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial," *Lancet* 402 (2023): 705–719.
13. V. R. Aroda, J. Aberle, L. Bardtrum, et al., "Efficacy and Safety of Once-Daily Oral Semaglutide 25 Mg and 50 Mg Compared With 14 Mg in Adults With Type 2 Diabetes (PIONEER PLUS): A Multicentre, Randomised, Phase 3b Trial," *Lancet* 402 (2023): 693–704.
14. US Food and Drug Administration, "FDA approves first new molecular entity under National Priority Voucher Program," accessed April 17, 2026, <https://www.fda.gov/news-events/press-announcements/fda-approves-first-new-molecular-entity-under-national-priority-voucher-program>.
15. S. Wharton, L. J. Aronne, A. Stefanski, et al., "Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment," *New England Journal of Medicine* 393 (2025): 1796–1806.
16. Eli Lilly and Company, "Lilly's orforglipron helped people maintain weight loss after switching from injectable incretins to oral GLP-1 therapy in first-of-its-kind phase 3 trial," accessed April 17, 2026, <https://investor.lilly.com/news-releases/news-release-details/lillys-orforglipron-helped-people-maintain-weight-loss-after>.
17. A. M. Jastreboff, L. J. Aronne, N. N. Ahmad, et al., "Tirzepatide Once Weekly for the Treatment of Obesity," *New England Journal of Medicine* 387 (2022): 205–216.
18. J. P. Friás, M. J. Davies, J. Rosenstock, et al., "Tirzepatide Versus Semaglutide Once Weekly in Patients With Type 2 Diabetes," *New England Journal of Medicine* 385 (2021): 503–515.
19. US Food and Drug Administration, "FDA approves first medication for obstructive sleep apnea," accessed April 17, 2026, <https://www.fda.gov/news-events/press-announcements/fda-approves-first-medication-obstructive-sleep-apnea>.
20. I. Lingvay, S. J. Bergenheim, J. B. Buse, et al., "Once-Weekly Semaglutide 7.2 Mg in Adults With Obesity and Type 2 Diabetes (STEP UP T2D): A Randomised, Controlled, Phase 3b Trial," *Lancet Diabetes and Endocrinology* 13 (2025): 935–948.
21. Eli Lilly and Company, "A study of investigational tirzepatide doses in participants with type 2 diabetes and obesity," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06037252>.
22. C. B. Hanmi, "Pharmaceutical reports epeglenatide cuts weight up to 30% in Korean phase 3 trial," accessed April 17, 2026, <https://biz.chosun.com/en/en-science/2025/10/27/TF077Y5HTVDPTOQR25J337Y34/>.
23. Hanmi Pharmaceutical Company Limited, "A multicenter, randomized, double-blind, phase 3 study to evaluate efficacy and safety of HM11260C in patients with type 2 diabetes mellitus inadequately controlled with metformin and dapagliflozin," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07379333>.
24. Metsera Inc, "Metsera reports positive phase 2b results for first- and best-in-class ultra-long acting GLP-1 RA candidate MET-097i, enabling rapid transition into phase 3," accessed April 17, 2026, <https://www.globenewswire.com/news-release/2025/09/29/3158095/0/en/Metsera-Reports-Positive-Phase-2b-Results-for-First-and-Best-in-Class-Ultra-long-Acting-GLP-1-RA-Candidate-MET-097i-Enabling-Rapid-Transition-into-Phase-3.html>.
25. Pfizer, "Pfizer's ultra-long-acting injectable GLP-1 RA shows robust and continued weight loss with monthly dosing in phase 2b trial," accessed April 17, 2026, <https://www.pfizer.com/news/press-release/press-release-detail/pfizers-ultra-long-acting-injectable-glp-1-ra-shows-robust>.
26. Ascletris Pharma (China) Co., Limited, "A phase I/IIa, randomized, double-blind, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of ASC30 injection, for subcutaneous use in participants with obesity," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06679959>.
27. J. J. Wu and V. Wang, "750-P: ASC30, an Oral GLP-1R Biased Small Molecule Agonist in Participants With Obesity—A First-In-Human Single Ascending Dose Study," *Diabetes* 74, no. Suppl 1 (2025): 750.
28. J. J. Wu and V. Wang, "ASC30, an Oral GLP-1R Biased Small Molecule Agonist Demonstrated Superior Weight Loss in Participants with Obesity: A 28-Day Multiple Ascending Dose Study," https://www.ascletris.com/data/upload/ueditor/20250618/Oral_presentation_ASC30_EASD_20250916_final_version.pdf.
29. H. Wu, M. Liu, Z. Cheng, et al., "752-P: Efficacy and Safety of Bofanglutide (GZR18), a Biweekly GLP-1RA, Compared With Semaglutide in Chinese Patients With T2D," *Diabetes* 74, no. Suppl 1 (2025): 752.
30. Boehringer Ingelheim, "A phase 3, randomised, double-blind, parallel-group, 76-week, efficacy and safety study of BI 456906 administered subcutaneously compared with placebo in participants with overweight or obesity without type 2 diabetes," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06066515>.
31. Boehringer Ingelheim, "A phase 3, randomised, double-blind, parallel-group, 76-week, efficacy and safety study of BI 456906 administered subcutaneously compared with placebo in participants with overweight or obesity and type 2 diabetes mellitus," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06066528>.
32. C. W. le Roux, S. Wharton, B. Bozkurt, et al., "Survodutide for Treatment of Obesity: Rationale and Design of Two Randomized Phase 3 Clinical Trials (SYNCHRONIZE-1 and -2)," *Obesity (Silver Spring)* 33 (2025): 67–77.
33. Hengrui Pharma and Kailera Therapeutics, "Hengrui Pharma and Kailera Therapeutics report positive topline data from phase 3 obesity trial in China of dual GLP-1/GIP receptor agonist HRS9531," accessed November 13, 2025, <https://www.kailera.com/press-release/hengrui-pharma-and-kailera-therapeutics-report-positive-topline-data-from-phase-3-obesity-trial-in-china-of-dual-glp-1-gip-receptor-agonist-hrs9531/>.

34. Jiangsu Hansoh Pharmaceutical Co., Ltd, "A study of HS-20094 versus dulaglutide once weekly as add-on therapy to metformin monotherapy or in combination with SGLT2 inhibitors in participants with type 2 diabetes," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07156539>.
35. Regeneron Pharmaceuticals, Inc, "Regeneron expands clinical-stage obesity portfolio with strategic in-licensing of novel dual GLP-1/GIP receptor agonist," accessed April 17, 2026, <https://investor.regeneron.com/news-releases/news-release-details/regeneron-expands-clinical-stage-obesity-portfolio-strategic/>.
36. 303-OR, "Efficacy and Safety of BGM0504 in Chinese Patients With Type 2 Diabetes—A Multicenter, Randomized, Double-Blind, Placebo-Controlled and Semaglutide Positive-Controlled Phase 2 Trial," *Diabetes* 74, no. Suppl 1 (2025): 303-OR.
37. M. Chakravarthy, M. A. Elliott, L. Acosta, et al., "Efficacy and Safety of CT-868, a Novel, Fully Biased, Dual Glucagon-Like Peptide-1/Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist, in Type 2 Diabetes: A Double-Blind, Randomized Placebo-Controlled Phase 2 Trial," *Diabetes, Obesity & Metabolism* 28, no. 3 (2025): 1673–1682.
38. Roche, "Roche announces positive phase II results for its dual GLP-1/GIP receptor agonist CT-388 in people living with obesity," accessed April 17, 2026, <https://www.roche.com/media/releases/med-cor-2026-01-27>.
39. Hoffmann-La Roche, "A phase III, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once-weekly RO7795068 administered to participants with obesity or overweight without type 2 diabetes," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07351045>.
40. Hoffmann-La Roche, "A phase III, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once-weekly RO7795068 administered to participants with obesity or overweight and type 2 diabetes," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07351058>.
41. S. H. Hsia, H. Bays, L. K. Billings, et al., "Mazdutide (LY3305677) in participants with obesity or overweight: a phase 2 dose-finding study," accessed April 17, 2026, https://assets.ctfassets.net/mpejy6umgthp/1y1DRY2Hmq1fxM6pJXLbsY/5802adfaed34b59c6fcfcdb2095ad9c7/VV-MAZPT3_OW2025_HSIA_MAZDUTIDE_SYMPOSIUM_DV-037120_V4.7.pdf.
42. L. Ji, H. Jiang, Y. Bi, et al., "GLORY-1 Investigators. Once-Weekly Mazdutide in Chinese Adults With Obesity or Overweight," *New England Journal of Medicine* 392 (2025): 1887–1900.
43. Innovent Biologics, "Mazdutide 9mg Supplementary Application Accepted for Review by China's NMPA, Potentially Offering a Novel Drug Option for Moderate-To-Severe Obese Population," accessed April 17, 2026, <https://en.innoventbio.com/InvestorsAndMedia/PressReleaseDetail?key=564>.
44. Innovent Biologics, "Innovent's Mazdutide Shows Superiority in Glycemic Control with Weight Loss over Semaglutide in a Head-to-head Phase 3 Clinical Trial DREAMS-3," accessed April 17, 2026, <https://en.innoventbio.com/InvestorsAndMedia/PressReleaseDetail?key=558>.
45. D. Zhu, J. Zhao, H. Cai, et al., "Mazdutide Versus Placebo in Chinese Adults With Type 2 Diabetes," *Nature* 652 (2025): 174–180, <https://doi.org/10.1038/s41586-025-10026-w>.
46. M. Nouredin, S. A. Harrison, R. Loomba, et al., "Safety and Efficacy of Weekly Pemvidutide Versus Placebo for Metabolic Dysfunction-Associated Steatohepatitis (IMPACT): 24-Week Results From a Multicentre, Randomised, Double-Blind, Phase 2b Study," *Lancet* 406, no. 10520 (2025): 2644–2655.
47. The United Bio-Technology (Hengqin) Co., Ltd, "A phase II clinical study to evaluate the efficacy and safety of UBT251 injection in obese/overweight chronic kidney disease population," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07134335>.
48. T. Coskun, Q. Wu, N. C. Schloot, et al., "Effects of Retatrutide on Body Composition in People With Type 2 Diabetes: A Substudy of a Phase 2, Double-Blind, Parallel-Group, Placebo-Controlled, Randomised Trial," *Lancet Diabetes and Endocrinology* 13 (2025): 674–684.
49. Eli Lilly and Company, "Lilly's triple agonist, retatrutide, delivered weight loss of up to an average of 71.2 lbs along with substantial relief from osteoarthritis pain in first successful phase 3 trial," accessed April 17, 2026, <https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-delivered-weight-loss-average>.
50. Eli Lilly and Company, "Lilly's triple agonist, retatrutide, demonstrated significant reductions in A1C and weight in first phase 3 trial for treatment of type 2 diabetes," accessed April 17, 2026, <https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-demonstrated-significant>.
51. Hanmi Pharmaceutical Company Limited. HM15275, "ObesityWeek poster," 2025, accessed April 17, 2026, https://www.hanmi.co.kr/science-pdf/HM15275/2025_ObesityWeek_Poster_HM15275_218.pdf.
52. Hanmi Pharmaceutical Company Limited, "A phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate efficacy, safety, and tolerability of HM15275 for 36 weeks in obese or overweight subjects without diabetes mellitus," accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07205900>.
53. A. M. Jastreboff, D. H. Ryan, H. E. Bays, et al., "MariTide Phase 2 Obesity Trial Investigators. Once-Monthly Maridebart Cafraglutide for the Treatment of Obesity—A Phase 2 Trial," *New England Journal of Medicine* 393, no. 9 (2025): 843–857.
54. Kailera Therapeutics, "Kailera Therapeutics announces \$600 million Series B financing to further advance pipeline of next-generation therapies for the treatment of obesity," accessed April 17, 2026, <https://investors.kailera.com/news-releases/news-release-details/kailera-therapeutics-announces-600-million-series-b-financing>.
55. W. T. Garvey, M. Blüher, C. K. Osorto Contreras, et al., "REDEFINE 1 Study Group. Coadministered Cagrilintide and Semaglutide in Adults With Overweight or Obesity," *New England Journal of Medicine* 393 (2025): 1088–1101.
56. S. Verma, M. Böttcher, P. Brown, et al., "CagriSema Reduces Blood Pressure in Adults With Overweight or Obesity: REDEFINE 1," *Hypertension* 83, no. 2 (2026): e26055.
57. I. Lingvay, et al., "Cagrilintide-Semaglutide in Adults With Overweight or Obesity and Type 2 Diabetes," *New England Journal of Medicine* 393 (2025): 1102–1116.
58. Novo Nordisk A/S, "CagriSema demonstrated superior HbA1c reduction of 1.91%-points and weight loss of 14.2% in adults with type 2 diabetes in the REIMAGINE 2 trial," accessed April 17, 2026, <https://www.globenewswire.com/news-release/2026/02/02/3230429/0/en/Novo-Nordisk-A-S-CagriSema-demonstrated-superior-HbA1c-reduction-of-1-91-points-and-weight-loss-of-14-2-in-adults-with-type-2-diabetes-in-the-REIMAGINE-2-trial.html>.
59. Novo Nordisk, "CagriSema demonstrated 23% weight loss in an open-label head-to-head REDEFINE 4 trial in people with obesity, the primary endpoint was not achieved," accessed April 17, 2026, <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916501>.
60. Roche, "Roche announces positive phase II results for petrelintide, an amylin analog developed for people living with overweight and obesity," accessed April 17, 2026, <https://www.roche.com/media/releases/med-cor-2026-03-05>.
61. AstraZeneca, "A phase I randomized, single-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AZD6234 following repeat dose

- administration in participants with overweight or obesity,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06132841>.
62. AstraZeneca, “A phase IIb randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of AZD6234 in participants living with obesity or overweight with comorbidity,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06595238>.
63. AstraZeneca, “A phase IIb randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of co-administration of AZD9550 and AZD6234 in participants living with obesity or overweight with co-morbidity (ASCEND),” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06862791>.
64. Gubra, “Gubra announces positive GUBamy phase 1 interim MAD results,” accessed April 17, 2026, https://www.gubra.dk/mfn_news/gubra-announces-positive-gubamy-phase-1-interim-mad-results/.
65. C. J. Bailey, P. R. Flatt, and J. M. Conlon, “Long-Acting Amylin-Related Peptides as Therapies for Obesity and Type 2 Diabetes,” *Peptides* 196 (2026): 171480.
66. Metsera, “A wholly owned subsidiary of Pfizer. A randomized, double-blind, single and multiple ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of MET233 in otherwise healthy adult participants with obesity or overweight,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07022977>.
67. Metsera, “A wholly owned subsidiary of Pfizer. A phase 1 randomized, double-blind, placebo-controlled, single and multiple ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of MET233 co-administered with MET097 in adult participants with obesity or overweight including participants with type 2 diabetes mellitus,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06924320>.
68. L. K. Billings, S. Hsia, H. Bays, et al., “Eloralintide, a Selective Amylin Receptor Agonist for the Treatment of Obesity: A 48-Week Phase 2, Multicentre, Double-Blind, Randomised, Placebo-Controlled Trial,” *Lancet* 406, no. 10520 (2025): 2631–2643.
69. N. Nordisk, “Novo Nordisk phase 2 trial with amycretin reports significant weight loss and HbA1c reduction in type 2 diabetes,” accessed April 17, 2026, <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916463>.
70. J. Rosenstock, S. Hsia, L. Nevarez Ruiz, et al., “Chen Y; ACHIEVE-1 Trial Investigators. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes,” *New England Journal of Medicine* 393, no. 11 (2025): 1065–1076.
71. Eli Lilly and Company, “Lilly’s oral GLP-1, orforglipron, demonstrated superior glycaemic control in two successful Phase 3 trials, reconfirming its potential as a foundational treatment in type 2 diabetes,” accessed April 17, 2026, <https://investor.lilly.com/news-releases/news-release-details/lillys-oral-glp-1-orforglipron-demonstrated-superior-glycaemic>.
72. J. Rosenstock, D. Yabe, D. Cox, et al., “ACHIEVE-3 Investigators. Efficacy and Safety of Once-Daily Oral Orforglipron Compared With Oral Semaglutide in Adults With Type 2 Diabetes (ACHIEVE-3): A Multinational, Multicentre, Non-Inferiority, Open-Label, Randomised, Phase 3 Trial,” *Lancet* 407, no. 10534 (2026): 1147–1160.
73. D. B. Horn, D. H. Ryan, S. G. Kis, et al., “Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, for the Treatment of Obesity in People With Type 2 Diabetes (ATTAIN-2): A Phase 3, Double-Blind, Randomised, Multicentre, Placebo-Controlled Trial,” *Lancet* 406 (2025): 2927–2944.
74. A. Haggag, L. Butcher, X. Sun, et al., “AZD5004/ECC5004, A Small Molecule GLP-1 Receptor Agonist May Be Administered Once Daily under Fed/Fasted Conditions,” accessed April 17, 2026, https://www.eccogene.com/wp-content/uploads/OW-2024_ECC5004-Food-Effects-Poster_FINAL_24Oct2024-1.pdf.
75. AstraZeneca, “A phase IIb randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of AZD5004 in participants living with obesity or overweight with comorbidity,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06579092>.
76. AstraZeneca, “A phase IIb, randomized, double-blind, placebo-controlled and open-label active comparator study to evaluate the efficacy, safety, and tolerability of AZD5004 in adults with type 2 diabetes mellitus,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06579105>.
77. L. Ji, L. Gao, C. Meng, X. Zhang, J. Huang, and B. Li, “743-P: Efficacy and Safety of VCT220 in Chinese Adults With Overweight or Obesity,” *Diabetes* 74, no. Supplement_1 (2025): 743.
78. L. guo, Z. Sun, L. Zhang, et al., “Efficacy and Safety of a Novel Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist (HRS-7535) in Type 2 Diabetes Mellitus Patients Inadequately Controlled by Metformin,” *Diabetes* 74, no. Supplement_1 (2025): 837.
79. G. Weijun, L. Zhang, L. Li, et al., “Efficacy and Safety of a Novel Oral Small Molecule GLP-1RA in Chinese Obese Adults Without Diabetes,” *Diabetes* 74, no. Supplement_1 (2025): 865.
80. Structure Therapeutics, “Structure Therapeutics reports positive topline data from phase 2 ACCESS II trial with once-daily oral small molecule GLP-1 receptor agonist, aleniglipron,” accessed April 17, 2026, <https://structuretx.gcs-web.com/news-releases/news-release-details/structure-therapeutics-reports-positive-topline-data-phase-2>.
81. TechTarget, “Structure announces mid-stage data for its oral GLP-1 candidate,” accessed April 17, 2026, <https://www.techtarget.com/pharmalifesciences/news/366636177/Structure-announces-mid-phase-data-for-its-oral-GLP-1-candidate>.
82. Viking Therapeutics, “Viking Therapeutics announces positive top-line results from phase 2 VENTURE-Oral dosing trial of VK2735 tablet formulation in patients with obesity,” accessed April 17, 2026, <https://ir.vikingtherapeutics.com/2025-08-19-Viking-Therapeutics-Announces-Positive-Top-Line-Results-from-Phase-2-VENTURE-Oral-Dosing-Trial-of-VK2735-Tablet-Formulation-in-Patients-with-Obesity>.
83. Viking Therapeutics, “Viking Therapeutics to Highlight Clinical Data From VK2735 Obesity Program in Presentations at ObesityWeek,” 2025, accessed April 17, 2026, <https://ir.vikingtherapeutics.com/2025-10-29-Viking-Therapeutics-to-Highlight-Clinical-Data-from-VK2735-Obesity-Program-in-Presentations-at-ObesityWeek-R-2025>.
84. Biomed Industries, “Biomed Industries Unveils Promising Phase 2 Results of NA-931, the First Oral Quadruple Agonist for Obesity, at ENDO,” 2025, accessed April 17, 2026, <https://www.biomedind.com/news-NA-931-ENDO2025.html>.
85. C. Buckeridge, S. Cobain, H. E. Bays, et al., “Efficacy and Safety of Danuglipron (PF-06882961) in Adults With Obesity: A Randomized, Placebo-Controlled, Dose-Ranging Phase 2b Study,” *Diabetes, Obesity and Metabolism* 27, no. 9 (2025): 4915–4926.
86. Terns Pharmaceuticals, “Terns Pharmaceuticals reports topline 12-week data from its phase 2 trial evaluating oral GLP-1 receptor agonist TERN-601 in obesity,” accessed April 17, 2026, <https://ir.ternspharma.com/news-releases/news-release-details/terns-pharmaceuticals-reports-topline-12-week-data-its-phase-2/>.
87. Kailera Therapeutics, “Efficacy and Safety of Oral KAI-7535 in Adult Participants Living With Obesity or Overweight With at Least 1 Weight-Related Comorbidity,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07497880>.
88. J. Rosenstock, D. Lender, F. Raiser, et al., “First Report on the Small Molecule Oral GLP-1 Receptor Agonist RGT-075 in Obesity—A

- Randomized, Placebo-Controlled Phase 2a Proof-Of-Concept Twelve-Week Study,” *Diabetes* 74, no. Supplement_1 (2025): 785.
89. S. B. Heymsfield, L. J. Aronne, P. Montgomery, et al., “Bimagrumb Plus Semaglutide Alone or in Combination for the Treatment of Obesity: A Randomized Phase 2 Trial,” *Nature Medicine* 32, no. 3 (2026): 869–882.
90. Regeneron Pharmaceuticals, “A Randomized, Double-Blind Study of the Efficacy and Safety of Trevogrumab, with or without Garetosmab, in Addition to Semaglutide in Patients with Obesity,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06299098>.
91. Regeneron Pharmaceuticals, Inc, “Results from phase 2 COURAGE trial demonstrating potential to improve quality of GLP-1 receptor agonist-induced weight loss by preserving lean mass, presented at EASD,” accessed April 17, 2026, <https://investor.regeneron.com/news-releases/news-release-details/results-phase-2-courage-trial-demonstrating-potential-improve/>.
92. Palatin Technologies, “Palatin announces MC4R agonist bremelanotide co-administered with GLP-1/GIP tirzepatide meets primary endpoint in phase 2 obesity study,” accessed April 17, 2026, https://palatin.com/press_releases/palatin-announces-mc4r-agonist-bremelanotide-co-administered-with-glp-1-gip-tirzepatide-meets-primary-endpoint-in-phase-2-obesity-study/.
93. B. S. Wulff, A. P. Chambers, C. K. Osorto Contreras, et al., “Long-Acting PYY3-36 Analogue With Semaglutide for Obesity: From Preclinical Assessment Through Randomized Clinical Studies,” *Obesity (Silver Spring)* 33, no. 8 (2025): 1457–1474.
94. L. Ji, L. Gao, H. Xue, et al., “Efficacy and Safety of a Biased GLP-1 Receptor Agonist Ecnoglutide in Adults With Overweight or Obesity: A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial,” *Lancet Diabetes & Endocrinology* 13, no. 9 (2025): 777–789.
95. D. Zhu, W. Wang, G. Tong, et al., “Efficacy and Safety of cAMP Signalling-Biased GLP-1 Analogue Ecnoglutide Monotherapy Versus Placebo in Patients With Type 2 Diabetes (EECOH-1): A Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial,” *Nature Communications* 17 (2026): 1420.
96. Y. He, N. Mi, Z. Cheng, et al., “Efficacy and Safety of cAMP-Biased GLP-1 Receptor Agonist Ecnoglutide Versus Dulaglutide in Patients With Type 2 Diabetes and Elevated Glucose Concentrations on Metformin Monotherapy (EECOH-2): A 52-Week, Multicentre, Open-Label, Non-Inferiority, Randomised, Phase 3 Trial,” *Lancet Diabetes and Endocrinology* 13 (2025): 863–873.
97. Eli Lilly and Company, “A parallel-group treatment, phase 2, double-blind study of once-weekly subcutaneous LY3457263 compared to placebo in participants with type 2 diabetes mellitus on a stable dose of semaglutide or tirzepatide who failed to achieve HbA1c goal,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06897475>.
98. Eli Lilly and Company, “A phase 2, parallel-group, double-blind, placebo-controlled study to investigate weight reduction with macupatide and eloralintide, alone or in combination, in adult participants with obesity or overweight and with type 2 diabetes,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT07215559>.
99. Eli Lilly and Company, “A phase 2, randomized, double-blind, placebo-controlled, proof-of-concept study of once-weekly tirzepatide plus mibavademab compared with tirzepatide alone in adult participants with obesity,” accessed April 17, 2026, <https://clinicaltrials.gov/study/NCT06373146>.
100. Veru Inc, “Veru reports positive results from phase 2b QUALITY and maintenance extension study showing enobosarm significantly reduced body weight regain, prevented fat regain, and preserved lean mass after semaglutide discontinuation,” accessed April 17, 2026, <https://ir.verupharma.com/news-events/press-releases/detail/236/veru-reports-positive-results-from-phase-2b-quality-and>.
101. Veru Inc, “Veru enrolls first patient in phase 2b PLATEAU clinical trial of enobosarm and semaglutide combination for high quality weight loss,” accessed April 17, 2026, <https://ir.verupharma.com/news-events/press-releases/detail/252/veru-enrolls-first-patient-in-phase-2b-plateau-clinical>.
102. F. K. Knop, G. Kunos, D. Dicker, et al., “Efficacy and Safety of Monlunabant in Adults With Obesity and Metabolic Syndrome: A Double-Blind, Randomised, Placebo-Controlled, Phase 2a Trial,” *Lancet Diabetes & Endocrinology* 13, no. 11 (2025): 911–923.
103. Skye Bioscience, Inc, “Skye Bioscience late-breaking oral abstract at ObesityWeek 2025 to highlight improvement in rebound weight gain,” accessed April 17, 2026, <https://ir.skyebioscience.com/news-releases/detail/246/skye-bioscience-late-breaking-oral-abstract-at-obesityweek-2025-to-highlight-improvement-in-rebound-weight-gain>.
104. Skye Bioscience, Inc, “Skye reports positive CBeyond phase 2a extension interim study results for nimacimab in combination with semaglutide,” accessed April 17, 2026, <https://ir.skyebioscience.com/news-releases/detail/253/skye-reports-positive-cbeyond-phase-2a-extension-interim-study-results-for-nimacimab-in-combination-with-semaglutide>.
105. L. Xiang, G. Wang, Y. Zhuang, et al., “Safety and Efficacy of GLP-1/FGF21 Dual Agonist HEC88473 in MASLD and T2DM: A Randomized, Double-Blind, Placebo-Controlled Study,” *Journal of Hepatology* 82 (2025): 967–978.
106. OrsoBio, “OrsoBio announces positive topline phase 1b/2a clinical data for its oral mitochondrial protonophore TLC-6740 in combination with tirzepatide,” accessed April 17, 2026, <https://orsobio.com/press-release/orsobio-announces-positive-topline-phase-1b-2a-clinical-data-for-its-oral-mitochondrial-protonophore-tlc-6740-in-combination-with-tirzepatide/>.
107. Vivani Medical, Inc, “Vivani Medical announces rapid advancement of NPM-139, a novel semaglutide implant, following positive weight loss data from an ongoing preclinical study of NPM-139 and promising results from the LIBERATE-1 phase 1 clinical study of NPM-115,” accessed April 17, 2026, <https://investors.vivani.com/investors/news-events/press-releases/detail/198/vivani-medical-announces-rapid-advancement-of-npm-139-a>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Adverse events, serious adverse events, and treatment discontinuation across selected emerging agents discussed in the review.