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GLP-1-based combination strategies for weight loss: Multi-target agents and combination therapies

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ABSTRACT

The emergence of glucagon-like peptide-1 receptor agonists (GLP-1RAs) represents a major breakthrough in the pharmacotherapy of obesity. However, their single-target mechanism has limitations. In recent years, combination strategies targeting multiple pathways and multiple targets have become a frontier in weight-loss drug development. This review systematically examines GLP-1RA-based combination weight-loss strategies, focusing on the scientific rationale and research progress in two main directions: single-agent multi-target agonists and multi-drug combination therapies. In single-agent multi-target strategies, glucagon-like peptide-1 receptor/glucose-dependent insulinotropic polypeptide receptor (GLP-1R/GIPR) dual agonists, glucagon-like peptide-1 receptor/glucagon receptor (GLP-1R/GCGR) dual agonists, glucagon-like peptide-1 receptor/amylin receptor (GLP-1R/AMYR) dual agonists, and triple agonists achieve weight loss beyond traditional single agents through synergistic regulation of appetite, energy metabolism, and lipolysis. In multi-drug combination therapy, free combinations offer flexibility, while fixed-dose combinations improve convenience and adherence. These strategies improve weight loss and metabolic outcomes, including hepatic fat and cardiometabolic parameters. In terms of safety, gastrointestinal events are the most common. However, as the number of targets increases and doses escalate, potential risks such as increased heart rate and hypoglycemia warrant attention, with particular consideration for thyroid and muscle safety during long-term use. Future research should focus on optimizing personalized treatment strategies, conducting head-to-head comparisons of agents with different mechanisms, developing oral formulations, and exploring long-term maintenance regimens to advance comprehensive obesity management.

Abbreviations: AMYR, amylin receptor; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; FDA, US Food and Drug Administration; FDC, fixed-dose combination; FDCs, fixed-dose combinations; GCG, glucagon; GCGR, glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HRQoL, health-related quality of life; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MAD, multiple ascending dose; N, sample size; NCT, National Clinical Trial identifier; NPY2R, neuropeptide Y receptor type 2; NPY2RA, neuropeptide Y receptor type 2 agonist; OSA, obstructive sleep apnea; OXM, oxyntomodulin; PYY, peptide YY; PYY3-36, peptide YY3-36; Q4w, every 4 weeks; Q8w, every 8 weeks; Q4W, every 4 weeks.; RA, receptor agonist; SAD, single ascending dose; S.c., subcutaneous; SGLT2, sodium-glucose cotransporter 2; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SUCRA, surface under the cumulative ranking curve; T2DM, type 2 diabetes mellitus; TBD, to be determined; VAS, visual analog scale.

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1. Introduction

The global obesity epidemic has emerged as one of the most serious public health challenges of the 21st century, affecting approximately 650 million people worldwide [1]. Based on body mass index (BMI) criteria, approximately 14% of adults globally have obesity, and a further 24% are classified as overweight [2]. Furthermore, these rates continue to show a persistent increasing trend. Recent projections indicate that by 2050, more than half of the world's adult population may be affected by overweight or obesity [3]. Obesity is not only a chronic disease in its own right but also a major risk factor for type 2 diabetes mellitus (T2DM), cardiovascular diseases, metabolic dysfunction-associated fatty liver disease (MAFLD), and various types of cancer. This places a substantial burden on both society and individuals [1,4]. Consequently, the development of effective and safe weight-loss medications has become a critical clinical priority that urgently needs to be addressed.

Currently, the primary interventions for obesity include lifestyle interventions, bariatric surgery, and pharmacotherapy. Lifestyle interventions often fail to maintain long-term effectiveness, while bariatric surgery is limited by its invasive nature and the risk of potential complications [5–7]. As a result, pharmacotherapy has become an important interventional approach for obesity. The main classes of weight-loss medications include: (i) fat absorption inhibitors (e.g., orlistat); (ii) incretin-based agents, primarily single-target GLP−1 receptor agonists (GLP−1RAs) and multi-target agonists; (iii) appetite suppressants acting on the central nervous system; and (iv) medications with weight-loss effects as a secondary benefit when used for other indications. More recently, amylin has emerged as a promising target for next-generation anti-obesity pharmacotherapy [8–12].

Presently, research and development of weight-loss medications is progressing rapidly worldwide. The major drug targets include GLP−1R, glucose-dependent insulinotropic polypeptide receptor (GIPR), and glucagon receptor (GCGR). Among these numerous therapeutic targets, the value of the GLP−1 target has been widely recognized [13]. GLP−1RAs target this key incretin hormone and activate the GLP−1 receptor. This action not only regulates blood glucose levels but also reduces energy intake by suppressing appetite via effects on the central nervous system and by delaying gastric emptying [14]. Therefore, they have become one of the most widely used treatment options for obesity.

However, the development and progression of obesity involve imbalances across multiple physiological systems, including appetite regulation, energy metabolism, and gastrointestinal hormones, making it a classic multi-target disease. Single-target drugs are often insufficient to comprehensively intervene in this complex pathological process. In recent years, the concept of combination interventions targeting *multiple pathways and multiple targets* has gradually emerged [14]. This approach has become an important direction for driving the development of a new generation of anti-obesity medications. Currently, it mainly encompasses two forms: (1) single-molecule multi-target agonists (e.g., dual or triple receptor agonists); and (2) the combined use of GLP−1RAs with drugs that have other mechanisms of action (Fig. 1). This strategy is expected to enhance therapeutic efficacy while reducing adverse effects, thereby achieving improved clinical outcomes.

Against this background, the present article examines GLP−1RAs as a cornerstone of combination therapy for obesity. It systematically reviews the scientific rationale and research progress regarding their use in combination strategies. The discussion primarily covers the development and clinical evidence for GLP−1-based multi-target agonists as well as the combined use of GLP−1RAs with other medications. Furthermore, it explores future opportunities and challenges, aiming to provide a reference for both research and clinical practice.

2. GLP−1RA

GLP−1RAs are a class of novel medications that target GLP−1R. GLP−1 is a hormone released by intestinal endocrine cells in response to food intake. It stimulates insulin secretion and suppresses glucagon secretion in a glucose-dependent manner, thereby reducing blood glucose levels (Fig. 2). Additionally, GLP−1 delays gastric emptying and

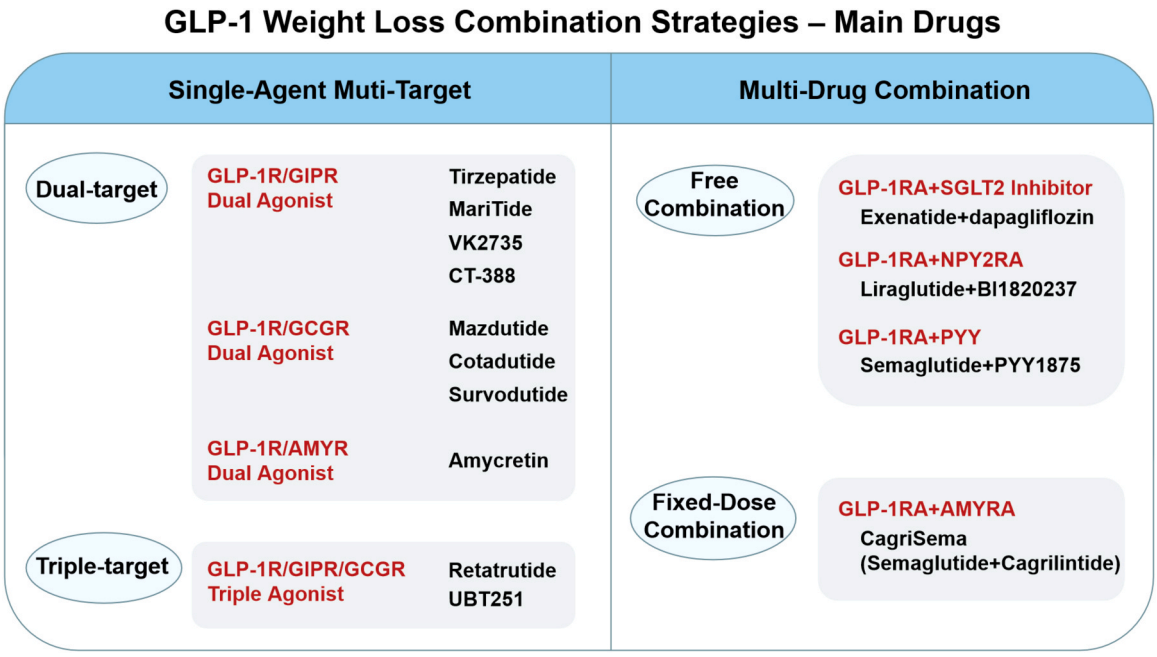

Fig. 1. Overview of key drugs and mechanism targets in GLP-1-based combination strategies for weight loss. Based on the mode of drug combination and primary pathophysiological targets, this figure categorizes drugs currently under clinical investigation into two main approaches: single-agent multi-target agonists (dual agonists: GLP-1 R/GIPR dual agonists, GLP-1 R/GCGR dual agonists, and GLP-1 R/AMYR dual agonists; triple agonists: GLP-1 R/GIPR/GCGR triple agonists) and multi-drug combination therapies (free combinations and fixed-dose combinations). *AMYR*, amylin receptor; *GCGR*, glucagon receptor; *GIPR*, glucose-dependent insulinotropic polypeptide receptor; *GLP-1*, glucagon-like peptide-1; *GLP-1 R*, glucagon-like peptide-1 receptor; *NPY2RA*, neuropeptide Y receptor type 2 agonist; *PYY*, peptide YY; *SGLT2*, sodium-glucose cotransporter 2.

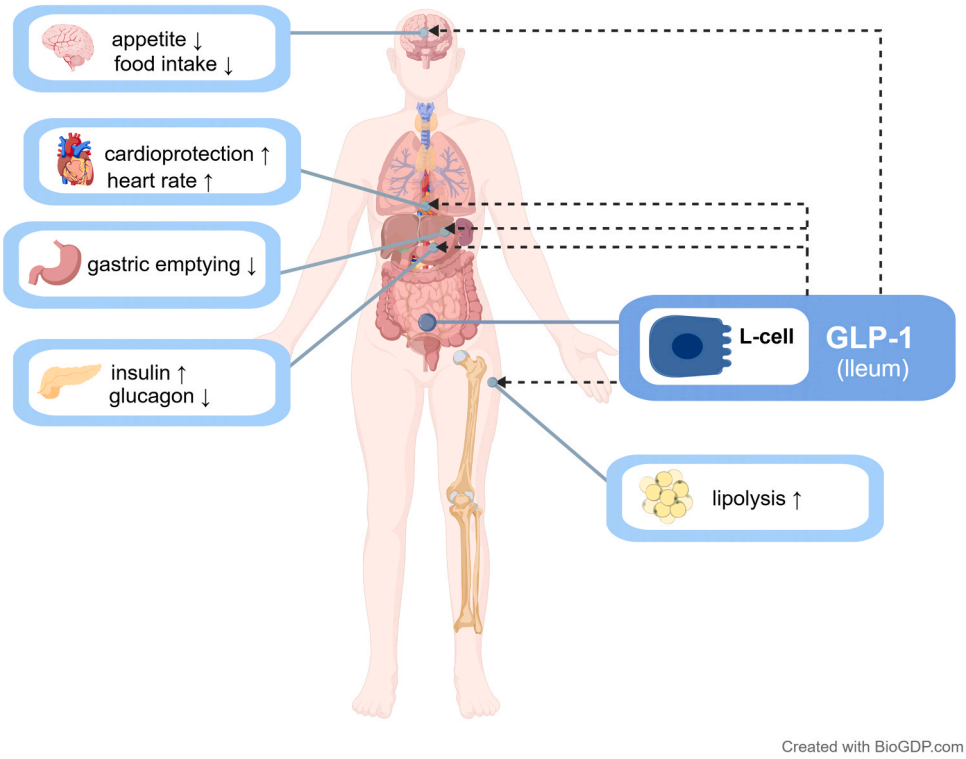

Fig. 2. Schematic overview of GLP−1 physiological effects. This figure illustrates the key physiological actions of glucagon-like peptide−1 (GLP−1), an incretin hormone secreted by L-cells in the ileum. GLP−1 exerts pleiotropic effects across multiple organ systems, including stimulation of insulin secretion, suppression of glucagon release, slowing of gastric emptying, reduction of appetite and food intake, and promotion of lipolysis. Cardiovascular effects include increased heart rate and cardioprotection. Created with BioGDP.com [150]. *GLP−1*, glucagon-like peptide−1.

suppresses food intake, thereby maximizing nutrient absorption while limiting weight gain [14–16]. However, native GLP−1 is degraded within minutes in the bloodstream, which limits its direct therapeutic utility. GLP−1RAs employ various chemical modification strategies—including amino acid sequence optimization, fusion proteins, fatty acid acylation, PEGylation, and polymer-based sustained-release formulations—to slow drug degradation and prolong their duration of action [17].

Currently, several GLP−1RAs are used in clinical practice. For instance, semaglutide and liraglutide have been approved for the treatment of obesity. GLP−1RAs have a favorable safety profile. They not only effectively reduce body weight but also significantly improve parameters associated with metabolic syndrome. Their remarkable weight-lowering efficacy represents a major breakthrough in the field of weight management. Building on this foundation, researchers are now developing multi-target agonists that act on both the GLP−1 receptor and other relevant receptors, such as GIPR and GCGR. Expanding upon GLP−1-based therapies, multi-target approaches may confer synergistic benefits across glycemic control, weight management, lipid metabolism, and cardioprotection, thereby optimizing metabolic and cardiovascular outcomes [17].

3. Clinical trials of single-agent multi-target GLP−1RAs

This drug class is defined by a single molecular entity that exerts concurrent activity at two or more distinct pharmacological targets (e.g., receptors, enzymes, ion channels). These agents exert their therapeutic effects through complex mechanisms involving synergistic or complementary actions. In the field of weight management, multi-target agonists that combine the GLP−1 receptor with other receptor targets are demonstrating substantial therapeutic potential. The following sections summarize the representative clinical trial progress for each class of GLP−1-based combination strategies for weight loss (Table 1).

3.1. Dual agonists

3.1.1. GLP−1R/GIPR dual agonists

GLP−1R/GIPR dual agonists are a novel class of multi-target drugs that achieve substantial weight loss by synergistically activating both GLP−1R and GIPR. Their remarkable efficacy arises from a triple synergistic mechanism. At the central level, simultaneous activation of both receptors in the hypothalamic feeding centers potently suppresses appetite. Regarding fat metabolism, these agents exert regulatory effects according to the body's energy status, promoting fat storage postprandially while accelerating fat breakdown during fasting. Furthermore, the GIP component mitigates the gastrointestinal adverse effects induced by GLP−1, thereby improving drug tolerability and allowing the use of higher GLP−1RA doses to enhance efficacy [18].

3.1.1.1. Tirzepatide. Tirzepatide is the first globally approved GLP−1R/GIPR dual agonist. By synergistically activating both incretin receptors, it substantially enhances weight-loss efficacy. As the most representative GLP−1R/GIPR dual agonist currently available, tirzepatide has had its efficacy and safety profile validated through multiple Phase 3 clinical trials, notably the *SURMOUNT* series [19] (Fig. 3).

In the *SURMOUNT−1* trial involving patients with obesity but without T2DM, 72 weeks of once-weekly tirzepatide achieved mean body weight reductions of 15.0%, 19.5%, and 20.9% from baseline with the 5 mg, 10 mg, and 15 mg doses, respectively—each significantly greater than the 3.1% reduction with placebo ($P < 0.001$ for all) [20]. Long-term follow-up (176 weeks) demonstrated sustained weight-loss effects, indicating durable efficacy with prolonged treatment [21].

In the *SURMOUNT−2* trial involving patients with obesity and T2DM, 72 weeks of once-weekly tirzepatide achieved mean body weight reductions of 12.8% and 14.7% for the 10 mg and 15 mg doses, respectively. Both were significantly superior to the 3.2% reduction observed with placebo [22]. A subgroup analysis of Japanese patients

Table 1
Key Clinical Trials of GLP−1 Receptor-Based Single-Agent Multi-Target Agonists and Combination Therapies.

No.	Drug Class	Drug Name	Trial Name	Phase	Population	Treatment Groups	Duration	Max Weight Loss (%)	NCT Number
3.1.1.1	GLP−1R/GIPR dual agonist	Tirzepatide	SURMOUNT−1	Phase 3	Obesity/ overweight without T2DM	Once-weekly s.c. tirzepatide 5/10/ 15 mg or placebo	72 weeks	−20.9% (15 mg)	NCT04184622
			SURMOUNT−2	Phase 3	Obesity/ overweight with T2DM	Once-weekly s.c. tirzepatide 10/ 15 mg or placebo	72 weeks	−14.7% (15 mg)	NCT04657003
			SURMOUNT−3	Phase 3	Obesity/ overweight without T2DM, with $\geq$ 5% weight loss after 12-week intensive lifestyle intervention	Once-weekly s.c. tirzepatide 10/ 15 mg or placebo	72 weeks	−18.4% (pooled tirzepatide)	NCT04657016
			SURMOUNT−4	Phase 3	Obesity/ overweight without T2DM	Lead-in (36 wks): once-weekly s.c. tirzepatide 10/ 15 mg; Subsequent (52 wks): once-weekly s.c. tirzepatide 10/ 15 mg or switch to placebo	88 weeks	−25.3% (pooled tirzepatide)	NCT04660643
			SURMOUNT-CN	Phase 3	Chinese adults with obesity/ overweight without T2DM	Once-weekly s.c. tirzepatide 10/ 15 mg or placebo	52 weeks	−17.5% (15 mg)	NCT05024032
			SURMOUNT-J	Phase 3	Japanese adults with obesity/ overweight without T2DM	Once-weekly s.c. tirzepatide 10/ 15 mg or placebo	72 weeks	−21.1% (15 mg)	NCT04844918
3.1.1.2	GLP−1R/GIPR dual agonist	Maridebart Cafraglutide (AMG133)	Single and Multiple Ascending Dose Study of AMG 133 in Participants With Obesity	Phase 1	Obesity/ overweight without T2DM	SAD: single s.c. AMG133 21/70/ 140/280/560/ 840 mg or placebo q4w; MAD: s.c. AMG133 140/ 280/420 mg or placebo q4w	SAD: 150 days; MAD: 207 days	−14.5% (MAD 420 mg, day 85)	NCT04478708
			MariTide Phase 2 Obesity Trial	Phase 2	Obesity/ overweight (with or without T2DM cohorts)	s.c. AMG133 140/ 280/420 mg (partial dose escalation) q4w or q8w, or placebo	52 weeks	−16.2% (obesity without T2DM cohort, 420 mg q4w)	NCT05669599
3.1.1.3	GLP−1R/GIPR dual agonist	VK2735	VENTURE	Phase 2	Obesity/ overweight without T2DM	Once-weekly s.c. VK2735 2.5/5/ 10/15 mg or placebo	13 weeks	−14.7% (15 mg)	NCT06068946
			VENTURE-Oral Dosing	Phase 2	Obesity/ overweight without T2DM	Once-daily oral VK2735 15/30/ 60/90/120 mg or placebo	13 weeks	−12.2% (120 mg)	NCT06828055
3.1.1.4	GLP−1R/GIPR dual agonist	CT−388	CT−388(103)	Phase 2	Obesity/ overweight without T2DM	CT−388 highest dose 24 mg (specific regimen TBD)	48 weeks	−22.5% (24 mg)	NCT06525935
3.1.2.1	GLP−1R/GCGR dual agonist	Mazdutide	A Study of IBI362 Evaluating Weight Loss in Obese and Overweight Chinese Subjects	Phase 2	Chinese adults with obesity/ overweight without T2DM	Once-weekly s.c. mazdutide 3/4.5/ 6/9 mg or placebo	24 weeks	−13.3% (9 mg)	NCT04904913
			A Study of IBI362 in Chinese Patients With Type 2 Diabetes	Phase 2	Chinese adults with T2DM	Once-weekly s.c. mazdutide 3/4.5/ 6 mg, dulaglutide 1.5 mg, or placebo	20 weeks	−7.14% (6 mg)	NCT04965506
			GLORY−1	Phase 3	Chinese adults with obesity/	Once-weekly s.c. mazdutide 4/ 6 mg or placebo	48 weeks	−14.01% (6 mg)	NCT05607680

(*continued on next page*)

Table 1 (*continued*)

No.	Drug Class	Drug Name	Trial Name	Phase	Population	Treatment Groups	Duration	Max Weight Loss (%)	NCT Number
					overweight without T2DM				
			GLORY−2	Phase 3	Chinese adults with obesity/ overweight without T2DM	Once-weekly s.c. mazdutide 9 mg or placebo	60 weeks	−18.55% (9 mg)	NCT06164873
3.1.2.2	GLP−1R/GCGR dual agonist	Cotadutide	A Study to Look at the Effect MEDI0382 Has on Blood Sugar in People With Type 2 Diabetes and Kidney Problems and Also to Check That MEDI0382 is Well Tolerated	Phase 2a	Obesity/ overweight with T2DM	Once-daily s.c. cotadutide (escalating from 50 μg to 300 μg) or placebo	32 days	−3.69% (cotadutide)	NCT03550378
			A Study to Evaluate the Efficacy and Safety of MEDI0382 in the Treatment of Overweight and Obese Subjects With Type 2 Diabetes	Phase 2b	Obesity/ overweight with T2DM	Once-daily s.c. cotadutide 100/ 200/300 μg, liraglutide 1.8 mg, or placebo	54 weeks	−5.02% (300 μg)	NCT03235050
3.1.2.3	GLP−1R/GCGR dual agonist	Survodutide	A Study to Test Whether Different Doses of BI 456906 Help People With Overweight or Obesity to Lose Weight	Phase 2	Obesity/ overweight without T2DM	Once-weekly s.c. survodutide 0.6/ 2.4/3.6/4.8 mg or placebo	46 weeks	−14.9% (4.8 mg)	NCT04667377
			A Study to Test Whether Different Doses of BI 456906 Are Effective in Treating Adults With Type 2 Diabetes	Phase 2	Obesity/ overweight with T2DM	Once-weekly s.c. survodutide 0.3/ 0.9/1.8/2.7 mg, semaglutide 1.0 mg, or placebo; twice-weekly s.c. survodutide 1.2/ 1.8 mg	16 weeks	−8.95% (twice-weekly 1.8 mg)	NCT04153929
3.1.3	GLP−1R/AMYR dual agonist	Amycretin	A Research Study to See How a New Medicine (NNC0487–0111) Works in People With Overweight or Obesity When Injected Under the Skin	Phase 1b/2a	Obesity/ overweight without T2DM	SAD: single s.c. amycretin 0.3/ 0.6/1.0 mg; MAD: once-weekly s.c. amycretin with q4w dose escalation: maintenance doses: 60 mg (B), 20 mg (C), 5 mg (D), 1.25 mg (E); placebo	B,C: 36 weeks; D: 28 weeks; E: 20 weeks	−24.3% (60 mg)	NCT06064006
			A Research Study Comparing How Well Different Doses of the Medicine NNC0487–0111 Lower Blood Sugar in People With Type 2 Diabetes	Phase 2	Obesity/ overweight with T2DM	Once-weekly s.c. amycretin 0.4/ 1.5/5/10/20/ 40 mg; once-daily oral amycretin 6/ 25/50 mg; or placebo	36 weeks	−14.5% (s.c. max); −10.1% (oral max)	NCT06542874
3.2.1	GLP−1R/GIPR/ GCGR triple agonist	Retatrutide	A Study of LY3437943 in Participants Who Have Obesity or Are Overweight	Phase 2	Obesity/ overweight without T2DM	Once-weekly s.c. retatrutide 1/4/ 8/12 mg (various escalation regimens) or placebo	48 weeks	−24.2% (12 mg)	NCT04881760
			A Study of LY3437943 in Participants With Type 2 Diabetes	Phase 2	Obesity/ overweight with T2DM	Once-weekly s.c. retatrutide 0.5/4/ 8/12 mg (various escalation regimens), dulaglutide 1.5 mg, or placebo	36 weeks	−19.64% (12 mg)	NCT04867785
3.2.2	GLP−1R/GIPR/ GCGR triple agonist	UBT251	UBT251 Injection Phase II Study	Phase 2	Obesity/ overweight without T2DM	Once-weekly s.c. UBT251 2/4/ 6 mg (various	24 weeks	−19.7% (max)	NCT07177469

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Table 1 (*continued*)

No.	Drug Class	Drug Name	Trial Name	Phase	Population	Treatment Groups	Duration	Max Weight Loss (%)	NCT Number
						escalation regimens) or placebo			
4.1.1	GLP−1RA + SGLT2i	Exenatide + Dapagliflozin	DURATION−8	Phase 3	T2DM	Once-weekly s.c. exenatide 2 mg + once-daily oral dapagliflozin 10 mg; once-weekly s.c. exenatide 2 mg; once-daily oral dapagliflozin 10 mg; or placebo	28 weeks	−3.71% (combination)	NCT02229396
4.1.2	GLP−1RA + NPY2RA	liraglutide + BI1820237	A Study in Men With Overweight to Test How Well Different Doses of BI 1820237 Are Tolerated When Given as an Injection Alone or in Combination With Liraglutide	Phase 1	Normal weight/ obesity/ overweight males	Single s.c. BI 1820237 0.025/ 0.075/0.2/0.5/ 1.2 mg or placebo combined with liraglutide 0.6 mg	48 days	/	NCT04903509
4.1.3	GLP−1RA + PYY	Semaglutide + PYY1875	A Research Study to Investigate How Well NNC0165–1875 in Combination With Semaglutide Works in People With Obesity	Phase 2b	Obesity/ overweight without T2DM	Once-weekly s.c. PYY1875 2.0 mg or placebo combined with semaglutide 2.4 mg	16 weeks	−5.25% (combination)	NCT04969939
4.2	GLP−1RA + AMYRA	CagriSema	Research Study to Look at How Well Cagrilintide Together With Semaglutide Works in People With Type 2 Diabetes	Phase 2	Obesity/ overweight with T2DM	Once-weekly s.c. CagriSema (2.4 mg/2.4 mg), semaglutide 2.4 mg, cagrilintide 2.4 mg, or placebo	32 weeks	−15.6% (CagriSema)	NCT04982575
			REDEFINE 1	Phase 3a	Obesity/ overweight without T2DM	Once-weekly s.c. CagriSema (2.4 mg/2.4 mg), semaglutide 2.4 mg, cagrilintide 2.4 mg, or placebo	68 weeks	−20.4% (CagriSema)	NCT05567796
			REDEFINE 2	Phase 3a	Obesity/ overweight with T2DM	Once-weekly s.c. CagriSema (2.4 mg/2.4 mg) or placebo	68 weeks	−13.7% (CagriSema)	NCT05394519
			REIMAGINE 2	Phase 3	T2DM	Once-weekly s.c. CagriSema (2.4 mg/2.4 mg or 1.0 mg/ 1.0 mg), semaglutide 2.4 mg/1.0 mg, cagrilintide 2.4 mg, or placebo	68 weeks	−14.2% (CagriSema 2.4/2.4 mg)	NCT06065540

Abbreviations: *AMYR* amylin receptor, *GCGR* glucagon receptor, *GIP* glucose-dependent insulinotropic polypeptide, *GLP−1* glucagon-like peptide−1, *NCT* national clinical trial identifier, *NPY2RA* neuropeptide Y receptor type 2 agonist, *PYY* peptide YY, *RA* receptor agonist, *s.c.* subcutaneous, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *T2DM* type 2 diabete mellitus

from this trial further confirmed its weight-loss efficacy [23].

SURMOUNT−3 investigated the additional weight-loss efficacy of tirzepatide following an intensive lifestyle intervention. In patients who had already achieved ≥ 5% weight loss after a 12-week intensive lifestyle program, subsequent treatment with tirzepatide for 72 weeks resulted in an additional mean weight loss of 18.4%. This was significantly superior to the 2.5% reduction observed with placebo ($P < 0.001$). Furthermore, in this population, 87.5% of patients in the tirzepatide group achieved an additional weight loss of ≥ 5%, compared with 16.5% in the placebo group. These findings collectively demonstrated that tirzepatide provides significant additional benefits even in individuals who have already lost weight [24]. Additionally, an analysis of this study population showed that tirzepatide significantly improved health-related quality of life (HRQoL) in adults with obesity or overweight. In subgroups with greater weight loss or those with physical function limitations at baseline, the improvements in HRQoL were generally more pronounced [25].

A randomized withdrawal trial (*SURMOUNT−4*) demonstrated that

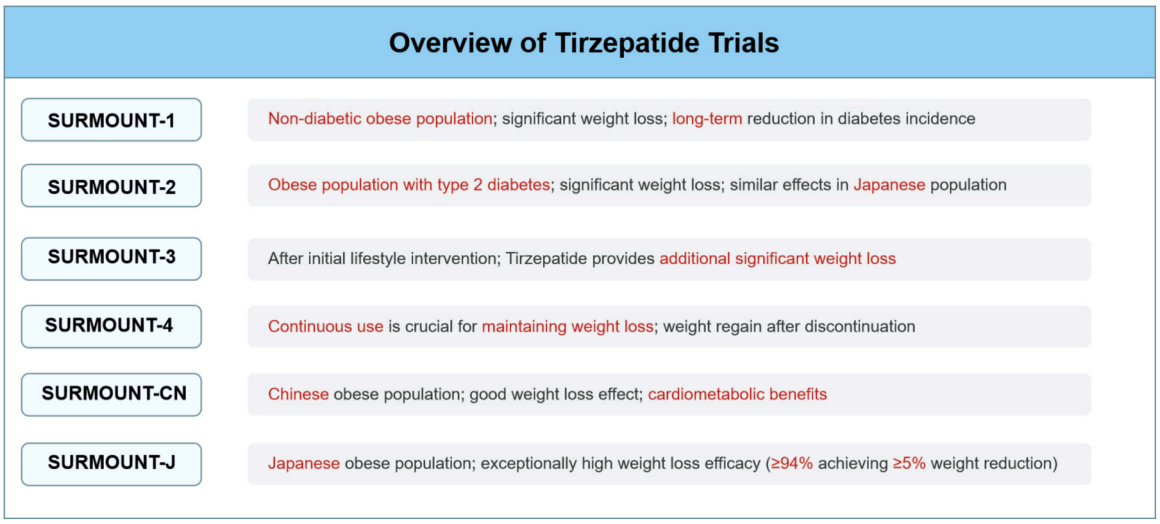

Fig. 3. Overview of Tirzepatide trials. This figure summarizes key efficacy and design data from the SURMOUNT clinical trial program evaluating tirzepatide for the treatment of obesity with or without type 2 diabetes. Included trials are *SURMOUNT−1* (non-diabetic obesity), *SURMOUNT−2* (obesity with type 2 diabetes), *SURMOUNT−3* (following lifestyle intervention), *SURMOUNT−4* (continuation after withdrawal), *SURMOUNT-CN* (Chinese population), and *SURMOUNT-J* (Japanese population). Key findings demonstrate significant weight loss across diverse populations, with additional benefits including reduced diabetes incidence in *SURMOUNT−1*, cardiometabolic improvements in *SURMOUNT-CN*, and exceptionally high weight loss efficacy (≥94% achieving ≥5% weight reduction) in *SURMOUNT-J*. Continuous treatment was shown to be crucial for maintaining weight loss in *SURMOUNT−4*. Data are presented as reported in the respective clinical trial publications or presentations.

52 weeks after tirzepatide discontinuation, body weight rebounded significantly (+14.0%). In contrast, patients who continued treatment achieved a further 5.5% reduction in body weight. With continuous treatment for 88 weeks from the start of the study, a total body weight reduction of up to 25.3% was achieved [26]. These findings indicated that in individuals with obesity or overweight, discontinuation of tirzepatide leads to substantial weight regain. Conversely, continued treatment helps maintain and further consolidate the initial weight-loss effects.

Phase 3 trials conducted in Chinese (*SURMOUNT-CN*) and Japanese (*SURMOUNT-J*) populations have confirmed the efficacy of tirzepatide in individuals with obesity in China and Japan. After 52–72 weeks of treatment, mean body weight reductions in the tirzepatide 10 mg and 15 mg groups ranged from 13.6% to 21.1% across study populations [27,28]. The proportion of participants achieving ≥ 5% weight loss ranged from 85.8% to 96%. All reductions were significantly greater than those observed with placebo.

A further post-hoc analysis indicated that patients with greater weight loss experienced more pronounced improvements in cardiometabolic parameters [29]. This suggested that early weight loss is closely associated with improvements in cardiometabolic risk factors. Another post-hoc analysis also showed that tirzepatide treatment was associated with a significantly reduced predicted risk of developing type 2 diabetes within 10 years, regardless of baseline BMI or prediabetes status [30].

Across trials, gastrointestinal events (nausea, diarrhea, and vomiting) were the most common adverse events associated with tirzepatide. These were generally mild to moderate, typically occurred during dose titration, and waned with continued treatment. Discontinuation due to adverse events was uncommon.

Several ongoing trials are exploring tirzepatide's expanded role in weight management: NCT06721507 is assessing preoperative use to optimize bariatric surgery outcomes; NCT06734273 is investigating synergy with sleeve gastrectomy [31,32]; NCT06803888 is conducting the first head-to-head comparison of surgical procedures (Roux-en-Y gastric bypass, sleeve gastrectomy) versus pharmacotherapy (tirzepatide, semaglutide) [33]; and a Phase 2 study is evaluating combination therapy with mibavademab for enhanced efficacy [34].

3.1.1.2. Maridebart Cafraglutide (AMG133) . Maridebart cafraglutide (MariTide) is a long-acting peptide–antibody conjugate that combines glucagon-like peptide−1 receptor agonism and glucose-dependent insulinotropic polypeptide receptor antagonism [35]. Trials have been initiated to investigate its use in the treatment of obesity.

A Phase 1, randomized, double-blind, placebo-controlled trial in patients with obesity evaluated the efficacy of single and multiple doses of MariTide. After single-dose administration, the highest dose group (840 mg) achieved a mean body weight reduction of 8.2% by day 92, with effects persisting through day 120. Multiple-ascending-dose administration demonstrated dose-dependent efficacy. The highest dose group (420 mg) achieved a mean body weight reduction of 14.5% by day 85, and a sustained weight loss of 11.2% remained 150 days after treatment discontinuation [36].

A Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study evaluated MariTide in two separate cohorts: one comprising individuals with obesity and another comprising individuals with obesity and T2DM. The results showed that in the obesity cohort, mean body weight reductions with MariTide ranged from 12.3% to 16.2% across doses, which was significantly superior to the 2.5% reduction observed with placebo. In the cohort of individuals with obesity and T2DM, mean body weight reductions in the active treatment groups ranged from 8.4% to 12.3%, compared with 1.7% in the placebo group [35]. These findings indicated that MariTide significantly reduces body weight in patients with obesity, regardless of whether they also have T2DM.

The most common adverse events with MariTide are gastrointestinal (nausea, vomiting), predominantly mild to moderate and transient. Tolerability can be improved through dose escalation or lower initial dosing [35,36].

MariTide is currently being systematically evaluated in multiple Phase 3 clinical trials to validate its efficacy and safety in obesity and its related complications. These include MARITIME−1, MARITIME−2, and MARITIME−3-J (a study in Japanese populations), which will evaluate the efficacy, safety, and tolerability of this agent in adults with obesity or overweight, with or without type 2 diabetes, including Japanese patients [37–39]. MARITIME-HF focuses on patients with obesity and heart failure with preserved or mildly reduced ejection fraction, aiming to investigate the effects of MariTide on heart failure-related events and

mortality, as well as its safety, in this population [40]. Additionally, two studies—MARITIME-OSA−1 (in patients receiving positive airway pressure therapy) and MARITIME-OSA−2 (in those not receiving positive airway pressure therapy)—are evaluating the efficacy and tolerability of MariTide in adults with overweight or obesity and obstructive sleep apnea [41,42].

3.1.1.3. VK2735. VK2735 is a dual agonist of GLP−1R and GIPR developed by Viking Therapeutics. It has been formulated for both oral and subcutaneous administration and is intended for the treatment of metabolic disorders including obesity.

In the Phase 2 VENTURE trial, subcutaneous VK2735 (15 mg) for 13 weeks resulted in a 14.7% mean body weight reduction from baseline (13.1% placebo-adjusted). Progressive weight loss was observed from week 1 across all dose groups, with no plateau by week 13. The key secondary endpoint of $\geq$ 10% weight loss was achieved by 88% of VK2735-treated patients versus 4% with placebo. All dose groups maintained most of their weight loss at 4 weeks after the final dose. These reductions remained significantly different from both baseline and the placebo group ($p < 0.0001$ for each cohort) [43].

Another 13-week Phase 2 trial demonstrated that oral VK2735 (15–120 mg) produced significant, dose-dependent weight loss. The highest-dose group (120 mg) achieved a mean weight reduction of 12.2%, with 80% of patients achieving $\geq$ 10% weight loss. In a maintenance cohort, transitioning from 90 mg for 4 weeks to 30 mg for 7 weeks yielded additional weight loss (from 8.1% to 9.2%). This suggested that lower-dose maintenance therapy with VK2735 may provide sustained weight control [44].

Clinical trials of both subcutaneous and oral VK2735 formulations showed that the most common adverse events were gastrointestinal (e.g., vomiting, diarrhea, constipation, and abdominal pain). Most events were mild to moderate, consistent with a favorable safety profile. Severe adverse events occurred in the 120 mg oral group.

Two ongoing 78-week Phase 3 trials, VANQUISH 1 and VANQUISH 2, are evaluating VK2735 in patients with obesity (without T2DM) and in those with overweight or obesity and T2DM [45,46].

3.1.1.4. CT−388. CT−388 is a GLP−1/GIP receptor dual agonist in development for obesity and its comorbidities, including T2DM. This agent selectively activates both receptors to integrate nutrient-related signals, regulating energy homeostasis and resulting in appetite suppression and improved glycemic control. A key design feature is potent receptor activation with minimal β-arrestin recruitment at either target. This biased agonism reduces receptor internalization and desensitization, promoting sustained pharmacological activity [47].

In a Phase 2 trial, once-weekly subcutaneous CT−388 (24 mg) produced a 22.5% weight reduction at 48 weeks in patients with obesity ($p < 0.001$), with no plateau observed. The agent was well tolerated; gastrointestinal events were predominantly mild to moderate [48].

Another Phase 2 study is evaluating the efficacy, safety, and tolerability of CT−388 in overweight or obese patients with T2DM [49]. The Phase 3 program for CT−388 in obesity (Enith 1 and Enith 2) is expected to start in Q1 2026. Beyond monotherapy, future studies will evaluate CT−388 in combination with the amylin analog petrelintide.

3.1.2. GLP−1R/GCGR dual agonists

GCGR is primarily expressed on hepatocytes. Its activation promotes glycogenolysis, gluconeogenesis, and lipolysis, thereby increasing hepatic glucose output and energy expenditure. GLP−1R is widely distributed in the central and peripheral nervous system. Its activation delays gastric emptying and suppresses appetite, reducing energy intake [50]. Together, these complementary mechanisms contribute to weight loss, supporting the development of GCGR/GLP−1R dual agonists as a therapeutic strategy for obesity.

3.1.2.1. Mazdutide. Mazdutide (IBI362), a mammalian oxyntomodulin analog, is co-developed by Innovent and Eli Lilly. It combines GLP−1R-mediated improvements in glycemic control and body weight with GCGR-mediated increases in energy expenditure and hepatic fat metabolism. Mazdutide has demonstrated significant weight-loss and glucose-lowering efficacy across multiple clinical studies, with additional improvements in waist circumference, lipid levels, blood pressure, serum uric acid, liver enzymes, and hepatic fat content (**Fig. 4**).

Two Phase 2 clinical trials conducted in Chinese populations have shown that mazdutide has significant weight-loss efficacy and a favorable safety profile. In patients with T2DM, after 20 weeks of treatment, the mazdutide groups (3 mg, 4.5 mg, and 6 mg) achieved a mean weight reduction of 7.1%, which was significantly superior to dulaglutide (2.7%) and placebo (1.4%). The proportions of patients achieving $\geq$ 5% and $\geq$ 10% weight loss were also higher with mazdutide [51]. In overweight or obese patients without T2DM, mazdutide produced dose-dependent weight loss at 24 weeks: 6.7%, 10.4%, and 11.3% in the 3, 4.5, and 6 mg groups, respectively, versus 1.0% weight gain with placebo [52]. The 9 mg cohort showed even greater efficacy, with a mean weight reduction of 13.3%. More than 80% of participants in this group achieved $\geq$ 5% weight loss, whereas no participant in the placebo group met this threshold. Additionally, mazdutide significantly improved several cardiometabolic risk factors and reduced hepatic fat content, thereby demonstrating clear cardiometabolic and hepatic benefits [53].

The Phase 3, double-blind, placebo-controlled *GLORY−1* trial assessed mazdutide's weight-loss efficacy in overweight or obese Chinese patients for 48 weeks. At 32 weeks, mean body weight reductions were 10.09% with 4 mg and 12.55% with 6 mg, versus 0.45% weight gain with placebo. The proportions of patients achieving $\geq$ 5% weight loss were 73.9% (4 mg) and 82.0% (6 mg), both significantly higher than 10.5% with placebo ($p < 0.001$ for both). Additionally, mazdutide demonstrated beneficial effects on all prespecified cardiometabolic parameters [54].

The Phase 3, double-blind, placebo-controlled *GLORY−2* trial evaluated mazdutide 9 mg in Chinese adults with obesity (16% with T2DM). At 60 weeks, mazdutide 9 mg achieved 18.55% mean weight reduction versus 3.02% with placebo. Achievement of $\geq$ 20% weight loss was 44.0% versus 2.6%. In patients without T2DM, weight loss was greater: 20.08% mean reduction, with 48.7% achieving $\geq$ 20% weight loss. Mazdutide also improved cardiometabolic parameters (waist circumference, systolic blood pressure, lipids, serum uric acid). In patients with baseline hepatic fat $\geq$ 10%, 60-week treatment reduced hepatic fat content by 71.9% versus a 5.1% increase with placebo [55].

These studies generally reported favorable tolerability of mazdutide; the most common adverse events were mild-to-moderate gastrointestinal events, including nausea and diarrhea.

Moreover, multiple Phase 3 clinical trials are ongoing to further evaluate the value of mazdutide in specific populations. GLORY−3 is being conducted in patients with overweight or obesity and metabolic dysfunction-associated fatty liver disease (MAFLD) to provide a head-to-head comparison of mazdutide 9 mg and semaglutide 2.4 mg [56]. GLORY-OSA is evaluating the efficacy of mazdutide in Chinese patients with obesity and moderate-to-severe obstructive sleep apnea (OSA) [57]. GLORY-YOUNG is evaluating the efficacy and safety of mazdutide in Chinese adolescents (aged 12–18 years) with obesity or overweight [58]. SMART is investigating the synergistic effects of mazdutide combined with bariatric surgery in patients with severe obesity [59]. These studies are expected to be completed between 2027 and 2029. Their results will help clarify the potential of mazdutide in broader populations and in combination treatment strategies.

3.1.2.2. Cotadutide. Cotadutide (MEDI0382), a synthetic OXM analog with fatty acid acylation for extended half-life, is a potent GLP−1R/GCGR dual agonist (EC_{50}: 6.9 pM and 10.2 pM, respectively). This

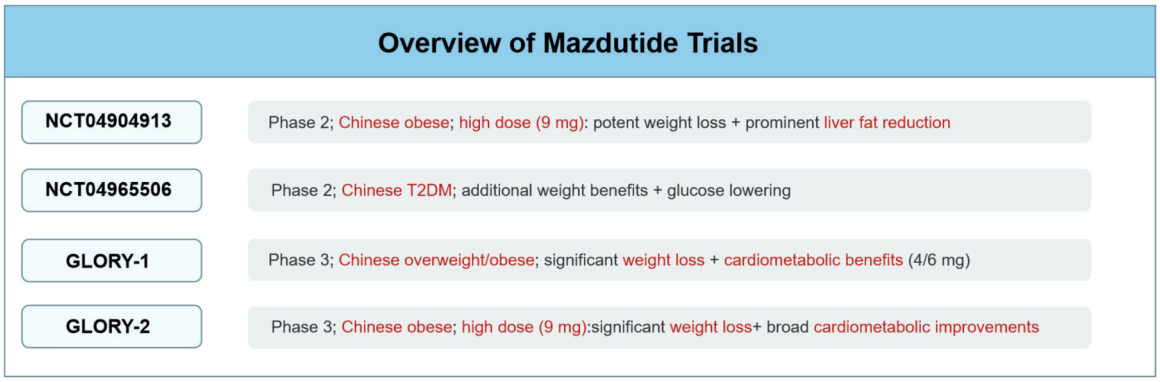

Fig. 4. Overview of Mazdutide trials. This figure summarizes key efficacy and design data from clinical trials evaluating mazdutide for the treatment of obesity and type 2 diabetes mellitus (T2DM) in Chinese populations. Included trials are NCT04904913 (Phase 2; obesity), NCT04965506 (Phase 2; T2DM), *GLORY−1* (Phase 3; overweight/obesity), and *GLORY−2* (Phase 3; obesity). Each entry displays trial identifier, phase, patient population, and key findings. Mazdutide demonstrated potent weight reduction across trials, with additional benefits including glucose lowering, liver fat reduction, and broad cardiometabolic improvements at higher doses (9 mg). Data are presented as reported in the respective clinical trial publications or presentations. *T2DM*, type 2 diabetes mellitus.

balanced dual agonism confers efficacy in weight management and glycemic control.

In a Phase 2a study, cotadutide achieved a mean weight reduction of 3.41 kg, versus 0.13 kg with placebo ($P < 0.001$), confirming its weight-loss efficacy [60].

A Phase 2b study showed that at week 54, cotadutide achieved significant weight reduction compared with placebo (−0.68%; $P < 0.001$). Specifically, 200 μg produced −3.22% weight reduction (comparable to liraglutide 1.8 mg at −3.33%), and 300 μg achieved −5.02% (superior to liraglutide and placebo). The study confirmed that cotadutide treatment for 54 weeks reduced body weight [61].

Regarding safety, the most common adverse events with cotadutide were nausea and vomiting, with most reactions diminishing over time with continued treatment.

3.1.2.3. Survodutide. Survodutide (BI 456906) is an investigational GLP−1R/GCGR dual agonist featuring fatty acid acylation for extended half-life [62]. This agent integrates dual receptor signaling to reduce food intake, increase energy expenditure, and decrease hepatic fat content, conferring a range of metabolic benefits, including weight loss [63]. Clinical studies have demonstrated efficacy in reducing body weight and improving metabolic dysfunction-associated steatohepatitis (MASH) [64].

A Phase 2, randomized, double-blind, placebo-controlled, dose-ranging trial demonstrated that at 46 weeks, once-weekly survodutide produced dose-dependent weight reductions: 6.2% (0.6 mg), 12.5% (2.4 mg), 13.2% (3.6 mg), and 14.9% (4.8 mg), all significantly superior to 2.8% with placebo [65]. A separate Phase 2 trial in patients with T2DM evaluated glycemic control and body weight. For the key secondary endpoint, after 16 weeks of treatment, survodutide (≥1.8 mg) achieved a mean weight reduction of 8.7%, which was greater than the 5.3% observed with semaglutide [66].

In both studies, gastrointestinal events (nausea, diarrhea) were the most common adverse events.

Currently, multiple global multicenter Phase 3 clinical trials are systematically evaluating the efficacy and safety of survodutide in different populations. The SYNCHRONIZE−1™ trial is focusing on adults with overweight or obesity without T2DM, while SYNCHRONIZE−2™ is targeting the same population but with T2DM [67,68]. Concurrently, studies specifically targeting Chinese and Japanese populations (NCT06214741; SYNCHRONIZE™ JP) are also underway [69,70]. Additionally, a mechanistic Phase 2 study (NCT06745284) is directly comparing survodutide and semaglutide for their differential effects on energy metabolism and lipolysis, aiming to elucidate survodutide's potential advantages [71]. This series of studies is expected to be completed between 2026 and 2027, collectively demonstrating the clinical value and positioning of survodutide in obesity treatment.

3.1.3. GLP−1R/AMYR dual agonists

3.1.3.1. Amycretin. Amycretin is a long-acting GLP−1R and amylin receptor (AMYR) dual agonist in development by Novo Nordisk. Its dual mechanism involves GLP−1R-mediated suppression of appetite, delayed gastric emptying, and enhanced insulin secretion, alongside amylin receptor-mediated enhancement of central satiety and increased fat oxidation and energy expenditure. Both oral and subcutaneous formulations are in development [72] (Fig. 5).

Two early-phase studies have evaluated the weight-loss potential of amycretin. In a Phase 1 trial of oral amycretin, Part C/D exploratorily assessed pharmacodynamic endpoints [73]. Results showed that after 12 weeks (85 days), weight loss ranged from 10.4% to 13.1% across doses, all significantly exceeding the 1.2% with placebo. A Phase 1b/2a study of subcutaneous amycretin showed that after 36 weeks, the highest dose (60 mg) achieved a mean weight reduction of 24.3%, significantly superior to the 1.1% with placebo [74].

A Phase 2 dose-ranging trial evaluated the glucose-lowering and weight-loss efficacy of both subcutaneous and oral formulations of amycretin in patients with T2DM. After 36 weeks of treatment, for the secondary outcome, subcutaneous amycretin achieved a maximum reduction of 14.5% versus 2.6% with placebo; oral amycretin achieved a maximum reduction of 10.1% versus 2.5% with placebo. Both reductions were significant, with no plateau evident in high-dose groups [72,75].

Across trials, the most common adverse events with amycretin were mild-to-moderate gastrointestinal events (nausea, vomiting). Their incidence was dose-dependent and manageable with dose escalation. The overall safety profile was consistent with that of GLP−1- and amylin-based therapies, indicating favorable tolerability.

Novo Nordisk plans to initiate a Phase 3 program for amycretin in overweight or obese adults in Q1 2026. The Phase 3 AMAZE 1 trial will further evaluate subcutaneous amycretin in this population, with completion expected in 2029 [76,77].

3.2. Triple agonists

3.2.1. GLP−1R/GIPR/GCGR triple agonists

Triple receptor agonist development is in early stages, with few candidates yet in clinical trials. GLP−1 receptor activation delays gastric emptying, suppresses appetite, and promotes insulin secretion; GIP receptor activation enhances postprandial insulin secretion and lipid

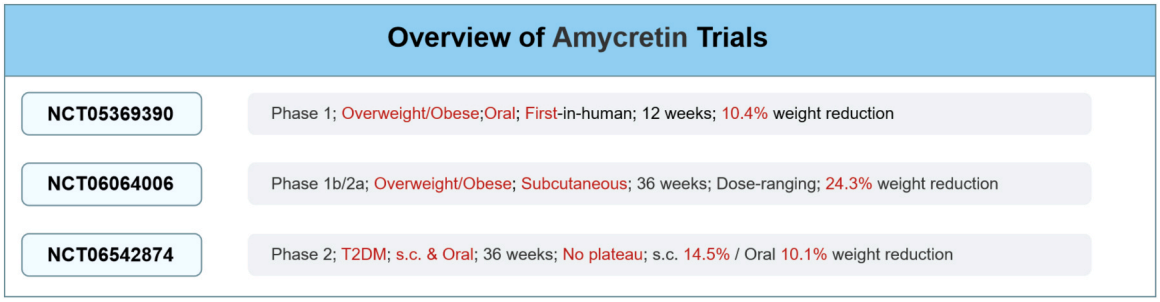

Fig. 5. Overview of Amycretin trials. This figure summarizes key efficacy and design data from clinical trials evaluating amycretin for the treatment of overweight/obesity with or without type 2 diabetes mellitus (T2DM). Included trials are NCT05369390 (Phase 1), NCT06064006 (Phase 1b/2a), and NCT06542874 (Phase 2). Each entry displays trial identifier, phase, patient population, route of administration (oral or subcutaneous), key findings, and treatment duration. Amycretin demonstrated dose-dependent weight reduction across trials, with up to 24.3% weight loss observed in the Phase 1b/2a study and no plateau noted in the Phase 2 trial. Data are presented as reported in the respective clinical trial publications or presentations. *s.c.*, subcutaneous; *T2DM*, type 2 diabetes mellitus.

metabolism; and glucagon receptor activation increases energy expenditure and fat oxidation. Together, these mechanisms offer an effective strategy for obesity treatment [78–80].

3.2.2. *Retatrutide*

Retatrutide is the first triple GLP−1R/GIPR/GCGR agonist developed by Eli Lilly,representing a new frontier in next-generation obesity pharmacotherapy.

A 48-week Phase 2 trial evaluated retatrutide in patients with obesity or overweight without T2DM. At 48 weeks, 12 mg achieved 24.2% weight reduction versus 2.1% with placebo. Response rates were 100% (≥5%), 93% (≥10%), and 83% (≥15%). These results indicate substantial, dose-dependent efficacy [81].

A 36-week Phase 2 trial in patients with T2DM demonstrated significant weight-loss efficacy with retatrutide. Weight reductions with ≥ 4 mg ranged from 10.37% to 16.94%, versus 3.00% with placebo and 2.02% with dulaglutide 1.5 mg [82]. A dual-energy X-ray absorptiometry (DXA) substudy confirmed that retatrutide reduced total fat mass by up to 26.1%, without disproportionate lean mass loss, indicating fat-driven weight loss and improved body composition [83].

The most common adverse events with retatrutide were dose-related gastrointestinal effects (e.g., nausea and vomiting), predominantly mild to moderate and manageable with a low starting dose. In addition, a dose-dependent increase in heart rate was observed, typically peaking mid-treatment and then subsiding [81].

Multiple Phase 3 trials are evaluating retatrutide in diverse populations with obesity, assessing comorbidity outcomes beyond weight loss. TRIUMPH−1 and TRIUMPH−2 target patients with obesity, with or without T2DM, respectively, including subgroups with knee osteoarthritis and obstructive sleep apnea [84,85]. TRIUMPH−3 evaluates severe obesity with established cardiovascular disease [86]. The head-to-head TRIUMPH−5 compares retatrutide and tirzepatide to assess the contribution of GCGR agonism [87]. TRIUMPH−4 and TRIUMPH−7 evaluate symptomatic improvements in knee osteoarthritis and chronic low back pain, respectively [88,89]. TRIUMPH−6 investigates long-term weight maintenance over 116 weeks [90]. TRIUMPH−8 evaluates efficacy in patients without T2DM [91]. The findings are expected to provide deeper insights into the multifaceted and personalized therapeutic applications of retatrutide.

3.2.3. *UBT251*

UBT251, a long-acting synthetic peptide triple receptor agonist targeting GLP−1, GIP, and GCG receptors, is being jointly developed by The United Bio-Technology (Hengqin) Co., Ltd. and Novo Nordisk [92].

A Phase 2 trial in China evaluated UBT251 in overweight or obese patients. At 24 weeks, UBT251 achieved 19.7% weight reduction versus 2.0% with placebo, a statistically significant difference [92,93].

UBT251 demonstrated a favorable safety and tolerability profile, consistent with incretin-based therapies.

Novo Nordisk is developing UBT251: a global Phase 1b/2a trial in approximately 330 patients with obesity, with primary data expected in 2027 [94]; and a Phase 2 trial in T2DM planned for H2 2026[92]. A separate Phase 2 trial in obesity and chronic kidney disease is being conducted by United Bio-Technology (Hengqin) [95].

4. Clinical trials of GLP−1RA-based multi-drug combinations

Multi-drug combination therapies include free combinations and fixed-dose combinations (FDCs). Both strategies combine drugs with different mechanisms of action to achieve synergistic effects, reduce or delay resistance, optimize regimen safety, and ultimately improve long-term adherence and overall efficacy. However, they differ in their specific implementation.

4.1. *Free combination*

Free-drug combinations preserve separate formulations, offering flexibility in dose and schedule while maintaining the independent pharmacokinetic properties of each agent. This approach combines GLP−1RAs with different anti-obesity agents, enabling personalized management for patients with complicated obesity.

4.1.1. *Exenatide + dapagliflozin*

GLP−1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors lower blood glucose and body weight through distinct mechanisms. GLP−1RAs suppress appetite and delay gastric emptying to reduce food intake, while SGLT2 inhibitors promote glucosuria, resulting in caloric loss [96]. In combination, these agents reduce energy intake and increase output, producing additive weight loss. This combination addresses glycemic control and weight management in patients with T2DM.

The DURATION−8 study showed that in patients withT2DM inadequately controlled on metformin, 28 weeks of exenatide plus dapagliflozin resulted in a mean weight reduction of 3.41 kg and a 33% rate of ≥ 5% weight loss. These outcomes were significantly superior to either monotherapy (exenatide alone: −1.54 kg, 14%; dapagliflozin alone: −2.19 kg, 20%), indicating a synergistic effect on weight loss. Common adverse events included diarrhea, injection-site nodules, nausea, and urinary tract infection. No severe or hypoglycemic events were reported, and the combination did not increase the risk of serious adverse events.

4.1.2. *Liraglutide + BI1820237*

The BI 1820237/liraglutide combination activates neuropeptide Y receptor type 2 (NPY2R) and GLP−1R, exerting central/peripheral synergy: dual appetite suppression and gastric delay reduce intake and enhance satiety, driving significant weight loss [97,98]. This

multi-target strategy benefits patients with inadequate GLP−1 monotherapy response.

In a Phase 1 study, BI 1820237 plus liraglutide synergistically delayed gastric emptying and reduced single-meal energy intake by 622–1069 kcal (at 1.8–2.4 mg). Visual analog scale (VAS) scores confirmed reduced hunger and enhanced satiety. The combination was well tolerated, with manageable gastrointestinal events. These findings support further clinical development [99].

4.1.3. Semaglutide + PYY1875

Peptide YY (PYY) is a potential adjunctive therapy to GLP−1 receptor agonists for obesity. GLP−1RAs suppress appetite via hypothalamic mechanisms and delay gastric emptying. Complementarily, PYY, a gut-derived anorexigenic hormone, acts via Y2 receptors to inhibit hunger signals [100].

A series of preclinical and clinical studies evaluated the long-acting PYY3–36 analog PYY1875, both as monotherapy and in combination with semaglutide, for obesity. The program included animal studies and Phase 1/2 trials. Phase 1 demonstrated tolerability of PYY1875 as monotherapy and in combination. In Phase 2, PYY1875 1.0 mg plus semaglutide achieved 5.25% weight reduction versus 3.10% with placebo plus semaglutide at 56 weeks, an additional 2.15% that was statistically significant but not clinically meaningful [101].

4.2. Fixed-dose combination (FDC)

This class of drugs refers to the combination of two or more agents into a single dosage form (e.g., tablets, injectables) at optimized ratios, which facilitates adherence to treatment.

4.2.1. CagriSema

Among FDCs, CagriSema is the most evidence-backed option. A network meta-analysis showed superior weight loss versus placebo (−14.03 kg) and tirzepatide (−8.47 kg); SUCRA rankings confirmed its highest efficacy [102]. This Novo Nordisk FDC pairs semaglutide with cagrilintide for synergistic weight management: cagrilintide enhances satiety and gastric delay via hypothalamic action, while semaglutide reduces intake via appetite suppression, insulin modulation, and gastric delay [103].Clinical trials support its potential (**Fig. 6**).

In the Phase 2 NCT04982575 trial in patients with T2DM, CagriSema for 32 weeks achieved 15.6% weight reduction versus 5.1% with semaglutide and 8.1% with cagrilintide [104].

The pivotal Phase 3a *REDEFINE 1* trial confirmed the long-term efficacy of CagriSema in overweight or obese patients with comorbidities. At 68 weeks, CagriSema achieved 20.4% weight reduction versus 3.0% with placebo, 11.5% with cagrilintide, and 14.9% with semaglutide [105].

REDEFINE 2 evaluated CagriSema (cagrilintide/semaglutide 2.4 mg each) in patients with obesity and T2DM. At 68 weeks, CagriSema achieved 13.7% weight reduction versus 3.4% with placebo. Additionally, 83.6% and 22.9% of patients achieved ≥ 5% and ≥ 20% weight loss, versus 30.8% and 0.5% with placebo, demonstrating significant efficacy [106].

REIMAGINE 2 demonstrated that CagriSema (2.4 mg/2.4 mg) for 68 weeks in metformin-treated patients with type 2 diabetes achieved 14.2% weight reduction versus 10.2% with semaglutide 2.4 mg. Additionally, 43% and 24% achieved ≥ 15% and ≥ 20% weight loss, respectively, with no plateau observed [107,108].

REDEFINE 4, a head-to-head trial in 800 adults with obesity, compared CagriSema and tirzepatide. At 84 weeks, CagriSema (2.4 mg/2.4 mg) achieved 23% weight reduction versus 25.5% with tirzepatide 15 mg, not demonstrating superiority [109,110].

These clinical trials consistently demonstrated that CagriSema was significantly superior to its monotherapy components and placebo for weight loss, but not superior to tirzepatide.

Its safety profile was consistent with that of the individual components. The most common adverse events were gastrointestinal (nausea, diarrhea), more common than with placebo but predominantly mild-to-moderate and transient. Overall, it was well tolerated.

The global Phase 3 *REDEFINE* program in obesity has enrolled adults across multiple trials. Among these, *REDEFINE 3* is a cardiovascular outcomes trial comparing CagriSema with placebo in adults with established cardiovascular disease [111]. *REDEFINE 6* is specifically targeting Chinese adults with overweight or obesity [112].

In T2DM, the Phase 3 *REIMAGINE* program evaluates CagriSema in diverse populations. *REIMAGINE 1* and *REIMAGINE 3* evaluate CagriSema in patients with inadequate lifestyle response and those on basal insulin, respectively [113,114]. *REIMAGINE 4* and *REIMAGINE 5* are head-to-head trials of CagriSema versus tirzepatide at different doses in patients inadequately controlled on metformin and/or SGLT2 inhibitors [115,116].

Additional studies evaluate long-term weight management, low-dose evaluation, and injection device comparisons, with completion expected in 2026–2028 [117–121]. Research extends to overweight or obese children and adolescents with type 2 diabetes, with trials ongoing until 2030 [122,123]. A Phase 1 study (NCT06267092) evaluates effects on appetite, energy intake, and brain function to elucidate mechanisms [124].

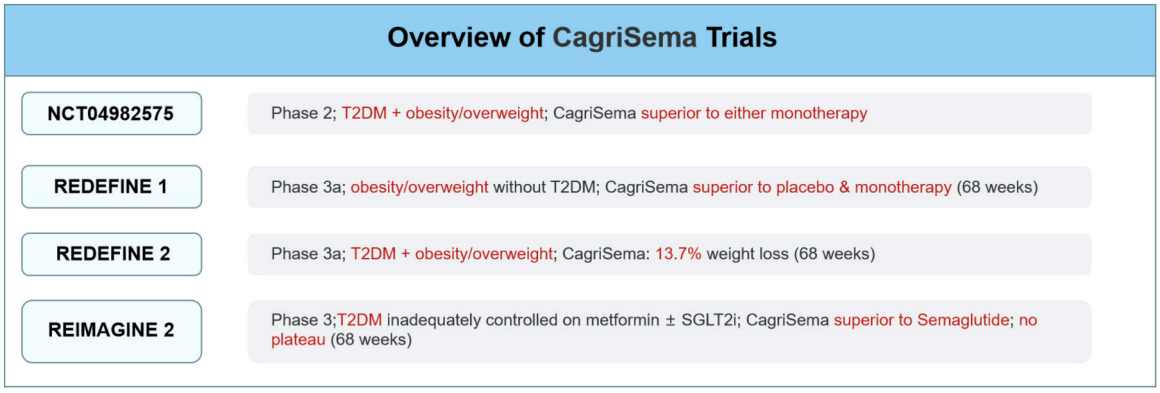

Fig. 6. Overview of CagriSema trials. This figure summarizes key efficacy and design data from clinical trials evaluating CagriSema (cagrilintide + semaglutide) for the treatment of obesity/overweight with or without type 2 diabetes (T2D). Included trials are NCT04982575 (Phase 2), REDEFINE 1 (Phase 3a), REDEFINE 2 (Phase 3a), and REIMAGINE 2 (Phase 3). Each entry displays trial identifier, phase, patient population, key findings, and treatment duration (where specified). CagriSema demonstrated superior weight loss compared with placebo and respective monotherapies across trials, with no plateau observed in REIMAGINE 2. Data are presented as reported in the respective clinical trial publications or presentations. *SGLT2i*, sodium–glucose cotransporter 2 inhibitors; *T2DM*, type 2 diabetes mellitus.

Novo Nordisk has submitted a New Drug Application to the FDA for once-weekly CagriSema (2.4 mg/2.4 mg), with review expected in 2026 [125].

5. Discussion

This review has examined combination weight-loss strategies centered on GLP−1 receptor agonists, focusing on single-agent multi-target agonists and multi-drug combinations. Multi-target agonists target GLP−1R, GIPR, GCGR and AMYR via a single molecule, potentially producing additive or synergistic effects and greater weight loss than monotherapy. These agents also improve metabolic parameters. Free-drug and fixed-dose combinations provide flexible treatment options. Clinical evidence suggests improved weight management and metabolic outcomes, suggesting obesity treatment may be entering a significant evolutionary phase, though gastrointestinal events are common. Combination strategies may increase heart rate and hypoglycemia risk, with thyroid and muscle safety requiring long-term evaluation. High costs and limited accessibility remain barriers. Future research will focus on personalized therapy, head-to-head comparisons, oral formulations, and long-term maintenance strategies.

5.1. Synergistic mechanisms of multi-target agonists: the key to potent weight loss

Compared with traditional single-target GLP−1 drugs, multi-target agonists act on multiple receptors via a single molecule, producing a synergistic "1 + 1 > 2" effect. This underpins their superior weight-loss outcomes [102,126–129]. These mechanisms enable marked improvements in weight-loss magnitude. Notably, the GLP−1R/GIPR/GCGR triple agonist Retatrutide integrates appetite suppression, lipolysis, and energy expenditure [130]. Its clinical data demonstrate the strongest weight-loss potential to date, with a 48-week reduction of up to 24.2%, clearly illustrating the power of multi-target synergy [81]. Additionally, these agents have shown comprehensive benefits in reducing hepatic fat and cardiometabolic risk factors, underscoring their value in managing metabolic diseases [29,131].

5.2. Free combinations vs. Fixed-dose combinations: distinct advantages

Evidence for free combinations of GLP−1RAs in weight management remains limited, and they have not demonstrated clear efficacy advantages over other regimens. However, this approach offers flexibility in dose titration and drug combinations, enabling individualized treatment [132]. FDCs, while less flexible, improve convenience and adherence, making them suitable for long-term management. Early studies have provided the rationale for determining the optimal composition of FDCs.

5.3. Safety: a key determinant of clinical utility

The most common adverse events with GLP−1R-based therapies are gastrointestinal (nausea, vomiting, diarrhea), predominantly mild-to-moderate and diminishing with continued treatment [133]. Combination strategies with higher doses and multiple targets may achieve greater weight loss, but require careful safety management [61,131,134]. Adverse events can be mitigated through dose escalation [35,81].

GLP−1-based therapies may lead to loss of skeletal muscle mass, which accounts for 25–30% of total weight reduction. This pattern mirrors that seen with diet-induced weight loss, although no evidence currently confirms that GLP−1-based therapies alone cause clinically significant sarcopenia. This muscle loss can be effectively managed through increased protein intake and resistance training [135]. With respect to psychiatric safety, multiple large clinical trials and pharmacovigilance studies have demonstrated that GLP−1 receptor agonists do not significantly increase the risk of depression, anxiety, or suicidal ideation. Nevertheless, careful monitoring remains warranted for patients with psychiatric disorders or those taking psychiatric medications [136]. Although early studies raised concerns about medullary thyroid carcinoma risk with GLP−1-based therapies [137,138], recent findings suggest a potential protective effect [139].

Certain safety signals, including effects on cardiovascular parameters and blood glucose levels, have been reported and warrant attention. Retatrutide demonstrated a dose-dependent increase in heart rate, peaking at 24 weeks and then gradually declining [81]. Mazdutide has also been associated with adverse events such as hypoglycemia and upper respiratory tract infection [51,52,131].

Future development should balance efficacy and safety. Optimizing safety in combination strategies remains important [137].

5.4. Economic cost: a key barrier to accessibility

The market for GLP−1RAs in obesity treatment is expanding rapidly. However, inadequate insurance coverage, regional disparities, and cold-chain logistics exacerbate inequalities in access [140–142]. Despite high costs, benefits in reducing T2DM, cardiovascular disease, and MAFLD progression may offset long-term complication costs [20,131,143–146]. Furthermore, weight loss may improve quality of life and yield socioeconomic benefits [81,105].

5.5. Future perspectives

Looking ahead, the following directions warrant particular attention:

5.5.1. Individualized therapy

Personalized treatment strategies are emerging. In patients with obesity and type 2 diabetes, tirzepatide and mazdutide have demonstrated significant weight-loss benefits [22,51]. Trials are investigating these agents in MAFLD, OSA, and heart failure [40–42,56,57]. Future research should define optimal patient subgroups for agents with different mechanisms (e.g., based on T2DM, MASH, or OSA status). Perioperative use of GLP−1RAs represents a comprehensive approach to severe obesity [31,59].

5.5.2. Head-to-head comparisons

Head-to-head studies directly comparing different therapies are essential for establishing treatment standards and providing critical evidence for clinical decision-making. Key head-to-head comparisons of GLP−1-based combination strategies currently include the following: comparisons of targets with different mechanisms, such as TRIUMPH−5 comparing retatrutide and tirzepatide to determine the added value of GCGR agonism [87]; multiple Phase 3 trials comparing the fixed-dose combination CagriSema with tirzepatide to evaluate the relative merits of different combination strategies [109,115,116]; and comparisons beyond weight loss, exemplified by GLORY−3 comparing mazdutide and semaglutide in patients with MAFLD [56].

Beyond formal head-to-head trials, cross-trial comparisons from representative studies offer preliminary insights into the relative efficacy of different GLP−1-based strategies (**Fig. 7**). As summarized in the figure, retatrutide (24.2% at 48 weeks), CagriSema (20.4% at 68 weeks), and tirzepatide (15–21% at 72 weeks) appear to demonstrate the most robust weight-loss efficacy among the agents shown. The triple agonist retatrutide and the fixed-dose combination CagriSema tend to outperform traditional dual agonists in these selected trials, suggesting that multi-target engagement or rational combination formulations may confer additional benefits. Notably, the amylin-including dual agonist amycretin also showed promising results (24.3% at 36 weeks), though its shorter treatment duration should be considered when comparing with agents tested over longer periods. In contrast, multi-drug free combinations generally yielded more modest weight loss. Overall, based on current evidence, retatrutide, CagriSema, and tirzepatide appear to be among the most promising GLP−1-based combination strategies for weight loss, although further direct head-to-head trials are needed for

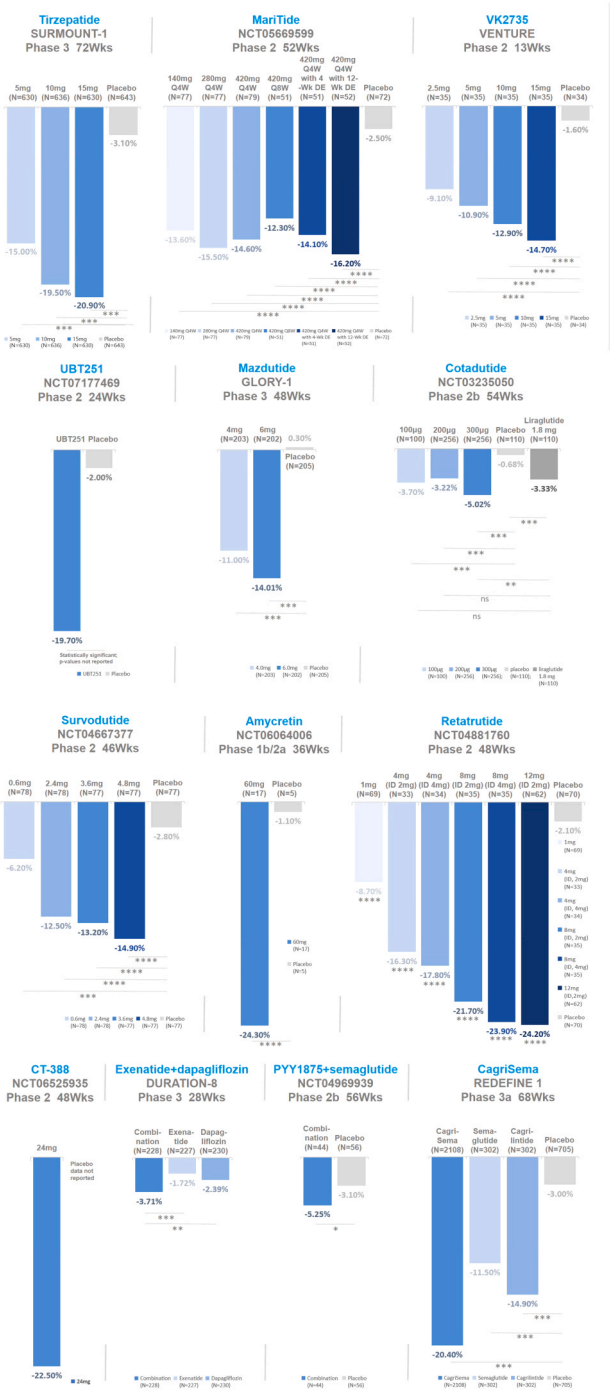

Fig. 7. Comparative overview of weight reduction (%) with GLP−1 combination therapies across select clinical trials. This figure summarizes efficacy and dosing data from multiple clinical trials spanning Phase 1b/2a through Phase 3, evaluating GLP−1-based combination therapies and related investigational agents for weight management, including tirzepatide, MariTide (AMG 133), VK2735, UBT251, mazdutide, cotadutide, survodutide, amycretin, retatrutide, CT−388, exenatide combined with dapagliflozin, PYY1875 combined with semaglutide, and CagriSema (cagrilintide + semaglutide). Each panel displays treatment arms, sample sizes (N), dosing regimens (*Q4W*= every 4 weeks; *μg*= microgram; *mg*= milligram), and study durations (weeks), with corresponding reductions in body weight (where available). Trials are organized by compound and study phase to facilitate cross-comparison of efficacy, dosing frequency, and trial duration. Data are presented as reported in the respective clinical trial publications or presentations. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus comparator arm; ns denotes non-significant differences where indicated.

confirmation.

5.5.3. *Development of oral formulations*

To improve convenience and adherence, oral formulations are a key priority; investigating their long-term efficacy is important for enhancing adherence and expanding options [147]. Oral amycretin demonstrated weight-loss effects comparable to subcutaneous administration at 12 weeks (10.4–13.1%) [72]. Similarly, oral VK2735 achieved dose-dependent weight loss up to 12.2% at 13 weeks [44]. These advances may enable more convenient options, though oral formulations must overcome challenges with bioavailability, gastrointestinal stability, and local effects [148].

5.5.4. *Long-term management and strategic exploration*

Obesity, as a chronic disease, requires long-term management [149]. Current efficacy data are largely from medium-term trials, with limited data beyond five years. SURMOUNT−4 demonstrated that discontinuation led to weight regain, while maintenance therapy sustained weight loss [26]. Low-dose regimens may offer flexible long-term options [44]. In patients needing further treatment, tirzepatide provided 18.4% additional weight reduction beyond lifestyle intervention alone [24]. Integrating pharmacotherapy with lifestyle interventions may optimize long-term outcomes.

5.6. *Research progress remains subject to dynamic updates*

Given the rapid progress and frequent updates in the field of GLP−1-based combination weight-loss strategies, this review has partially cited press releases or clinical trial registrations (e.g., results for oral VK2735, UBT251, and certain CagriSema and amycretin trials) rather than peer-reviewed publications, to present the most current information. Therefore, the efficacy and safety of these agents should be interpreted with caution to avoid overinterpretation, and the relevant conclusions await further validation and updating as more peer-reviewed articles are formally published.

6. Conclusion

In summary, GLP−1RA-based strategies are evolving from single-agent multi-target approaches to multi-drug combinations, toward complementary mechanisms and comprehensive management. These therapies produce substantial weight loss and improve metabolic outcomes. As long-term data accumulate and personalized strategies evolve, these advances may improve obesity management and expand treatment options.

Code availability

Not applicable.

Author contributions

Xinyao Wang conceived and drafted the manuscript, performed literature search, synthesized the available evidence and finished reference management. Rutao Lin contributed to the conceptual framework, and participated in writing and editing. Qinmei Sun assisted with data organization. Qin Feng and Xin Xin supervised the project, reviewed the manuscript critically for important intellectual content, and are the corresponding author. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Xinyao Wang: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition. **Qin Feng:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources,

Funding acquisition, Conceptualization. **Xin Xin:** Writing – review & editing, Writing – original draft, Software, Resources, Investigation, Data curation, Conceptualization. **Qinmei Sun:** Validation, Supervision, Software, Resources. **Rutao Lin:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization.

Consent to participate

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Consent for publication

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Ethics approval

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Declaration of Competing Interest

We have nothing to declare.

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Data availability

No data was used for the research described in the article.

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