Adv Ther
https://doi.org/10.1007/s12325-026-03576-6

REVIEW

Future Directions in the Medical Treatment of Obesity: A Narrative Review

Aya Bassatne · Ivania Rizo

Received: December 17, 2025 / Accepted: March 17, 2026

ABSTRACT

Obesity remains a major global health challenge with increasing prevalence rates despite decades of long-standing efforts focused on lifestyle interventions, pharmacotherapy, and surgery. The rapid development of highly effective incretin-based therapies has transformed obesity care by achieving clinically significant and substantial weight loss. Building on this success, an expanding therapeutic pipeline—including dual and triple agonists, amylin analogues, and other multimodal agents—targets complementary pathways and more closely aligns treatment with the biological complexity of obesity. Together, these advancements offer a promising future for long-term, sustainable obesity management and may help shift population-level trends. This review summarizes current evidence from published trials on the mechanisms, efficacy, and safety of approved and investigational medications, and highlights the potential impact of these therapies on the evolving landscape of obesity care.

A. Bassatne · I. Rizo (✉)
Section of Endocrinology Diabetes and Nutrition, Department of Medicine, Boston University Chobanian and Avedisian School of Medicine, 72 E. Concord Street C3, Boston, MA 02118, USA
e-mail: ivamrizo@bu.edu

Keywords: Next-generation obesity pharmacotherapy; Entero-pancreatic hormones; Incretin therapy; Obesity; Pharmacotherapy; Weight loss

Key Summary Points

Obesity remains a major global health challenge. However, the emergence of highly effective incretin-based therapies has marked a turning point in obesity management.

Incretin-based therapy demonstrates substantial weight loss while also improving cardiometabolic, renal, hepatic, and functional outcomes.

Emerging therapies, including triple agonists, amylin analogues, and myostatin-activin pathway inhibitors, target complementary hormonal and metabolic pathways and may further enhance weight loss and body composition outcomes.

Novel formulations, including oral and long-acting injectables, have the potential to enhance adherence and expand access to care. The long-term success of newer obesity therapies will depend on sustained adherence, equitable access, and effective integration into chronic disease management frameworks.

Published online: 09 April 2026

INTRODUCTION

Obesity is a global epidemic posing major health challenges worldwide. Its prevalence has risen significantly over the past several years, reaching approximately 40% among adults in the USA based on data from 2021 to 2023 [1]. It is associated with increased risk of developing non-communicable diseases including cardiovascular [2], musculoskeletal [3], diabetes [4], cancer [5], and increased risk of mortality [6]. In addition, it significantly contributes to healthcare costs, with annual costs in the USA exceeding $260 billion [7, 8].

Despite the recognition of obesity as a major healthcare threat and the implementation of interventions including lifestyle modification, first-generation obesity pharmacotherapy, and bariatric surgery [9], the prevalence of obesity continued to rise significantly for decades up until 2023 [10]. At that point, for the first time in years, the prevalence of obesity seems to have stabilized [10]. This pivotal turning point coincides with the increased use of incretin-based therapies suggesting their potent effect and fundamental use in the treatment of obesity [10] and its comorbidities [11]. Despite early signs of stabilization, long-term projections anticipate that, without major public health interventions, US adult obesity rates will remain high or resume increasing, potentially affecting over half of US adults by 2030–2050 [12, 13].

Building on the accomplishment of highly effective hormone-based medications that target glucagon-like peptide 1 (GLP-1) and glucose insulinotropic peptide (GIP), new-generation obesity pharmacotherapies targeting multiple metabolic pathways are being investigated [14]. Understanding the pharmacology, efficacy, and broader health effects of these medications is critical to optimize clinical care and anticipate future directions in obesity medicine. This review aims to provide a comprehensive review of the current entero-pancreatic hormone-based therapies and emerging therapies emphasizing their mechanisms of action, clinical efficacy, and implications in addressing the global obesity epidemic. In this context, "future directions" refers not only to investigational agents but also to advances beyond single-hormone therapies, including multimodal approaches, innovative formulations, and the integration of these treatments into long-term management of obesity as a chronic disease. To ensure methodological consistency and clinical relevance, we included data from phase 2 or phase 3 trials of newer agents reporting weight-related outcomes.

INCRETIN HORMONES

Glucagon-Like Peptide 1 Agonist

Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin, suppresses glucagon, slows gastric emptying, and reduces appetite (Fig. 1) [15]. Throughout this review, efficacy data are reported according to the treatment regimen estimand (unless specified otherwise), which reflects outcomes regardless of adherence, discontinuation, or rescue medications.

Subcutaneous Semaglutide

Semaglutide is a human GLP-1 analogue [19]. It is structurally similar to native human GLP-1 but includes specific amino acid substitutions and the addition of a C-18 fatty diacid chain. These modifications extend the drug's half-life, enabling weekly dosing [19].

The Semaglutide Treatment Effect in People with Obesity (STEP) phase 3 trials investigated the efficacy of semaglutide 2.4 mg/week with lifestyle intervention on weight loss in adults with obesity or overweight [20–27]. Semaglutide resulted in 14.9% weight loss at 68 weeks compared to 2.4% with placebo (Table 1). Among participants receiving semaglutide, 86.4%, 69.1%, and 50.5% achieved more than 5%, 10%, and 15% weight loss, respectively (Table 1) [20]. The percentage-point change in total fat mass, lean mass, and visceral fat mass proportions, measured by dual energy X-ray absorptiometry (DXA), was −3.5%, 3.0%, and −2.0%, respectively, with semaglutide compared to −0.2%, 0.1%, and −0.01% with placebo [20] (Table 1). In individuals with

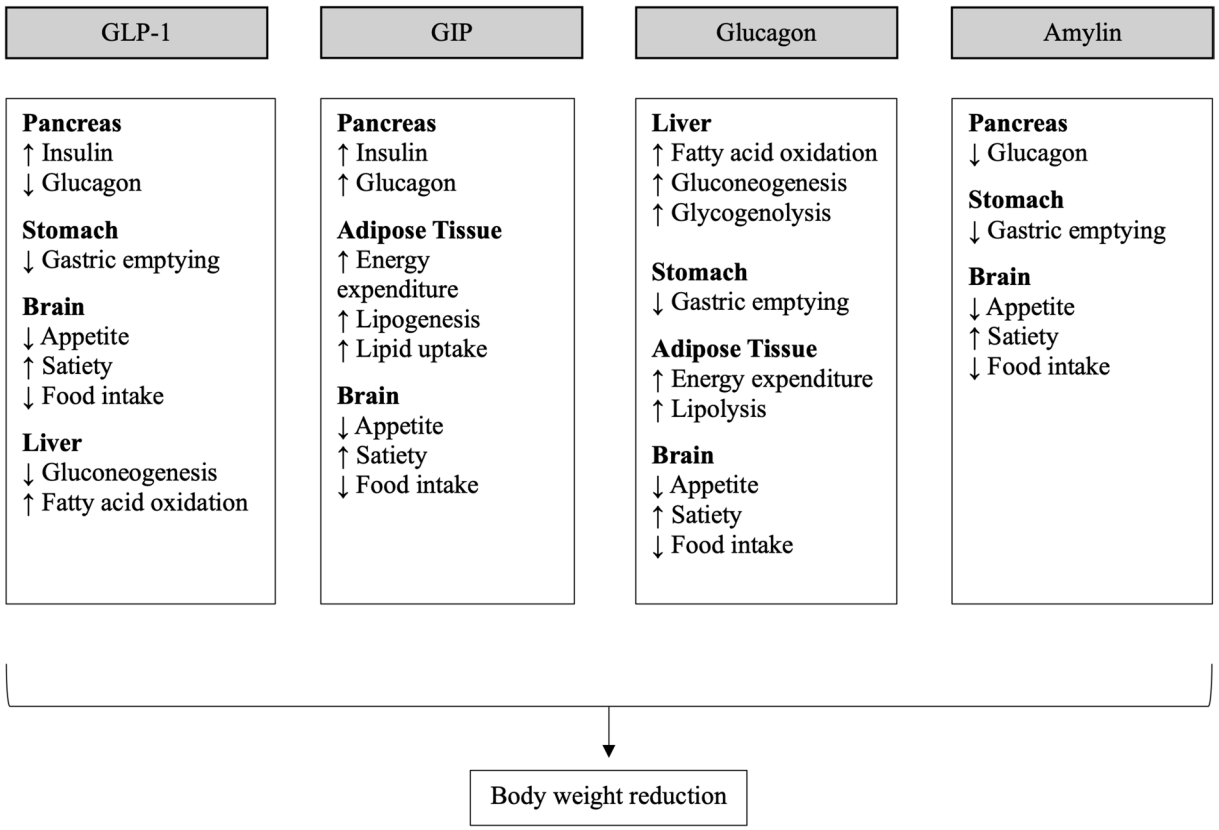

Fig. 1 Predominant mechanisms of action of entero-pancreatic hormones targeted in newer generation obesity pharmacotherapy. Data derived from references [16–18]. *GLP-1* glucagon-like peptide 1, *GIP* glucose insulinotropic peptide

concomitant type 2 diabetes (T2D), weight loss reached 9.6% and 7% with semaglutide 2.4 mg/week and 1 mg/week, respectively, versus 3.4% with placebo [21]. Glycated hemoglobin (HbA1c) decreased by 1.6%, 1.4%, and 0.4% with semaglutide 2.4 mg/week, 1 mg/week, and placebo, respectively [21]. When semaglutide was combined with intensive lifestyle intervention, weight loss reached up to 16% versus 5.7% with placebo [22]. The STEP UP trial investigated the efficacy of a higher dose of semaglutide (7.2 mg/week), which resulted in a more pronounced weight loss of 18.7% versus 15.6% with semaglutide 2.4 mg/week, and 3.9% with placebo [28]. The percentage change in total fat mass, lean mass, and visceral fat mass with semaglutide, measured by MRI, was −25.1%, −6.7%, and −31.3% respectively compared to −0.9%, +0.2%, and −6.3% in the placebo group [28] (Table 1).

Beyond its established benefits in diabetes [44] and weight management [20–27], semaglutide confers additional health benefits. Semaglutide reduced the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal strokes by 20% compared to placebo [45], with a more pronounced risk reduction (26%) in patients with type 2 diabetes [46]. In adults with obesity and heart failure with preserved ejection fraction (HFpEF), semaglutide increased the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score, a standardized questionnaire including symptoms and physical function domains with higher scores reflecting better overall health, by 16.6 points compared to 8.7 points with placebo [47]. In addition, the 6-min walk distance improved by 21.5 m compared to 1.2 m with placebo [47]. Furthermore, in adults with type 2 diabetes and peripheral artery disease, semaglutide 1 mg/week improved

Table 1 Summary of efficacy outcomes of obesity pharmacotherapy trials in participants without diabetes

Trial Author (year)	Trial phase	*N* participants	Age (years)	Sex (%F)	Race (% White)	BMI (kg/m^2)	Intervention	Comparator	Duration	Weight loss (%)	≥ 5% weight loss	≥ 10% weight loss	≥ 15% weight loss	≥ 20% weight loss	Change in total fat mass (%)	Change in total lean mass (%)	Change in visceral fat mass (%)
Glucagon-like peptide 1 agonist																	
STEP 1[a] Wilding (2021) [20]	Phase 3	1961 I: 1306 C: 655	46	74.1	75.1	37.9	Semaglutide 2.4 mg SC weekly	Placebo	68 weeks	I: − 14.9 C: − 2.4	I: 86.4% C: 31.5%	I: 69.1% C: 12%	I: 50.5% C: 4.9%	I: 32.0% C: 1.7%	I: − 3.5 C: − 0.2	I: 3.0 C: 0.1	I: − 2.0 C: − 0.01
STEP UP Wharton (2025) [28]	Phase 3	1407 I1: 1005 I2: 201 C: 201	47 ± 12	73.7	85.5	39.9 ± 7.1	I1: Semaglutide 7.2 mg I2: Semaglutide 2.4 mg SC weekly	Placebo	72 weeks	I1: − 18.7 I2: − 15.6 C: − 3.9	I1: 90.7% I2: 89.9% C: 36.8%	I1: 82.4% I2: 75.1% C: 20.5%	I1: 66.5% I2: 54.5% C: 7.6%	I1: 47.7% I2: 33.3% C: 2.9%	I: − 25.1 C: − 0.9	I: − 6.7 C: 0.2	I: − 31.3 C: − 6.3
SLIMMER Ji (2025) [29]	Phase 3	664 I1: 166 I2: 166 I3: 167 C: 165	34.2 ± 7.6	50	0 (China)	32.5 ± 4.1	I1: Ecnoglutide 1.2 mg I2: Ecnoglutide 1.8 mg I3: Ecnoglutide 2.4 mg SC weekly	Placebo	48 weeks[b]	I1: − 9.1 I2: − 10.9 I3: − 13.2 C: 0.1	I1: 77% I2: 84% I3: 87% C: 16%	I1: 51% I2: 76% I3: 80% C: 5%	I1: 24% I2: 40% I3: 64% C: 1%	I1: 9% I2:16% I3: 28% C: 0	NA	NA	NA
OASIS-1 Knop (2023) [30]	Phase 3	667 I: 334 C: 333	50 ± 13	73	74	37.5 ± 6.5	Semaglutide 50 mg PO daily	Placebo	68 weeks	I: − 15.1 C: − 2.4	I: 85% C: 26%	I: 69% C: 12%	I: 54% C: 6%	I: 34% C: 3%	NA	NA	NA
OASIS-4 Wharton (2025) [31]	Phase 3	307 I: 205 C: 102	I: 48 ± 13 C: 47 ± 13	78.8	91.5	37.6	Semaglutide 25 mg PO daily	Placebo	71 weeks[c]	I: − 13.6 C: − 2.2	I: 79.2% C: 31.1%	I: 63.0% C: 14.4%	I: 50% C: 5.6%	I: 29.7% C: 3.3%	NA	NA	NA
ATTAIN-1 Wharton (2025) [32]	Phase 3	3127 I1: 723 I2: 725 I3: 730 C: 949	45.1 ± 12.1	64.2	56.5	37.0 ± 6.5	I1: Orforglipron 6 mg I2: Orforglipron 12 mg I3: Orforglipron 36 mg PO daily	Placebo	72 weeks	I1: − 7.5 I2: − 8.4 I3: − 11.2 C: − 2.1	I1: 60.6 I2: 63.5 I3: 71.8 C: 26.8	I1: 33.3 I2: 40.0 I3: 54.6 C: 12.9	I1: 15.1 I2: 20.3 I3: 36.0 C: 5.9	I1: 6.4 I2: 9.0 I3: 18.4 C: 2.8	I1: − 12.0 I2: − 9.4 I3: − 20.0 C: − 1.7	I1: − 3.7 I2: − 3.2 I3: − 6.6 C: 0.3	I1: − 16.3 I2: − 12.6 I3: − 28.2 C: 7.4
Dual glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide agonist																	
SURMOUNT-1 Jastreboff (2022) [33]	Phase 3	2359 I1: 630 I2: 636 I3: 630 C: 643	44.9 ± 12.5	67.5	70.6	38.0 ± 6.81	I1: Tirzepatide 5 mg I2: Tirzepatide 10 mg I3: Tirzepatide 15 mg SC weekly	Placebo	72 weeks	I1: − 15.0 I2: − 19.5 I3: − 20.9 C: − 3.1	I1: 85.1% I2: 89.9% I3: 90.9% C: 34.5%	I1: 68.5%; I2: 78.1% I3: 83.5 C: 18.8%	I1: 48.0% I2: 66.6% I3: 70.6% C: 8.8%	I1: 30.0% I2: 50.1% I3: 56.7 C: 3.1%	I: − 33.9 C: − 8.2	I: − 10.9 C: − 2.6	NA

Table 1 continued

Trial Author (year)	Trial phase	*N* participants	Age (years)	Sex (%F)	Race (% White)	BMI (kg/m^2)	Intervention	Comparator	Duration	Weight loss (%)	≥ 5% weight loss	≥ 10% weight loss	≥ 15% weight loss	≥ 20% weight loss	Change in total fat mass (%)	Change in total lean mass (%)	Change in visceral fat mass (%)
VENTURE Bays (2026) [34]	Phase 2	176 I1: 35 I2: 35 I3: 36 I4: 35 C: 35	I1: 49.7 ± 13.9 I2: 51.8 ± 14.1 I3: 47.1 ± 13.4 I4: 51.3 ± 15.4 C: 47.6 ± 16.4	I1: 77.1 I2: 77.1 I3: 88.9 I4: 77.1 C: 82.9	I1: 80.0 I2: 88.6 I3: 72.2 I4: 80.0 C: 74.3	I1: 38.0 ± 5.6 I2: 35.9 ± 4.0 I3: 36.6 ± 4.2 I4: 36.6 ± 5.3 C: 38.9 ± 6.3	I1: VK-2735 2.5 mg I2: VK-2735 5 mg I3: VK-2735 10 mg I4: VK-2735 15 mg SC weekly	Placebo	13 weeks	I1: − 9.1 I2: − 10.9 I3: − 12.9 I4: − 14.7 C: − 1.7	I1: 80.8% I2: 97.0% I3: 93.8% I4: 100% C: 11.5%	I1: 40.1% I2: 65.1% I3: 70.4% I4: 89.1% C: 3.0%	I1: 12.8% I2: 11.6% I3: 31.2% I4: 31.5% C: 0	NA	NA	NA	NA
Dual glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide antagonist																	
Jastreboff (2023)[d] [35]	Phase 2	465 I1: 77 I2: 77 I3: 79 I4: 51 I5: 51 I6: 52 C: 78	47.9 ± 12.3	63	67	37.9 ± 7.5	Maridebart cafraglutide (MariTide) I1: MariTide 140 mg I2: MariTide 280 mg I3: MariTide 420 mg I4: MariTide 420 mg without dose escalation I5: MariTide 420 mg with 4-week dose escalation I6: MariTide 420 mg with 12-week dose escalation SC q4 weeks[e]	Placebo	52 weeks	I1: − 13.6 I2: − 15.5 I3: − 14.6 I4: − 12.3 I5: − 14.1 I6: − 16.2 C: − 2.5	I1: 85.7% I2: 85.7% I3: 84.8% I4: 80.4% I5: 84.3% I6: 80.8% C: 26.3%	I1: 71.4% I2: 77.9% I3: 72.2% I4: 56.9% I5: 70.6% I6: 73.1% C: 11.8%	I1: 45.5% I2: 62.3% I3: 54.4% I4: 47.1% I5: 58.8% I6: 61.5% C: 2.6%	I1: 23.4% I2: 36.4% I3: 30.4% I4: 25.5% I5: 23.5% I6: 38.5% C: 0	I1: − 27.0 I2: − 36.8 I3: − 26.2 I4: − 28.3 I5: − 27.6 I6: − 33.2 C: − 9.1	I1: − 8.6 I2: − 11.0 I3: − 11.2 I4: − 10.2 I5: − 9.2 I6: − 11.6 C: − 2.1	NA
Dual glucagon-like peptide 1 and glucagon agonist																	
GLORY-1 Ji (2025) [36]	Phase 3	610 I1: 203 I2: 202 C: 205	34.2 ± 8.0	51	0 (done in China)	31.1 ± 3.5	I1: Mazdutide 4 mg I2: Mazdutide 6 mg SC weekly	Placebo	48 weeks[f]	I1: − 10.1 I2: − 12.6 C: 0.45	I1: 73.9% I2: 82.0% C: 10.5%	I1: 49.0% I2: 61.6% C: 0.6%	I1: 27.2% I2: 43.6% C: 0	I1: 13.2% I2: 20.5% C: 0	I1: − 14.4 I2: − 24.7 C: 2.4	I1: − 7.4 I2: − 11.1 C: 0.5	NA
Roux (2024) [37]	Phase 2	384 I1: 77 I2: 78 I3: 76 I4: 76	49.1 ± 12.9	68	78	37.1 ± 6.1	I1: Survodutide 0.6 mg I2: Survodutide 2.4 mg I3: Survodutide 3.6 mg I4: Survodutide 4.8 mg SC weekly	Placebo	46 weeks	I1: − 6.2 I2: − 12.5 I3: − 13.2 I4: − 14.9 C: − 2.8	I1: 60.7% I2: 81.0% I3: 82.0% I4 82.8% C: 25.9%	I1 33.9% I2: 65.5% I3: 65.6% I4: 68.8% C: 11.1%	I1: 12.5% I2: 37.9% I3: 45.9% I4: 54.7% C: 5.6%	I1: 0 I2: 20.7% I3: 29.5% I4: 32.8% C: 0	NA	NA	NA

Table 1 continued

Trial Author (year)	Trial phase	*N* participants	Age (years)	Sex (%F)	Race (% White)	BMI (kg/m^2)	Intervention	Comparator	Duration	Weight loss (%)	≥ 5% weight loss	≥ 10% weight loss	≥ 15% weight loss	≥ 20% weight loss	Change in total fat mass (%)	Change in total lean mass (%)	Change in visceral fat mass (%)
Triple glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, and glucagon agonist																	
Jastreboff (2023) [38]	Phase 2	338 I1: 69 I2: 33 I3: 34 I4: 35 I5: 35 I6: 62 C: 70	48.2 ± 12.7	48	88%	37.3 ± 5.7	I1: Retatrutide 1 mg I2: Retatrutide 4 (start with 2 mg) I3: Retatrutide 4 mg I4: Retatrutide 8 mg (start with 2 mg) I5: Retatrutide 8 mg (start with 4 mg) I6: Retatrutide 12 mg (start with 2 mg) SC weekly	Placebo	48 weeks[g]	I1: − 7.2 I2: − 11.8 I3: − 13.9 I4: − 16.7 I5: − 17.9 I6: − 17.5 C: − 1.6	I1: 64% I2: 87% I3: 91% I4: 100% I5: 100% I6: 100% C: 27%	I1: 27% I2: 73% I3: 76% I4: 90% I5: 91% I6: 93% C: 9%	I1: 16% I2: 55% I3: 64% I4: 73% I5: 77% I6: 83% C: 2%	I1: 6% I2: 31% I3: 29% I4: 50% I5: 70% I6: 63% C:1%	NA	NA	NA
Amylin agonist																	
Lau (2021) [39]	Phase 2	706 I1: 101 I2: 100 I3: 102 I4:102 I5: 101 C1: 99 C2: 101	52.3 ± 10.6	62	77	37.8 ± 7.0	I1: Cagrilintide 0.3 mg I2: Cagrilintide 0.6 mg I3: Cagrilintide 1.2 mg I4: Cagrilintide 2.4 mg I5: Cagrilintide 4.5 mg SC weekly	C1: Placebo C2: Liraglutide 3 mg	26 weeks	I1: − 6.1 I2: − 6.8 I3: − 8.4 I4: − 9.5 I5: − 10.6 C1: − 2.8 C2: − 8.4	I1: 57.5% I2: 62.0% I3: 75.8% I4: 74.1% I5: 88.7% C1:30.9% C2:76.2%	I1: 15.3% I2: 24.1% I3: 35.8% I4: 44.0% I5: 53.5% C1:10.4% C2:39.4%	I1: 3.1% I2: 5.4% I3: 14.5% I4: 21.7% I5: 18.7% C1: 2.9% C2:14.0%	NA	NA	NA	NA
Billings (2025) [40]	Phase 2	263 I1: 28 I2: 24 I3: 28 I4: 54 I5: 24 I6: 52 C: 53	49 ± 12.6	78	78	39.1 ± 6.8	I1: Eloralintide 1 mg I2: Eloralintide 3 mg I3: Eloralintide 6 mg I4: Eloralintide 9 mg I5: Eloralintide 3–9 mg I6: Eloralintide 6–9 mg SC weekly	Placebo	48 weeks	I1: − 7.3 I2: − 10.5 I3: − 13.8 I4: − 17.5 I5: − 15.8 I6: − 14.6 C: − 2.3	I1: 71% I2: 88% I3: 86% I4: 93% I5: 96% I6: 90% C: 30%	I1: 54% I2: 63% I3: 79% I4: 81% I5: 92% I6: 79% C: 13%	I1: 32% I2: 33% I3: 61% I4: 70% I5: 67% I6: 52% C: 9%	I1: 21% I2: 13% I3: 36% I4: 57% I5: 50% I6: 35% C: 6%			

Table 1 continued

Trial Author (year)	Trial phase	*N* participants	Age (years)	Sex (%F)	Race (% White)	BMI (kg/m^2)	Intervention	Comparator	Duration	Weight loss (%)	≥ 5% weight loss	≥ 10% weight loss	≥ 15% weight loss	≥ 20% weight loss	Change in total fat mass (%)	Change in total lean mass (%)	Change in visceral fat mass (%)
Dual glucagon-like peptide 1 and amylin agonist																	
REDEFINE-1 Garvey (2025) [41]	Phase 3	3417 I1: 2108 I2: 302 I3: 302 C: 705	47.0 ± 11.8	67.6	72	37.9 ± 6.7	I1: Cagrilintide 2.4 mg + Semaglutide 2.4 mg I2: Semaglutide 2.4 mg I3: Cagrilintide 2.4 mg SC weekly	Placebo	68 weeks	I1: − 20.4 I2: − 14.9 I3: − 11.5 C: − 3	I1: 91.9% I2: 84.1% I3: 78.7% C: 31.5%	I1: 83.5% I2: 69.1% I3: 55.1% C: 14.3%	I1: 70.1% I2: 47.1% I3: 31.0% C: 5.2%	I1: 53.6% I2: 26.5% I3: 15.4% C: 1.9%	I1: − 35.7 I2: − 27.1 I3: − 20.6 C: − 5.7	I1: − 14.4 I2: − 9.2 I3: − 10.3 C: − 4.2	I1: − 40.8 I2: − 32.4 I3: − 13.4 C: − 5.9
Dahl (2025)[h] [42]	Phase 1b/2a	Part B: I: 17 C: 5 Part C: I: 34 C: 5 Part D: I: 16 C: 4 Part E: I: 16 C: 4	37.3 ± 9.0	53	66	32.2 ± 3.3	Part B: Amycretin 60 mg Part C: Amycretin 20 mg Part D: Amycretin 5 mg Part E: Amycretin 1.25 mg SC weekly	Placebo	36 weeks[i]	Part B: I: − 24.3 C: − 1.1 Part C: I: − 22.0 C: 1.9 Part D: I: − 16.2 C: 2.3 Part E: I: − 9.7 C: 2.0	NA	NA	NA	NA	NA	NA	NA
Myostatin-activin pathway inhibitors																	
Heymsfield (2021) [43]	Phase 2	75 I: 37 C: 38	60.4 ± 7.7	47	76	32.9 ± 3.4	Bimagrumab 10 mg/kg IV q 4 weeks	Placebo	48 weeks	I: − 6.5 C: − 0.8	NA	NA	NA	NA	I: − 20.5 C: − 0.5	I: 3.6 C: − 0.8	NA

C comparator, *I* intervention, *IV* intravenous, *PO* oral, *q* every, *SC* subcutaneous

[a]STEP1 body composition change from baseline was reported as percentage-points change in total fat mass proportion, percentage points change in total lean body mass proportion, and percentage-points change in regional visceral fat mass proportion

[b]Primary outcomes (% weight loss and participants with ≥ 5% bodyweight reduction) reported at 40 weeks; other outcomes reported at 48 weeks

[c]Outcomes reported at 64 weeks

[d]Data represented from the obesity cohort

[e]Exception I4 intervention SC q8 weeks

[f]Outcomes reported at 32 weeks

[g]Primary outcome (% weight loss reported at 24 weeks), other outcome reported at 48 weeks

[h]The study was conducted in five parts: single ascending doses (SAD; Part A) and multiple ascending doses (MAD; Parts B–E) of subcutaneous amycretin. We report data from Part B–E

[i]Part C: 36 week; Part D: 28 week; Part E: 20 week

overall walking distance, pain-free walking distance, quality of life, and reduced need for rescue treatments [48]. In adults with steatohepatitis and liver fibrosis, semaglutide 2.4 mg/week compared to placebo, achieved higher rates of resolution of steatohepatitis with no worsening fibrosis (62.9%) as well as reduction in fibrosis with no worsening steatohepatitis (36.8%) [49]. Semaglutide 1 mg/week administered to patients with type 2 diabetes and CKD resulted in a 24% decreased risk of composite outcome including initiation of long-term dialysis or transplantation, reduction in eGFR < 15, sustained reduction in eGFR, or death from kidney-related or cardiovascular causes [50]. Finally, in patients with obesity and osteoarthritis, administration of semaglutide 2.4 mg/week reduced the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score and improved the physical function score [51].

The most common side effects are gastrointestinal adverse effects—nausea, vomiting, diarrhea, and constipation—which are generally characterized as mild to moderate in severity [20]. Gastrointestinal adverse events were more common with semaglutide 7.2 mg (70.8%) compared to 2.4 mg (61.2%) or placebo (42.8%) [28]. In clinical trials involving individuals with T2D or obesity, gallbladder-related side effects, mainly cholecystitis and gallstones, have been observed with GLP-1 medications, typically affecting less than 1% of those exposed. Gastrointestinal symptoms are also the leading cause of treatment discontinuation, although only a minority of patients stop therapy for this reason [52]. In the STEP UP T2D study, dysesthesia, which includes unusual skin sensations like tingling or burning, was more frequently observed at a dose of 7.2 mg. This side effect, not related to the gastrointestinal system, occurs in approximately 19% of participants taking 7.2 mg, compared to about 5% with a 2.4 mg dose, and is absent in those receiving a placebo [53].

Ecnoglutide

Ecnoglutide is a novel biased GLP-1 receptor agonist (RA) which favors cAMP production over β-arrestin recruitment, suggesting increased efficacy compared to non-biased GLP-1 RA such as semaglutide [54]. The SLIMMER phase 3 trial was conducted in China and evaluated the efficacy of once-weekly ecnoglutide injection compared to placebo in adults with obesity or overweight [29]. Ecnoglutide 1.2 mg, 1.8 mg, and 2.4 mg resulted in 9.1%, 10.9%, and 13.2% weight loss, respectively, after 40 weeks, compared to 0.1% weight gain in the placebo group [29]. Among participants receiving ecnoglutide, 77–87% achieved more than 5% weight loss (Table 1) [29]. HbA1c decreased by 0.14–0.20% with ecnoglutide, compared to an increase of 0.16% with placebo [29]. It is important to note that, given the absence of diabetes at baseline in the study population, the magnitude of HbA1c reduction was modest despite substantial weight loss. This is consistent with data noting HbA1c-lowering is greater in populations with poor glycemic control than in well-controlled populations with the same degree of weight loss [55]. Ecnoglutide produced robust weight loss with a safety profile consistent with existing GLP-1 RA and no new safety signals. These results suggest that cAMP-biased GLP-1 RA may support more sustained weight reduction than conventional non-biased GLP-1 RA, warranting future additional clinical evaluation [29].

Oral Semaglutide

Oral GLP-1 RAs are being developed to provide injectable-like weight loss efficacy with greater convenience, patient acceptability, and scalability, potentially improving long-term adherence and access. Compared with injectables, they avoid needles and cold chain logistics, can be prescribed more easily in primary care, and may ultimately be manufactured at lower cost while still allowing clinicians to individualize therapy based on patient preference and tolerability [56]. Oral semaglutide is a once-daily GLP-1 peptide analogue co-formulated with sodium *N*-(8-[2-hydroxylbenzoyl]amino) caprylate, which facilitates its absorption by increasing local pH, protecting it against proteolytic degradation [57, 58]. The bioavailability of oral semaglutide is 0.8% measured 30 min after the dose in a fasting state, and bioavailability increases with longer fasting times post-administration, requiring its administration in a fasting state [57, 58].

In the OASIS-1 trial, 50 mg of daily oral semaglutide resulted in 15.1% weight loss after 68 weeks of treatment compared to 2.4% in the placebo group [30]. Of those treated with oral semaglutide, 85% and 34% reached more than 5% and 20% weight loss, respectively (Table 1) [30]. In the OASIS-2 trial, participants in East Asia with type 2 diabetes achieved 14.3% weight loss with 50 mg daily oral semaglutide compared to 1.3% with placebo. HbA1c decreased by 0.78% with semaglutide compared to an increase of 0.03% with placebo [59]. In the OASIS-4 trial, conducted in adults with overweight or obesity without type 2 diabetes, a lower dose of oral semaglutide (25 mg daily) decreased weight by 13.6% compared to 2.2% in the placebo group [31]. In addition, 79.2% and 29.7% of participants receiving semaglutide 25 mg reached more than 5% and 20% weight loss, respectively (Table 1) [31]. HbA1c decreased by 0.3% with semaglutide 25 mg daily compared to 0.1% with placebo [31].

Gastrointestinal adverse events (most commonly nausea, vomiting, diarrhea, constipation, and dyspepsia) were mild to moderate, transient, and dose dependent, occurring in 74–80% of participants with oral semaglutide 25–50 mg, with higher frequency and discontinuation rates seen at the 50 mg dose during dose escalation [30, 31].

Orforglipron

Orforglipron is an oral small non-peptide partial GLP-1 RA with selective activation of G protein over β-arrestin recruitment at the GLP-1 receptor [60]. This selective signaling offers therapeutic advantages as β-arrestin proteins contribute to receptor internalization, intracellular trafficking, and desensitization. Consequently, reduced β-arrestin engagement has been associated with enhanced GLP-1 RA efficacy [60, 61]. Orforglipron demonstrates an oral bioavailability of approximately 20–40%, allowing for a more flexible dosing regimen that does not require fasting [61].

In the ATTAIN-1 phase 3 trial, orforglipron achieved 7.5%, 8.4%, and 11.2% weight loss after 72 weeks of treatment with 6 mg, 12 mg, and 36 mg, respectively, compared to 2.1% with placebo [32]. At 72 weeks, a significantly higher proportion of patients receiving orforglipron, particularly the 36 mg dose group (54.6%), achieved and surpassed a clinically meaningful body-weight reduction compared to the placebo group (12.9%) with improvement in cardiometabolic risk factors (Table 1) [32]. The percent change of total fat mass, lean mass, and visceral fat mass, measured by DXA, reached up to −20%, −6.6%, and −28.2%, respectively, with orforglipron, compared to −1.7%, 0.3%, and 7.4% with placebo [32] (Table 1). In the ATTAIN-2 trial including those with T2D and HbA1c of 7–10%, at week 72, weight loss reached 5.1%, 7%, 9.6% and HbA1c decreased by 1.22%, 1.50%, 1.66% with orforglipron 6 mg, 12 mg, 36 mg, compared to 2% and 0.47% with placebo, respectively [62]. The safety and tolerability profile of orforglipron was consistent with the known GLP-1 RA class, with the most common adverse events being mild-to-moderate gastrointestinal issues [32].

Dual Glucagon-Like Peptide 1 and Glucose-Dependent Insulinotropic Polypeptide Agonist

Glucose-dependent insulinotropic polypeptide (GIP) is an incretin secreted by the K cells in the jejunum in response to nutrient ingestion, with glucose-dependent insulinotropic and context-dependent glucagonotropic actions [15, 63]; GIP also promotes lipogenesis and lipid uptake in adipose tissue, enhancing lipid buffering capacity and limiting ectopic fat deposition (Fig. 1) [63, 64]. Furthermore, the activation of GIP receptors in the brain decreases appetite and food intake, complementing GLP-1 effects on weight loss [65].

Tirzepatide

Tirzepatide is a single peptide dual GLP-1 and GIP RA [66]. The addition of a C-20 fatty diacid acyl chain allows its once-weekly dosing [66]. The SURMOUNT phase 3 trial series investigated weekly tirzepatide in adults with obesity or overweight [66–70]. In the SURMOUNT-1 trial, weekly tirzepatide 5 mg, 10 mg, and 15 mg

resulted in 15%, 19.5%, and 20.9% weight loss, respectively, compared to 3.1% with placebo [33]. Among those who received tirzepatide 85.1%, 89.9%, and 90.9% achieved over 5% weight loss with 5 mg, 10 mg, and 15 mg, respectively, while 30%, 50.1%, and 56.7% lost more than 20% of their weight (Table 1) [33]. The percentage change in total fat mass and lean mass, measured by DXA, reached − 33.9% and − 10.9% with tirzepatide, respectively, compared to − 8.2% and − 2.6% with placebo [33] (Table 1). In patients with T2D, weekly tirzepatide 10 or 15 mg decreased weight significantly by 12.8% and 14.7%, respectively, compared to − 3.2% with placebo. HbA1c improved by 2.1% with tirzepatide 10 mg and 15 mg and 0.5% with placebo [67]. The SURMOUNT-5 trial evaluated the efficacy of tirzepatide (10 or 15 mg/week) compared to semaglutide (1.7 or 2.4 mg/week). Participants receiving tirzepatide achieved more weight loss compared to those receiving semaglutide (− 20.2% versus − 13.7%) [70]. The safety and side effect profiles of tirzepatide are similar to those of semaglutide [66].

In addition to its effect on diabetes [71] and weight loss [66–70], tirzepatide provides additional health benefits. Tirzepatide 15 mg/week administered to adults with HFpEF, reduced the risk of death from cardiovascular causes or worsening heart failure events resulting in hospitalization, intensification of oral diuresis, or intravenous drugs in urgent care setting by 38% compared to placebo [72]. In participants with steatohepatitis and liver fibrosis, tirzepatide provided resolution of liver steatohepatitis with no worsening fibrosis in 44%, 56%, and 62% of participants receiving 5 mg, 10 mg, and 15 mg, respectively, compared to 10% in the placebo group. It also decreased fibrosis without worsening steatohepatitis [73]. In participants with moderate to severe obstructive sleep apnea, tirzepatide significantly decreased the Apnea–Hypopnea Index (AHI) by 25–29 events per hour compared to − 5 events per hour with placebo [74].

VK-2735

VK-2735 is a novel dual receptor agonist to GLP-1 and GIP receptors [34]. The VENTURE study was a 13-week phase 2 trial assessing the efficacy of VK-2735 compared to placebo on weight management in individuals with obesity or overweight without diabetes [34]. Weekly VK-2735 subcutaneous injection at a dose of 2.5 mg, 5 mg, 10 mg, and 15 mg resulted in a 9.1%, 10.9%, 12.9%, and 14.7% weight loss, respectively, compared to 1.7% in the placebo group [34]. Among those who received VK-2735, 80.8%, 97%, 93.8%, and 100% achieved more than 5% weight loss with 2.5 mg, 5 mg, 10 mg, and 15 mg, respectively. Furthermore, 12.8%, 11.6%, 31.2%, and 41.5% achieved more than 15% weight loss with 2.5 mg, 5 mg, 10 mg, and 15 mg, respectively [34]. VK-2735 decreased A1c by 0.27% to 0.36% compared to an increase of 0.03% with placebo [34]. The most reported adverse events were gastrointestinal (nausea, vomiting, diarrhea, and constipation). These generally occurred early in the study and with higher initial doses [34].

Glucagon-Like Peptide 1 Agonist and Glucose-Dependent Insulinotropic Polypeptide Antagonist

While GIP RA can promote weight loss, particularly when combined with GLP-1 RA, genetic data suggest that variants causing reduced GIP receptor signaling are associated with lower body mass index, therefore indicating benefits of GIP antagonism as well [75].

Maridebart Cafraglutide

Maridebart cafraglutide (MariTide) is a long-acting peptide-antibody conjugate consisting of two GLP-1 peptide analogues conjugated to a monoclonal antibody antagonist to the GIP receptor [76]. The half-life of MariTide is 21 days, which supports monthly or less frequent injections [76].

The multinational MariTide phase 2 obesity trial evaluated the efficacy and safety of MariTide at doses from 140 to 420 mg with or without escalation over 52 weeks, in adults with obesity with or without diabetes [35]. In the obesity only cohort, the percent change of body weight ranged between − 12.3% and

−16.2% with MariTide compared to −2.5% with placebo (Table 1) [35]. Whereas in the obesity-diabetes cohort, the percent change of body weight ranged between −8.4% and −12.3% with MariTide compared to −1.7% in the placebo group [35]. In the obesity cohort, approximately 85% of the participants receiving MariTide 140–420 mg achieved at least 5% weight loss, with similar high responder rates of about 62.5–78.1% across all doses in the obesity-diabetes cohort [35]. The percent change in total fat mass, measured by DXA, reached up to −36.8% and the change in lean mass reached up to −11.6% with MariTide, compared to −9.1% and −2.1% with placebo [35] (Table 1). MariTide decreased A1c by 0.3–0.4% in the obesity cohort and by 1.2–1.6% in the obesity-diabetes cohort [35].

The most common side effects of MariTide are gastrointestinal adverse events (nausea, vomiting, constipation, retching, diarrhea) which occurred more often in participants who did not undergo dose-escalation [35]. Gallbladder events occurred in 1–6% of the MariTide-treated participants in the obesity cohort (versus 0% with placebo), with higher rates at the 420 mg dose. Discontinuation rates ranged from 8% to 27% depending on escalation strategy [35].

ADDITIONAL ENTERO-PANCREATIC HORMONES FOR THE MANAGEMENT OF OBESITY

Dual Glucagon-Like Peptide 1 and Glucagon Agonist

Glucagon (GCG) is synthesized and secreted from pancreatic alpha cells in the islets of Langerhans. Its primary physiological site of action is in the liver, where it stimulates hepatic glucose production. GCG agonism increases energy expenditure through enhanced lipolysis, hepatic fatty acid oxidation, and stimulating thermogenesis, while improving hepatic lipid metabolism, collectively contributing to weight loss (Fig. 1) [77]. The combination of GLP-1 and GCG RA has shown multiple metabolic benefits, particularly maintaining glucose homeostasis. GLP-1 counteracts the hyperglycemic effects of GCG primarily by stimulating glucose-dependent insulin secretion, while suppressing glucagon release in a glucose-dependent manner [78].

Mazdutide

Mazdutide is a once-weekly synthetic peptide analogue of mammalian oxyntomodulin, which activates GLP-1 and GCG receptors [79, 80]. The phase 3 GLORY-1 trial was conducted in China and investigated the effects of mazdutide 4 mg and 6 mg weekly compared to placebo on weight loss in patients with obesity or overweight based on the Chinese criteria of overweight (BMI 24–27) or obesity (BMI of ≥28) [36]. At 32 weeks, mazdutide 4 mg and 6 mg resulted in weight loss of 10.09% and 12.55%, respectively, compared to a 0.45% weight gain in the placebo group. Weight loss reached 11% and 14% with mazdutide 4 mg and 6 mg, respectively, at 48 weeks [36]. Among participants receiving mazdutide 4 mg and 6 mg, 73.9% and 82% achieved more than 5% weight reduction, respectively (Table 1) [36]. The percent change in total fat mass, measured by DXA, reached up to −24.7% and the change in lean mass reached up to −11.1% with mazdutide, compared to 2.4% and 0.5% with placebo [36] (Table 1). In participants with type 2 diabetes, mazdutide 4 mg and 6 mg resulted in 5.6% and 7.8% weight loss, respectively, compared to 1.3% with placebo [81]. A1c improved by 1.6–2.2% with mazdutide compared to 0.1% with placebo [81]. The most common reported side effects with mazdutide were gastrointestinal, mild to moderate in severity, and more frequent in participants receiving higher doses of mazdutide [36]. An increase in heart rate was observed during dose escalation, which subsequently declined again over the maintenance period [36].

Survodutide

Survodutide is a dual GLP-1 and GCG agonist. It is a 29-amino acid peptide derived from endogenous glucagon with incorporation of potent GLP-1 residues [82]. It contains a C-18 diacid chain which mediates binding to albumin, therefore prolonging its half-life and enabling

weekly subcutaneous dosing [82]. A multinational phase 2 randomized controlled trial investigated the effects of survodutide on weight loss in individuals with obesity without diabetes [37]. Survodutide was administered weekly at four different doses (0.6 mg, 2.4 mg, 3.6 mg, and 4.8 mg) and mean change in weight after 46 weeks of treatment reached −6.2%, −12.5%, −13.2%, and −14.9% with each dose, respectively, compared to −2.8% in the placebo group [37]. Among participants receiving survodutide 60.7–82.8% achieved more than 5% weight loss (Table 1) [37]. Survodutide decreased HbA1c by 0.2–0.3% compared to an increase of 0.1% with placebo [37]. The most common adverse events were gastrointestinal disorders, occurring predominantly during dose escalation, with approximately 25% of the participants receiving survotudide and 4% in the placebo group discontinuing treatment, most often because of gastrointestinal disorders [37]. The mean heart rate was higher in the survodutide group than in those receiving placebo [37].

Additional GLP-1 and GCG agonists, including pemvidutide and efinopeglutide, are in clinical development for obesity, with particular interest in their potential benefits for metabolic dysfunction-associated liver disease (MASLD) [83].

Triple Glucagon-Like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide, and Glucagon Agonist

Retatrutide

Retatrutide is a single 39-amino acid peptide engineered from a GIP peptide backbone and conjugated to a fatty diacid moiety. It acts as a triagonist that stimulates the GLP-1, GIP, and GCG receptors [84]. Compared with endogenous receptor ligands, retatrutide demonstrates lower potency at the GLP-1 and GCG receptors, but markedly higher potency at the GIP receptor [84]. Retatrutide is designed to modulate multiple biological pathways, thereby offering the potential for greater weight reduction and metabolic benefits [84].

A phase 2 trial conducted in the USA investigated the effect of weekly subcutaneous retatrutide at different doses and dose-escalations in participants with obesity and no diabetes [38]. At 24 weeks, the mean change body weight was −7.2% with 1 mg, −11.8% with 4 mg (starting with 2 mg), −13.9% with 4 mg (starting with 4 mg), −16.7% with 8 mg (starting with 2 mg), −17.9% with 8 mg (starting with 4 mg), and −17.5% with 12 mg (starting with 2 mg), compared to −1.6% in the placebo group [38]. At 48 weeks, the mean change in body weight reached −8.7%, −16.3%, −17.8%, −21.7%, −23.9%, and −25.2%, respectively (Table 1) [38]. These reductions represent the largest weight losses observed in any phase 2 trial of a pharmacologic agent for obesity as of February 2026. At 48 weeks, 91% of the participants in the 4 mg group, 100% in the 8 mg group, and 100% in the 12 mg group achieved at least 5% body weight reductions [38]. HbA1c decreased by 0.1–0.4% with retatrutide compared to a 0.1% increase with placebo at 24 weeks [38]. The most frequent adverse events were gastrointestinal and occurred primarily during dose-escalation and were more common with the higher 8 mg and 12 mg doses [38]. The trial identified a dose-dependent increase in heart rate that peaked at 24 weeks and declined thereafter [38]. In a news release, Lilly reported preliminary findings for phase 3 TRIUMPH-4 evaluating the safety and efficacy of 9 mg and 12 mg investigational doses of retratrutide, in adults with obesity or overweight and knee osteoarthritis [85]. Per efficacy estimand, retratutide 12 mg lowered weight up to an average of −28.7% [85]. Full presentation of results and peer reviewed publication is pending.

Amylin-Based Therapy

Amylin is a 37-amino acid hormone co-secreted with insulin from pancreatic beta cells in response to nutrient stimuli [86]. Amylin receptors (AMY1R, AMY2R, and AMY3R) are heterodimers composed of a calcitonin receptor

core component paired with receptor activity-modifying proteins (RAMPs) 1, 2, or 3, respectively [86]. Amylin and its analogues exhibit differential affinity and potency across the three amylin receptor subtypes [86]. Amylin inhibits postprandial glucagon secretion, delays gastric emptying, and reduces energy intake by acting as a satiation signal to limit meal size (Fig. 1) [87]. Its main role in weight loss occurs through its central nervous system activation, where it induces satiation and reduces food intake [87, 88].

Cagrilintide

Cagrilintide is a long-acting human amylin analogue with affinity for the three amylin subtype (AMY1R, AMY2R, AMY3R) receptors and the calcitonin receptor core [89]. In a phase 2 trial, the efficacy of weekly subcutaneous cagrilintide at different doses was compared to liraglutide and placebo in participants with obesity or overweight without diabetes [39]. At 26 weeks, cagrilintide 0.3 mg, 0.6 mg, 1.2 mg, 2.4 mg, and 4.5 mg resulted in 6.1%, 6.8%, 8.4%, 9.5%, and 10.6% weight loss, respectively, compared to 8.4% with liraglutide 3 mg/day and 2.8% with placebo [39]. Among participants receiving the highest dose of cagrilintide, 89% achieved 5% or more weight loss from baseline compared to 76% in the liraglutide group (Table 1) [39]. No apparent change in HbA1c was observed with any of the cagrilintide doses [39]. The most common side effects were gastrointestinal disorders (nausea, constipation, and diarrhea). These occurred more frequently than with placebo, but less frequently than with liraglutide [39].

Eloralintide

Eloralintide is a novel weekly subcutaneous selective long-acting amylin analogue with higher potency to AMY1R compared to calcitonin receptor [90]. Selectivity to AMY1R is thought to provide enhanced clinical efficacy and improve safety profile and tolerability [90]. In a 48-week phase 2 trial of people with obesity or overweight and one weight-related comorbidity without type 2 diabetes, the mean percent weight change was −7.3%, −10.5%, −13.8%, −17.5%, with weekly eloralintide 1 mg, 3 mg, 6 mg, and 9 mg, respectively, compared to −2.3% with placebo (Table 1) [40]. In participants receiving dose escalation to 9 mg, the percent weight change was slightly lower (−14.6% to −15.8%) [40]. HbA1c decreased by 0.3–0.4% with eloralintide compared to 0.1% with placebo [40]. The most common adverse events were gastrointestinal adverse effects, which were dose-dependent, and more common in higher doses [40]. Fatigue was not reported in participants receiving 1 mg, but occurred in 46% of participants at the 6–9 mg dose range, representing a substantial dose-dependent increase in incidence. Fatigue occurred in 12% of participants on placebo [40].

Dual Glucagon-Like Peptide 1 and Amylin Agonist

Cagrilintide-Semaglutide

The combination of cagrilintide and semaglutide provides synergistic and more potent effects on weight loss through complementary mechanisms of action [41]. The REDEFINE-1 phase 3 trial investigated the weekly co-administration of cagrilintide-semaglutide (CagriSema) on weight loss in participants with obesity or overweight [41]. The combination of cagrilintide 2.4 mg/week and semaglutide 2.4 mg/week resulted in 20.4% weight loss compared to 14.9% with semaglutide alone and 11.5% with cagrilintide alone at week 68 [41]. Among participants receiving CagriSema, 91.9% achieved more than 5% and 53.6% achieved more than 20% weight loss (Table 1) [41]. The change in total fat mass, lean mass, and visceral fat mass, measured by DXA, was −35.7%, −14.4%, and −40.8%, respectively, with CagriSema compared to −27.1%, −09.2%, and −32.4% with semaglutide alone, and −20.6%, −10.3%, and −13.4%

with cagrilintide alone [41] (Table 1). The REDEFINE-2 investigated the efficacy of CagriSema in participants with obesity/overweight and T2D [91]. The combination therapy resulted in 13.7% weight loss and 1.8% HbA1c decrease compared to 3.4% and 0.4% in the placebo group. Among participants receiving CagriSema, 83.6% achieved ≥ 5% weight reduction and 22.9% achieved ≥ 20% weight reduction [91].

The most reported side effects with CagriSema were gastrointestinal symptoms, which were mainly transient and mild-to-moderate in severity, particularly during dose escalation [41]. Other adverse events including fatigue, increased heart rate, dizziness, alopecia, injection-site reactions, and gallbladder-related disorders also occurred more frequently with CagriSema [41].

Amycretin

Amycretin is a unimolecular peptide with agonist activity towards GLP-1, amylin, and calcitonin receptors that targets areas of the brain that regulate food intake to control satiety and reduce energy intake [92]. A phase 1b/2a trial investigated the safety and efficacy of amycretin on weight in participants with obesity or overweight without diabetes [42]. At week 36, amycretin 60 mg/week (the highest tolerated dose) resulted in 24.3% weight loss compared to 1.1% in the placebo group [42]. In other subgroups, amycretin weekly maintenance at 20 mg, 5 mg, or 1.25 mg resulted in −22%, −16.2%, and −9.7% weight loss, respectively, compared to 1.9–2.3% weight gain in the placebo group (Table 1) [42]. HbA1c decreased by 0.2–0.6% with amycretin compared to a change ranging from −0.1% to +0.1% in the placebo group [42]. The most common adverse events were gastrointestinal symptoms (nausea, vomiting, diarrhea, and vomiting). These were dose-dependent, and occurred most frequently at higher doses, and particularly during dose escalation. The gastrointestinal adverse effects did not appear to increase further beyond the 5–20 mg/week dose range. There was one reported case of recurrent gallstone pancreatitis [42]. Increases in heart rate were also noted with amycretin therapy [42].

OTHER PHARMACOTHERAPIES INDEPENDENT OF ENTERO-PANCREATIC HORMONE PATHWAYS

Myostatin-Activin Pathway Inhibitors (MAPS)

MAPS represents a mechanistically distinct approach from incretin-based therapies that dominate the current obesity pharmacotherapy landscape and pipeline. MAPS work by blocking the activin type II receptor (ActRII), which is expressed on both skeletal muscle and adipose tissue [93]. By preventing the binding of natural ligands such as myostatin and activin—which normally suppress muscle growth—these agents simultaneously promote skeletal muscle hypertrophy (increasing lean mass) while reducing fat mass. This dual effect on body composition distinguishes MAP inhibitor agents from other obesity medications, which typically reduce total body weight without preserving or enhancing lean muscle mass [93].

Bimagrumab

Bimagrumab is a human monoclonal antibody that blocks ActRII [94]. A phase 2 trial investigated the effect of intravenous bimagrumab 10 mg/kg (maximum dose of 1200 mg) every 4 weeks in patients with type 2 diabetes and obesity [43]. At 48 weeks, the total body fat mass, measured by DXA, decreased by 20.5% while lean mass increased by 3.6% compared to a decrease of 0.5% and 0.8% in fat and muscle mass, respectively, with placebo. In addition, bimagrumab resulted in 6.5% weight loss compared to 0.8% with placebo (Table 1) [43]. HbA1c decreased by 0.8% with bimagrumab compared to an increase of 0.04% in the placebo group [43]. The BELIEVE trial phase 2b trial investigated the effect of combining bimagrumab and semaglutide on weight loss [95]. At 48 weeks, preliminary results of the high dose bimagrumab-semaglutide combination resulted in 20.2% mean weight change with lean muscle

mass largely preserved (2.6% decrease in lean mass versus 7.9% with high dose semaglutide and 0.5% with placebo, measured by DXA). The combination has generally been well tolerated and adverse effects included diarrhea, muscle spasms, and acne [95]. Other combinations of tirzepatide with a myostatin inhibitor or semaglutide with antimyostatin antibody with or without an anti-activin antibody are in clinical trials [96].

WEIGHT REGAIN AND LONG-TERM MAINTENANCE

Currently available and developing obesity pharmacotherapy are associated with substantial weight regain following treatment discontinuation. In the STEP-4 trial, participants who discontinued semaglutide after 20 weeks regained 6.9% of body weight, while those who continued treatment lost an additional 7.9% in the subsequent year [23]. In the STEP-1 extension trial, participants who discontinued semaglutide after 68 weeks regained a mean of 11.6%-points of body weight over the subsequent year, compared to 1.9%-points in the placebo group [97]. Similarly, in the SURMOUNT-4 trial, participants who discontinued tirzepatide after 36 weeks regained 14%-points of body weight, while those who continued treatment achieved an additional 5.5% weight loss [69]. These findings underscore the biology of obesity as a chronic relapsing multifactorial disease [98]. Incretin-based therapies and next-generation dual and triple agonists address key components of this pathophysiology by enhancing satiety signaling, reducing hunger and food-related reward, delaying gastric emptying, and improving metabolic efficiency. By modulating these central and peripheral pathways, these agents counteract the homeostatic mechanisms that promote weight regain [99]. Current evidence indicates that these therapies function as treatments rather than cures, and sustained pharmacologic therapy is generally required to sustain weight reduction and cardiometabolic benefit [100]. Future research should prioritize strategies to optimize maintenance therapy, define the appropriate treatment duration, evaluate long-term safety, and identify patient characteristics associated with durable response.

IMPLEMENTATION BARRIERS AND ACCESS TO CARE

Although newer obesity pharmacotherapies demonstrate substantial efficacy, their real-world population-level impact is strongly influenced by cost, insurance coverage, and health-system capacity [101]. Despite recognition of obesity as a chronic disease by major professional organizations and data suggesting long-term cost-effectiveness, insurance coverage remains inconsistent and suboptimal [101]. Consequently, access is often restricted to patients with private insurance or those able to pay out of pocket, contributing to socioeconomic disparities [102]. Effective integration of obesity pharmacotherapy into routine care will require alignment with existing chronic disease management frameworks, broader insurance coverage, and improved access to care [103]. Addressing affordability, reimbursement policies, and implementation readiness will be essential to ensure equitable access. Without these structural changes, the clinical benefits observed in randomized clinical trials may not translate into meaningful population-level impact.

CONCLUSION

The emergence of highly effective entero-pancreatic based therapies has fundamentally reshaped the therapeutic landscape of obesity medicine. These agents have demonstrated substantial and sustained weight loss with continued therapy, along with significant metabolic and cardiovascular benefits across a range of conditions, including type 2 diabetes, chronic kidney disease, and metabolic dysfunction-associated fatty liver disease. The development of newer agents targeting multiple, complementary pathways offers even greater potency and aligns treatment with the biological complexity of obesity as a chronic disease.

As these therapies continue to evolve, their effective implementation at scale—supported by evidence-based policy, sustainable reimbursement models, and health-system integration—has the potential to meaningfully influence population-level obesity trends and contribute to mitigating the obesity epidemic.

However, important challenges remain. Long-term safety data are still evolving, and optimal duration of treatment and maintenance strategies have yet to be defined. In addition, barriers related to cost, equitable access, health-system integration, and implementation may limit population-level impact. Therefore, while emerging therapies represent a major scientific and clinical advance, their ultimate contribution will depend not only on pharmacologic efficacy but also on rigorous long-term evaluation, sustainable delivery models, and equitable access within comprehensive, multidisciplinary care frameworks.

Author Contributions. All authors contributed to the study conception and design. Material preparation and data collection were performed by all authors. The first draft of the manuscript was written by Aya Bassatne and Ivania Rizo commented and provided major input on previous versions of manuscript. All authors read and approved the final manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Ivania Rizo reports advisory fees from Novo Nordisk and Genentech. Aya Bassatne declares no competing interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Emmerich SD FC, Stierman B, Ogden CL. Obesity and severe obesity prevalence in adults: United States, August 2021–August 2023. NCHS Data Brief, no 508 Hyattsville, MD: National Center for Health Statistics. 2024.

2. Khan SS, Ning H, Wilkins JT, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. JAMA Cardiol. 2018;3(4):280–7.

3. Wearing SC, Hennig EM, Byrne NM, Steele JR, Hills AP. Musculoskeletal disorders associated with obesity: a biomechanical perspective. Obes Rev. 2006;7(3):239–50.

4. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge. N Engl J Med. 2007;356(3):213–5.

5. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC Working Group. N Engl J Med. 2016;375(8):794–8.

6. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388(10046):776–86.

7. Thorpe KE, Joski PJ. Estimated reduction in health care spending associated with weight loss in adults. JAMA Netw Open. 2024;7(12):e2449200-e.

8. Cawley J, Biener A, Meyerhoefer C, et al. Direct medical costs of obesity in the United States and the most populous states. J Manag Care Spec Pharm. 2021;27(3):354–66.

9. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med. 2017;376(3):254–66.

10. Rader B, Hazan R, Brownstein JS. Changes in adult obesity trends in the US. JAMA Health Forum. 2024;5(12):e243685-e.

11. Gholami M, Balajam NZ, Rakhsha S, Sajjadi-Jazi SM, Shafiee G, Heshmat R. GLP-1 receptor agonists efficacy in managing comorbidities associated with diabetes mellitus: a narrative review. J Diabetes Metab Disord. 2025;24(1):92.

12. GBD 2021 US Obesity Forecasting Collaborators. National-level and state-level prevalence of overweight and obesity among children, adolescents, and adults in the USA, 1990–2021, and forecasts up to 2050. Lancet. 2024;404(10469):2278–98.

13. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. N Engl J Med. 2019;381(25):2440–50.

14. Chakhtoura M, Haber R, Ghezzawi M, Rhayem C, Tcheroyan R, Mantzoros CS. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. EClinicalMedicine. 2023;58:101882.

15. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368(9548):1696–705.

16. Melson E, Ashraf U, Papamargaritis D, Davies MJ. What is the pipeline for future medications for obesity? Int J Obes (Lond). 2025;49(3):433–51.

17. Drucker DJ. GLP-1-based therapies for diabetes, obesity and beyond. Nat Rev Drug Discov. 2025;24(8):631–50.

18. Holst JJ. GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management. Nat Metab. 2024;6(10):1866–85.

19. Jensen L, Helleberg H, Roffel A, et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. Eur J Pharm Sci. 2017;104:31–41.

20. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989–1002.

21. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971–84.

22. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. JAMA. 2021;325(14):1403–13.

23. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA. 2021;325(14):1414–25.

24. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022;28(10):2083–91.

25. Kadowaki T, Isendahl J, Khalid U, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2022;10(3):193–206.

26. Mu Y, Bao X, Eliaschewitz FG, et al. Efficacy and safety of once weekly semaglutide 2.4 mg for weight management in a predominantly east Asian population with overweight or obesity (STEP 7): a double-blind, multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 2024;12(3):184–95.

27. Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. JAMA. 2022;327(2):138–50.

28. Wharton S, Freitas P, Hjelmesæth J, et al. Once-weekly semaglutide 7.2 mg in adults with obesity (STEP UP): a randomised, controlled, phase 3b trial. Lancet Diabetes Endocrinol. 2025;13(11):949–63.

29. Ji L, Gao L, Xue H, 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 Endocrinol. 2025;13(9):777–89.

30. Knop FK, Aroda VR, do Vale RD, et al. 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. 2023;402(10403):705–19.

31. Wharton S, Lingvay I, Bogdanski P, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. N Engl J Med. 2025;393(11):1077–87.

32. Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. N Engl J Med. 2025;393(18):1796–806.

33. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205–16.

34. Bays HE, Toth P, Alkhouri N, et al. Weekly subcutaneous VK2735, a GIP/GLP-1 receptor dual agonist, for weight management: phase 2, randomized, 13-week VENTURE study. Obesity. 2026. https://doi.org/10.1002/oby.70106.

35. Jastreboff AM, Ryan DH, Bays HE, et al. Once-monthly maridebart cafraglutide for the treatment of obesity—a phase 2 trial. N Engl J Med. 2025;393(9):843–57.

36. Ji L, Jiang H, Bi Y, et al. Once-weekly mazdutide in Chinese adults with obesity or overweight. N Engl J Med. 2025;392(22):2215–25.

37. le Roux CW, Steen O, Lucas KJ, Startseva E, Unseld A, Hennige AM. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. Lancet Diabetes Endocrinol. 2024;12(3):162–73.

38. Jastreboff AM, Kaplan LM, Frías JP, et al. Triple–hormone-receptor agonist Retatrutide for obesity—a phase 2 trial. N Engl J Med. 2023;389(6):514–26.

39. Lau DCW, Erichsen L, Francisco AM, et al. Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. Lancet. 2021;398(10317):2160–72.

40. Billings LK, Hsia S, Bays H, 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. 2025;406(10520):2631–43.

41. Garvey WT, Blüher M, Contreras CKO, et al. Coadministered cagrilintide and semaglutide in adults with overweight or obesity. N Engl J Med. 2025;393(7):635–47.

42. Dahl K, Toubro S, Dey S, et al. Amycretin, a novel, unimolecular GLP-1 and amylin receptor agonist administered subcutaneously: results from a phase 1b/2a randomised controlled study. Lancet. 2025;406(10499):149–62.

43. Heymsfield SB, Coleman LA, Miller R, et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. JAMA Netw Open. 2021;4(1):e2033457.

44. Sorli C, Harashima S-i, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(4):251–60.

45. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221–32.

46. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44.

47. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389(12):1069–84.

48. Bonaca MP, Catarig A-M, Houlind K, et al. Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial. Lancet. 2025;405(10489):1580–93.

49. Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med. 2025;392(21):2089–99.

50. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391(2):109–21.

51. Bliddal H, Bays H, Czernichow S, et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med. 2024;391(17):1573–83.

52. Chao AM, Tronieri JS, Amaro A, Wadden TA. Semaglutide for the treatment of obesity. Trends Cardiovasc Med. 2023;33(3):159–66.

53. Lingvay I, Bergenheim SJ, Buse JB, 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 Endocrinol. 2025;13(11):935–48.

54. Guo W, Xu Z, Zou H, et al. Discovery of ecnoglutide—a novel, long-acting, cAMP-biased glucagon-like peptide-1 (GLP-1) analog. Mol Metab. 2023;75:101762.

55. Gummesson A, Nyman E, Knutsson M, Karpefors M. Effect of weight reduction on glycated haemoglobin in weight loss trials in patients with type 2 diabetes. Diabetes Obes Metab. 2017;19(9):1295–305.

56. Gallwitz B, Giorgino F. Clinical perspectives on the use of subcutaneous and oral formulations of semaglutide. Front Endocrinol (Lausanne). 2021;12:645507.

57. Overgaard RV, Navarria A, Ingwersen SH, Bækdal TA, Kildemoes RJ. Clinical pharmacokinetics of oral semaglutide: analyses of data from clinical pharmacology trials. Clin Pharmacokinet. 2021;60(10):1335–48.

58. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10:467.

59. Kadowaki T, Heftdal LD, Ko H-J, et al. Oral semaglutide in an east asian population with overweight or obesity, with or without type 2 diabetes: the OASIS 2 randomized clinical trial. JAMA Intern Med. 2025;185(10):1206–17.

60. Pratt E, Ma X, Liu R, et al. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: a phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants. Diabetes Obes Metab. 2023;25(9):2634–41.

61. Kawai T, Sun B, Yoshino H, et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. Proc Natl Acad Sci. 2020;117(47):29959–67.

62. Horn DB, Ryan DH, Kis SG, 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. 2026;406(10522):2927–44.

63. Christensen M, Vedtofte L, Holst JJ, Vilsbøll T, Knop FK. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. Diabetes. 2011;60(12):3103–9.

64. Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Front Endocrinol (Lausanne). 2024;15:1431292.

65. Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? Trends Endocrinol Metab. 2020;31(6):410–21.

66. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. Mol Metab. 2018;18:3–14.

67. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023;402(10402):613–26.

68. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med. 2023;29(11):2909–18.

69. Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. JAMA. 2024;331(1):38–48.

70. Aronne LJ, Horn DB, Roux CWl, et al. Tirzepatide as compared with semaglutide for the treatment of obesity. N Engl J Med. 2025;393(1):26–36.

71. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398(10295):143–55.

72. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med. 2025;392(5):427–37.

73. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med. 2024;391(4):299–310.

74. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med. 2024;391(13):1193–205.

75. Campbell JE. Targeting the GIPR for obesity: to agonize or antagonize? Potential mechanisms. Mol Metab. 2021;46:101139.

76. Véniant MM, Lu S-C, Atangan L, et al. A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. Nat Metab. 2024;6(2):290–303.

77. Pocai A. Unraveling oxyntomodulin, GLP1's enigmatic brother. J Endocrinol. 2012;215(3):335.

78. Sánchez-Garrido MA, Brandt SJ, Clemmensen C, Müller TD, DiMarchi RD, Tschöp MH. GLP-1/glucagon receptor co-agonism for treatment of obesity. Diabetologia. 2017;60(10):1851–61.

79. Ji L, Gao L, Jiang H, et al. Safety and efficacy of a GLP-1 and glucagon receptor dual agonist mazdutide (IBI362) 9 mg and 10 mg in Chinese adults with overweight or obesity: a randomised, placebo-controlled, multiple-ascending-dose phase 1b trial. EClinicalMedicine. 2022;54:101691.

80. Dong W, Bai J, Yuan Q, et al. Mazdutide, a dual agonist targeting GLP-1R and GCGR, mitigates diabetes-associated cognitive dysfunction: mechanistic insights from multi-omics analysis. EBioMedicine. 2025;117:105791.

81. Zhu D, Zhao J, Cai H et al. Mazdutide versus placebo in Chinese adults with type 2 diabetes. Nature (2025). https://doi.org/10.1038/s41586-025-10026-w

82. Klein T, Augustin R, Hennige AM. Perspectives in weight control in diabetes—survodutide. Diabetes Res Clin Pract. 2024;207:110779.

83. McGowan B, Ciudin A, Baker JL, et al. Framework for the pharmacological treatment of obesity and its complications from the European Association for the Study of Obesity (EASO). Nat Med. 2025;31(10):3229–32.

84. Coskun T, Urva S, Roell WC, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: from discovery to clinical proof of concept. Cell Metab. 2022;34(9):1234-47.e9.

85. Lilly. 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 2025. https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-delivered-weight-loss-average. Accessed 15 Dec 2025.

86. Bower RL, Hay DL. Amylin structure-function relationships and receptor pharmacology: implications for amylin mimetic drug development. Br J Pharmacol. 2016;173(12):1883–98.

87. Dehestani B, Stratford NR, le Roux CW. Amylin as a future obesity treatment. J Obes Metab Syndr. 2021;30(4):320–5.

88. D'Ascanio AM, Mullally JA, Frishman WH. Cagrilintide: a long-acting amylin analog for the treatment of obesity. Cardiol Rev. 2024;32(1):83–90.

89. Kruse T, Hansen JL, Dahl K, et al. Development of cagrilintide, a long-acting amylin analogue. J Med Chem. 2021;64(15):11183–94.

90. Briere DA, Qu H, Lansu K, et al. Eloralintide (LY3841136), a novel amylin receptor agonist for the treatment of obesity: from discovery to clinical proof of concept. Mol Metab. 2025;102:102271.

91. Davies MJ, Bajaj HS, Broholm C, et al. Cagrilintide–semaglutide in adults with overweight or obesity and type 2 diabetes. N Engl J Med. 2025;393(7):648–59.

92. Kuhre RE, Ballarín-González B, Brand CL, et al. The effect of amycretin, a unimolecular glucagon-like peptide-1 and amylin receptor agonist, on body weight and metabolic dysfunction in mice and rats. EBioMedicine. 2025. https://doi.org/10.1016/j.ebiom.2025.105862.

93. Aimelet V, Holst JJ. Pharmacological intervention: challenges and promising outcomes for fat loss and preservation of lean body mass in the treatment of overweight and type 2 diabetes. Diabetes Obes Metab. 2026;28(2):803–816.

94. Kaur M, Misra S. Bimagrumab: an investigational human monoclonal antibody against activin type II receptors for treating obesity. J Basic Clin Physiol Pharmacol. 2024;35(6):325–34.

95. American Diabetes Association. BELIEVE spotlights quality and quantity approach to weight management with combo therapy 2025. https://www.adameetingnews.org/believe-spotlights-quality-and-quantity-approach-to-weight-management-with-combo-therapy/. Accessed 15 Dec 2025.

96. Gonzalez-Rellan MJ, Drucker DJ. New molecules and indications for GLP-1 medicines. JAMA. 2025;334(14):1231–4.

97. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. Diabetes Obes Metab. 2022;24(8):1553–64.

98. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18(7):715–23.

99. Alfaris N, Waldrop S, Johnson V, Boaventura B, Kendrick K, Stanford FC. GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review. EClinicalMedicine. 2024;75:102782.

100. West S, Scragg J, Aveyard P, et al. Weight regain after cessation of medication for weight management: systematic review and meta-analysis. BMJ. 2026;392:e085304.

101. Pearson SD, Whaley CM, Emond SK. Affordable access to GLP-1 obesity medications: strategies to guide market action and policy solutions in the US. J Comp Eff Res. 2025;14(9):e250083.

102. Sarpatwari A, Soto MJ, Ganguli I, Sloan CE, Goss F, Sinaiko AD. Glucagon-like peptide-1 receptor agonist order fills and out-of-pocket costs by race, ethnicity, and indication. JAMA Health Forum. 2025;6(10):e254258-e.

103. Jolin JR, Kwon M, Brock E, et al. Policy interventions to enhance medical care for people with obesity in the United States-challenges, opportunities, and future directions. Milbank Q. 2024;102(2):336–50.