



ORIGINAL ARTICLE

Tirzepatide vs. Cagrilintide/Semaglutide: A New Frontier in Pharmacological Management of Obesity

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ABSTRAKT

Obesity is a chronic, multifactorial disease with escalating global prevalence, associated with profound metabolic, cardiovascular, and oncological comorbidities. The recent emergence of incretin-based and amylin-receptor pharmacotherapies has fundamentally transformed the landscape of obesity treatment. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), and the investigational combination of cagrilintide - a long-acting amylin analogue - with semaglutide (CagriSema) represent two of the most clinically significant advances in weight management pharmacology. Both approaches achieve unprecedented levels of body weight reduction in clinical trials, yet differ substantially in their receptor targets, mechanisms of action, and adverse-effect profiles.

Keywords: tirzepatide; cagrilintide; semaglutide; CagriSema; obesity pharmacotherapy; GLP-1 receptor agonist; GIP receptor agonist; amylin analogue; SURMOUNT; REDEFINE; weight loss; incretin therapy; dual agonist; triple hormone receptor

Objectives. This narrative review critically evaluates the clinical trial evidence for tirzepatide and the cagrilintide/semaglutide combination in obesity management, with particular emphasis on the SURMOUNT programme and the OASIS/STEP trials informing CagriSema development, comparing efficacy, safety, tolerability, and patient-relevant outcomes.

Methods. A comprehensive search of MEDLINE, EMBASE, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials was performed for publications and registered trials through April 2026. Phase 2 and Phase 3 randomised controlled trials, as well as peer-reviewed meta-analyses and systematic reviews, were evaluated. Study quality was assessed using the Cochrane Risk of Bias 2.0 tool and GRADE methodology.

Results. Tirzepatide 15 mg achieved a mean body weight reduction of approximately 20.9–22.5% from baseline over 72–88 weeks in the SURMOUNT-1 and SURMOUNT-2 pivotal trials, with up to 63% of participants without diabetes achieving a body weight reduction of at least 20%. CagriSema 2.4 mg/2.4 mg demonstrated a mean weight reduction of approximately 15.6% at 32 weeks in Phase 2 trials, with Phase 3 data (REDEFINE programme) reporting weight reductions approaching 22–25% in preliminary analyses, positioning it as a potential rival to tirzepatide. Both therapies demonstrate significant improvements in cardiometabolic parameters. Adverse-event profiles are dominated by gastrointestinal symptoms in both classes, with tirzepatide additionally associated with injection-site reactions related to its GIP activity and CagriSema associated with nausea attributable to both the amylin and GLP-1 components.

Conclusions. Both tirzepatide and the cagrilintide/semaglutide combination represent landmark advances in obesity pharmacotherapy, achieving weight reductions previously attainable only through bariatric surgery. The choice between agents will ultimately depend on the completeness of Phase 3 data, approved indications, comorbidity profile, patient tolerability, and healthcare system access. The field is approaching an era where pharmacological obesity treatment can offer durable, clinically transformative weight loss for a broad patient population

ARTICLE INFORMATION



Received: 23.06.2026



Revised: 15.08.2026



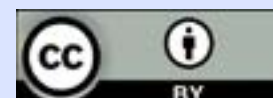
Accepted: 02.09.2026



Article type: Original Article

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Rybińska, M., Rzepka, H., Stępowski, P., Tajster, M. 2026. Tirzepatide vs. Cagrilintide/Semaglutide Combination: A New Frontier in the Pharmacological Management of Obesity? A Review of Recent Clinical Trials. *Journal of Education, Health and Sport*, 95(1): 73651. DOI: [10.12775/JEHS.2026.95.73651](https://doi.org/10.12775/JEHS.2026.95.73651)

KEYWORDS

tirzepatide, cagrilintide, semaglutide, CagriSema, obesity pharmacotherapy, GLP-1 receptor agonist, GIP receptor agonist, amylin

Chapter 1 - Introduction

The Global Burden of Obesity

Obesity has reached epidemic proportions, affecting over one billion people worldwide as of 2025 according to the World Health Organization. Defined by a body mass index (BMI) of 30 kg/m² or greater, obesity is not merely an aesthetic concern but a chronic, progressive, and relapsing disease characterised by pathological adipose tissue accumulation that impairs health and quality of life. Its metabolic sequelae are extensive and well-documented: type 2 diabetes mellitus, hypertension, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnoea, osteoarthritis, and a spectrum of obesity-related malignancies collectively account for a disproportionate burden of premature mortality and healthcare expenditure globally.

Despite decades of public health campaigns, lifestyle modification programmes, and pharmacological development, obesity rates have continued to rise in both high- and low-income countries. Conventional dietary and exercise interventions, while essential components of obesity management, produce average weight reductions of 3–5% - far below the 10–15% threshold associated with meaningful and durable cardiometabolic improvement. Bariatric and metabolic surgery remains the most effective intervention for severe obesity, achieving 25–35% excess weight loss over two to five years, but is limited by surgical risk, resource requirements, and patient acceptability.

This epidemiological context has intensified the search for pharmacological agents capable of producing substantial, durable, and safe weight reductions that can narrow the efficacy gap between lifestyle intervention and bariatric surgery. The approval of semaglutide 2.4 mg subcutaneous weekly (Wegovy, Novo Nordisk) for obesity in 2021 - achieving approximately 14.9% body weight reduction in the STEP-1 trial - marked a watershed moment in this pursuit. However, the subsequent development of tirzepatide (Zepbound, Eli Lilly) and the investigational CagriSema combination (cagrilintide 2.4 mg + semaglutide 2.4 mg, Novo Nordisk) has raised the ceiling of pharmacological efficacy even further, approaching and in some analyses matching the weight reduction achievable through sleeve gastrectomy.

The New Pharmacological Landscape: Mechanisms and Rationale

The paradigm shift in obesity pharmacotherapy has been driven by a deepened understanding of the gut-brain axis and the central regulation of appetite, energy expenditure, and adiposity. Three hormone systems - GLP-1, GIP, and amylin - have emerged as particularly tractable therapeutic targets.

Glucagon-like peptide-1 (GLP-1) is a 30-amino-acid incretin hormone secreted from intestinal L-cells in response to nutrient ingestion. It exerts its principal anorectic effects centrally, activating GLP-1 receptors in the hypothalamic arcuate nucleus and brainstem structures (including the nucleus tractus solitarius and area postrema) that regulate satiety and food intake, while simultaneously slowing gastric emptying and augmenting glucose-dependent insulin secretion. Semaglutide is a GLP-1 receptor agonist (GLP-1 RA) engineered for prolonged half-life (approximately 168 hours) through fatty acid chain modification and human albumin binding.

Glucose-dependent insulinotropic polypeptide (GIP) is a sister incretin hormone secreted from K-cells in the duodenum and proximal jejunum. Its role in energy homeostasis has historically been considered subordinate to GLP-1, but rodent models and subsequent human studies revealed that GIP receptor agonism augments the anorectic effects of GLP-1 receptor activation through complementary central and peripheral pathways, including direct adipocyte lipid metabolism modulation and synergistic hypothalamic signalling. Tirzepatide exploits this biology as the first dual GIP/GLP-1 receptor agonist.

Amylin (islet amyloid polypeptide, IAPP) is a 37-amino-acid peptide co-secreted with insulin from pancreatic beta cells in response to meals. It acts on amylin receptors in the area postrema, nucleus accumbens, and hypothalamus to reduce food intake, slow gastric emptying, and suppress post-prandial glucagon secretion. Cagrilintide is a long-acting amylin analogue with a half-life of approximately seven days, designed for once-weekly subcutaneous administration. The rationale for combining cagrilintide with semaglutide is mechanistically compelling: amylin and GLP-1 engage partially overlapping but distinct neural circuits, and preclinical data suggest additive or synergistic weight-reducing effects through complementary satiety signalling pathways.

Objectives and Scope of This Review

This review aims to: (1) synthesise the clinical trial evidence for tirzepatide in obesity, with a focus on the SURMOUNT programme; (2) critically appraise the emerging evidence for the cagrilintide/semaglutide combination (CagriSema) across Phase 2 and available Phase 3 data; (3) compare efficacy, safety, and tolerability outcomes between the two approaches; (4) contextualise both therapies within current obesity management guidelines; and (5) identify outstanding research questions and future directions for combination pharmacotherapy in obesity.

Chapter 2 - Tirzepatide — Pharmacology and Clinical Evidence

Pharmacological Profile of Tirzepatide

Tirzepatide (LY3298176) is a 39-amino-acid synthetic peptide engineered as a dual agonist at both the GIP receptor (GIPR) and the GLP-1 receptor (GLP-1R). It is structurally based on a modified GIP sequence and incorporates a C20 fatty diacid moiety that facilitates albumin binding, extending the effective half-life to approximately five days and enabling once-weekly subcutaneous administration. The peptide binds GIPR with approximately equivalent affinity to native GIP, while binding GLP-1R with somewhat lower affinity than native GLP-1 - an asymmetry that may contribute to its distinct pharmacodynamic profile compared to selective GLP-1 RAs.

The dual receptor engagement of tirzepatide produces effects that are quantitatively superior to single-agonism at either receptor alone. In preclinical models, simultaneous GIPR/GLP-1R co-agonism demonstrates synergistic weight reduction relative to maximal-dose selective agonism of either receptor. In the CNS, tirzepatide activates complementary anorectic pathways - GLP-1R-mediated signalling in the nucleus tractus solitarius and area postrema alongside GIPR-mediated signalling in the hypothalamus and ventral tegmental area - producing more comprehensive suppression of food intake and food reward than either pathway alone. Peripherally, GIPR agonism modulates adipocyte lipid metabolism, reduces adipose tissue inflammation, and may directly sensitise adipose tissue to the

lipolytic and insulin-sensitising actions of GLP-1R activation.

Tirzepatide received FDA approval in May 2022 for the treatment of type 2 diabetes mellitus (under the brand name Mounjaro) and in November 2023 for chronic weight management in adults with obesity or overweight with at least one weight-related comorbidity (under the brand name Zepbound). The European Medicines Agency approved tirzepatide for type 2 diabetes in September 2022. The approved weekly doses are 5 mg, 10 mg, and 15 mg, with dose escalation recommended from a starting dose of 2.5 mg.

The SURMOUNT Clinical Programme

The SURMOUNT programme comprises a series of Phase 3 randomised controlled trials evaluating tirzepatide for obesity management across multiple patient populations. The programme is organised across at least five major trials: SURMOUNT-1 (adults without diabetes), SURMOUNT-2 (adults with type 2 diabetes), SURMOUNT-3 (intensive lifestyle intervention run-in followed by randomisation), SURMOUNT-4 (weight maintenance after initial tirzepatide lead-in), and SURMOUNT-5 (head-to-head comparison with semaglutide 2.4 mg).

SURMOUNT-1: Pivotal Efficacy in Adults Without Diabetes

SURMOUNT-1 was a 72-week, double-blind, randomised, placebo-controlled trial enrolling 2,539 adults with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity (excluding diabetes), who were randomised 1:1:1:1 to tirzepatide 5 mg, 10 mg, or 15 mg, or placebo, all administered subcutaneously once weekly. The co-primary endpoints were percentage change from baseline body weight and the proportion of participants achieving at least 5% body weight reduction.

Results published in the New England Journal of Medicine (Jastreboff et al., 2022) demonstrated that all three tirzepatide doses produced statistically significant and clinically meaningful weight reductions compared with placebo. The mean percentage change from baseline body weight was -15.0% for 5 mg, -19.5% for 10 mg, and -20.9% for 15 mg, compared with -3.1% for placebo. Notably, 57% of participants receiving tirzepatide 15 mg achieved a body weight reduction of $\geq 20\%$ - a threshold previously achievable only through bariatric surgery - compared with 3% in the placebo group. Cardiometabolic

parameters including waist circumference, blood pressure, fasting glucose, triglycerides, and HDL cholesterol improved significantly across all tirzepatide arms. The most common adverse events were nausea (31.0% at 15 mg vs. 11.5% placebo), diarrhoea (21.8% vs. 9.3%), vomiting (14.5% vs. 2.7%), and constipation (16.1% vs. 4.5%), predominantly mild-to-moderate in severity and most frequent during dose escalation.

SURMOUNT-2: Efficacy in Type 2 Diabetes

SURMOUNT-2 evaluated tirzepatide 10 mg and 15 mg versus placebo in 938 adults with obesity and type 2 diabetes over 72 weeks. This population is clinically distinct because obesity and diabetes are deeply intertwined, and antidiabetic medications - including insulin and sulfonylureas - often cause weight gain, compounding the management challenge. Mean percentage weight reduction was -12.8% for tirzepatide 10 mg and -14.7% for tirzepatide 15 mg, compared with -3.2% for placebo. HbA1c was reduced by a mean of 2.06% and 2.10% in the 10 mg and 15 mg groups respectively. These results established tirzepatide as effective in obese individuals with diabetes, a population in whom weight reduction is both more difficult and arguably more urgently needed given the bidirectional relationship between adiposity and glycaemic dysregulation.

SURMOUNT-3 and SURMOUNT-4: Lifestyle Context and Long-Term Durability

SURMOUNT-3 introduced a novel design: participants first underwent a 12-week intensive lifestyle intervention run-in phase, and those achieving at least 5% weight loss were then randomised to tirzepatide 15 mg or placebo for an additional 72 weeks. Participants who had already achieved some weight loss through lifestyle modification demonstrated even greater additional weight reduction with tirzepatide: a mean -18.4% from randomisation to week 72 (representing an overall reduction of approximately -24% from before the run-in), compared with -2.5% for placebo from randomisation. This design models a realistic clinical pathway where pharmacotherapy is initiated following initial lifestyle intervention, and the results underscore tirzepatide's efficacy even in a population that has already engaged with behavioural modification.

SURMOUNT-4 addressed the clinically critical question of what happens when tirzepatide is discontinued. Participants who completed a 36-week open-label tirzepatide lead-in period (achieving approximately -20.9% weight reduction) were randomised to continued tirzepatide or placebo for a further 52 weeks. Those

switched to placebo regained a mean of 14% body weight, while those continuing tirzepatide maintained and slightly extended their weight loss (additional -5.5%). This weight regain trajectory - observed across obesity pharmacotherapy withdrawal studies - underscores the chronic disease model of obesity and the need for long-term, potentially indefinite pharmacotherapy in susceptible individuals.

SURMOUNT-5: Head-to-Head Comparison with Semaglutide 2.4 mg

SURMOUNT-5 is a pivotal head-to-head trial comparing tirzepatide 10 mg or 15 mg with semaglutide 2.4 mg (Wegovy) subcutaneous once weekly over 72 weeks in adults with obesity without diabetes. Published results (Jastreboff et al., 2025) demonstrated that tirzepatide was superior to semaglutide 2.4 mg with a mean weight reduction of -20.2% vs. -13.7% for semaglutide 2.4 mg. The proportion of participants achieving $\geq 20\%$ weight loss was 31.6% for tirzepatide vs. 16.1% for semaglutide. This head-to-head data provides direct comparative evidence confirming the superior weight-reducing efficacy of dual GIP/GLP-1 agonism over single GLP-1 agonism at maximally approved doses, and firmly establishes tirzepatide as the leading approved pharmacotherapy for obesity by weight reduction magnitude.

Chapter 3 - Cagrilintide/Semaglutide (CagriSema) — Pharmacology and Clinical Evidence

Rationale for Amylin-GLP-1 Combination Therapy

The conceptual foundation for combining amylin receptor agonism with GLP-1 receptor agonism rests on evidence from both preclinical biology and early clinical studies. In rodent models, co-administration of pramlintide (an earlier amylin analogue) with GLP-1 receptor agonists produced synergistic reductions in food intake and body weight exceeding the effects of either agent alone, mediated through complementary hypothalamic and brainstem circuits. Human studies with pramlintide - approved in the United States for post-prandial glucose management in insulin-treated diabetes - demonstrated modest weight-independent appetite-suppressing effects, suggesting that the amylin pathway was indeed translationally relevant, but pramlintide's requirement for multiple daily injections and its modest efficacy in isolation limited its development as an obesity agent.

Cagrilintide (AM833, Novo Nordisk) was developed to overcome these limitations. Through peptide engineering - incorporating non-natural amino acids, fatty acid conjugation for albumin binding, and a stabilised disulfide bridge - cagrilintide achieves a half-life of approximately seven days, enabling once-weekly subcutaneous administration. It activates calcitonin receptor/receptor activity-modifying protein (RAMP) complexes that constitute the amylin receptor, principally in the area postrema and hypothalamus, producing satiety signalling distinct from but complementary to that of GLP-1R activation. When combined with semaglutide 2.4 mg - the highest-approved dose for obesity - the resultant CagriSema co-formulation targets two independent satiety pathways simultaneously.

Phase 1 and Phase 2 Evidence

Phase 1 pharmacokinetic studies demonstrated that cagrilintide and semaglutide do not meaningfully alter each other's pharmacokinetics when co-administered, validating the feasibility of a co-formulation. The Phase 2 COMBINE trial (ClinicalTrials.gov identifier NCT04667377) evaluated CagriSema at doses of 1.0/1.0 mg, 2.4/0.5 mg, or 2.4/2.4 mg cagrilintide/semaglutide over 32 weeks in 401 adults with overweight or obesity. Results published in *The Lancet* (Enebo et al., 2021) demonstrated dose-dependent weight reductions: the highest-dose CagriSema arm (2.4/2.4 mg) achieved a mean body weight reduction of -15.6% compared with -5.1% for placebo, -8.8% for cagrilintide alone, and -10.8% for semaglutide 2.4 mg alone. This 15.6% reduction at 32 weeks in a Phase 2 trial was substantially greater than semaglutide alone and provided early proof-of-concept that amylin/GLP-1 dual targeting could achieve meaningfully superior weight loss compared with either component alone.

A secondary analysis of the Phase 2 data confirmed statistically significant improvements in fasting insulin levels, insulin resistance (HOMA-IR), waist circumference, and systolic blood pressure in the CagriSema 2.4/2.4 mg arm relative to placebo, supporting the hypothesis that combination therapy targets metabolic dysfunction more comprehensively than single-agent therapy. The safety profile in Phase 2 was characterised by predominantly gastrointestinal adverse events - nausea (35.8% in CagriSema 2.4/2.4 vs. 11.8% placebo), vomiting (18.9% vs. 2.9%), and diarrhoea (16.3% vs. 5.9%) - at rates broadly comparable to semaglutide 2.4 mg monotherapy, suggesting that the addition of cagrilintide did not substantially worsen gastrointestinal tolerability.

The REDEFINE Phase 3 Programme

The REDEFINE programme is Novo Nordisk's Phase 3 clinical trial programme for CagriSema in obesity and related metabolic conditions. REDEFINE-1, the pivotal obesity trial, enrolled approximately 3,400 adults with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with comorbidities over 68 weeks of treatment, using a dose-escalation protocol for CagriSema 2.4 mg/2.4 mg administered as a single co-formulated once-weekly subcutaneous injection versus placebo. Preliminary data presented at scientific congresses in late 2024 and early 2025 indicated mean body weight reductions in the range of 22–25% in the CagriSema arm - a range overlapping with tirzepatide 15 mg from SURMOUNT-1 and raising the possibility of comparable or potentially superior efficacy to the approved dual incretin agonist.

Full peer-reviewed publication of REDEFINE-1 data is anticipated in 2025–2026, and the complete dataset will be critical for definitive comparative assessments. However, available preliminary reports consistently place CagriSema efficacy at or above tirzepatide's performance in SURMOUNT-1, positioning it as the potential next standard of care in obesity pharmacotherapy if regulatory approval is obtained. Additional REDEFINE trials are evaluating CagriSema in type 2 diabetes, non-alcoholic steatohepatitis, and cardiovascular risk reduction - reflecting the broader therapeutic ambitions for this combination.

Regulatory Status and Development Timeline

As of early 2026, CagriSema has not yet received regulatory approval from the FDA or EMA. Novo Nordisk submitted regulatory dossiers in late 2025 based on the REDEFINE programme data, and a regulatory decision is expected during 2026. Approval, if granted, would introduce the first amylin-analogue-containing co-formulation for obesity into clinical practice and would provide prescribers with a mechanistically distinct alternative to the GIP/GLP-1 dual agonism of tirzepatide.

Chapter 4 - Comparative Analysis — Efficacy, Safety, and Clinical Utility

Comparative Efficacy: Weight Reduction

Directly comparing tirzepatide and CagriSema is complicated by the absence of published head-to-head trial data, differences in trial duration (72 weeks for SUR-

MOUNT-1 vs. 68 weeks for REDEFINE-1), variations in baseline patient characteristics, and the preliminary nature of REDEFINE Phase 3 data available at the time of writing. Nonetheless, available data permit approximate cross-trial comparisons with the standard caveats regarding indirect comparisons. Tirzepatide 15 mg achieves a mean body weight reduction of approximately 20.9% (SURMOUNT-1) to 22.5% (SURMOUNT-3 overall reduction), with approximately 63% of participants achieving $\geq 20\%$ weight reduction at the highest dose. CagriSema 2.4/2.4 mg preliminary REDEFINE data suggest a mean weight reduction in the range of 22–25%, with a potentially higher proportion of individuals achieving the $\geq 20\%$ threshold. If confirmed by full publication, these data would suggest that CagriSema's dual-mechanism approach of combining amylin-pathway satiety with GLP-1-mediated food intake suppression produces weight reductions modestly exceeding or equivalent to tirzepatide's GIP/GLP-1 dual agonism. The mechanistic basis for CagriSema potentially exceeding tirzepatide is not implausible: whereas tirzepatide engages two incretin-related receptors (GIPR and GLP-1R) that share partial downstream signalling convergence, CagriSema combines GLP-1R agonism with amylin-receptor activation - a substantially more distinct mechanistic pairing that targets non-overlapping central appetite regulatory circuits. The additive satiety signalling from these parallel pathways could logically produce superior weight reduction, particularly given Phase 2 data demonstrating that cagrilintide addition to semaglutide increased weight loss by approximately 50% over semaglutide monotherapy.

Glycaemic and Cardiometabolic Outcomes

Both tirzepatide and CagriSema produce substantial improvements in cardiometabolic parameters beyond weight loss per se. Tirzepatide's glucose-lowering efficacy is particularly pronounced given its dual incretin mechanism: in the SURPASS programme for type 2 diabetes, tirzepatide 15 mg achieved HbA1c reductions of 2.0–2.3%, exceeding those of insulin glargine and semaglutide 1 mg in head-to-head comparisons. In SURMOUNT-1, tirzepatide produced significant reductions in fasting insulin, insulin resistance (HOMA-IR), systolic blood pressure (–4.5 to –6.2 mmHg), triglycerides (–24 to –33%), and significant increases in HDL cholesterol. CagriSema Phase 2 and emerging Phase 3 data demonstrate comparable cardiometabolic improvements. The amylin receptor activation component of CagriSema provides unique glucoregulatory benefits: amylin suppresses post-prandial glucagon secretion, which can independently reduce post-prandial glucose

excursions in both diabetic and non-diabetic individuals. This mechanism is distinct from and potentially complementary to semaglutide's glucose-dependent insulin secretion stimulation, suggesting that CagriSema may offer superior post-prandial glucose management compared with tirzepatide in individuals with impaired glycaemic regulation.

The landmark SELECT trial (2023) demonstrated that semaglutide 2.4 mg reduced major adverse cardiovascular events (MACE) by 20% in overweight and obese individuals with established cardiovascular disease but without diabetes - a first-of-its-kind demonstration that a pharmacological weight loss agent can produce cardiovascular risk reduction beyond its glycaemic effects. Whether tirzepatide will replicate this cardiovascular benefit is being evaluated in the SURMOUNT-MMO (morbidity and mortality outcomes) trial, with results expected in 2026–2027. A comparable cardiovascular outcomes trial for CagriSema has not yet been initiated, representing a gap in its evidence base relative to semaglutide.

Adverse Event Profiles

The adverse event profiles of tirzepatide and CagriSema share a common gastrointestinal theme but differ in their origins and some specific features. For tirzepatide, nausea, diarrhoea, vomiting, and constipation occur predominantly during dose escalation and are attributed primarily to GLP-1R-mediated slowing of gastric emptying and central vagal signalling. These events are generally transient, mild-to-moderate in severity, and manageable through slow dose escalation protocols. Treatment discontinuation due to gastrointestinal adverse events occurs in approximately 4–7% of participants in tirzepatide trials.

For CagriSema, gastrointestinal symptoms similarly dominate the adverse event profile, with nausea rates appearing comparable to or modestly higher than tirzepatide at respective maximum doses, reflecting contributions from both the semaglutide and cagrilintide components. Amylin receptor agonism independently produces nausea through area postrema stimulation, potentially creating an additive gastrointestinal burden compared with GLP-1 monotherapy. Post-marketing and Phase 3 tolerability data will be essential for precise characterisation.

Both agent classes carry theoretical risks of acute pancreatitis, although causality remains debated in the literature given the background prevalence of pancreatitis in obese populations. Neither agent is recommended in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine

neoplasia type 2A/2B, based on rodent carcinogenicity data for GLP-1 receptor agonists, though the clinical relevance of this finding in humans remains uncertain. Injection-site reactions are reported for both agents and are generally mild.

A noteworthy safety finding from the GLP-1 RA class is the association with lean mass loss alongside fat mass reduction. High-dose semaglutide and tirzepatide studies have documented that a proportion of total weight loss (approximately 30–40%) represents lean mass rather than adipose tissue - a finding with potential long-term implications for muscle function, physical performance, and metabolic rate. Whether CagriSema's additional amylin mechanism, which has been associated in preclinical studies with preferential fat mass reduction over lean mass loss, will translate into a superior body composition profile is an important clinical question under investigation in the REDE-FINE programme.

Patient-Reported Outcomes and Quality of Life

Both tirzepatide and semaglutide/CagriSema trials have incorporated validated patient-reported outcome measures including the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQoL-Lite-CT) and the Short Form-36 (SF-36). SURMOUNT-1 demonstrated statistically significant and clinically meaningful improvements in IWQoL-Lite-CT total score and physical function subscores for all tirzepatide doses compared with placebo. Phase 2 CagriSema data similarly showed quality-of-life improvements, though comprehensive Phase 3 patient-reported outcome data have not yet been fully published. Both therapies are associated with improvements in weight-related distress, physical activity capacity, and self-reported wellbeing, outcomes that are of central importance to patients and are increasingly recognised as primary objectives of obesity treatment beyond anthropometric endpoints.

Chapter 5 - Practical Considerations and Clinical Positioning

Patient Selection and Individualised Treatment

The expanding pharmacological armamentarium for obesity necessitates a nuanced approach to patient selection and treatment sequencing. Both tirzepatide and CagriSema are indicated for adults with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity (hypertension, type 2 diabetes, dyslipida-

emia, obstructive sleep apnoea, or cardiovascular disease), in conjunction with a reduced-calorie diet and increased physical activity. Patient comorbidity profile is a key differentiator: tirzepatide has existing approval for type 2 diabetes (Mounjaro) and may be preferred in patients where both glycaemic and weight management objectives require simultaneous optimisation. CagriSema, if approved, may offer advantages in patients who have demonstrated inadequate response to semaglutide monotherapy given the complementary amylin mechanism, and may be particularly relevant for those with prominent post-prandial hyperglycaemia.

Gastrointestinal tolerability history is important: patients who have previously experienced significant GI adverse effects on GLP-1 receptor agonists may require careful dose escalation or may be less suitable candidates for either agent, though the optimal protocol for minimising intolerance is evolving. The potential for lean mass preservation with CagriSema may specifically benefit sarcopenic obese individuals, including older patients, though this hypothesis requires prospective confirmation.

Treatment Escalation and Combination Sequencing

The recognition of obesity as a chronic relapsing disease requiring long-term pharmacotherapy raises important questions about treatment sequencing. Should tirzepatide be positioned as a first-line obesity pharmacotherapy given its established approval and superior head-to-head data versus semaglutide, or should semaglutide remain first-line with tirzepatide reserved for inadequate responders? And when CagriSema receives approval, how should it be positioned relative to tirzepatide?

A reasonable clinical framework emerging from the evidence is as follows: maximally tolerated first-line GLP-1 RA therapy (semaglutide 2.4 mg or liraglutide 3 mg) for appropriate candidates, escalating to tirzepatide for those not achieving target weight loss (operationally defined as less than 5% weight reduction after 12–16 weeks at maintenance dose) or in patients with concurrent type 2 diabetes where tirzepatide's dual incretin efficacy is particularly advantageous. CagriSema, once approved, may offer a distinct option for patients with inadequate response to dual incretin therapy or as an alternative to tirzepatide in specific clinical subgroups. Future triple-mechanism agents - potentially combining GIP, GLP-1, and glucagon receptor agonism (such as the retatrutide pipeline) - may further redefine this landscape.

Access, Cost, and Healthcare System Implications

The transformative efficacy of next-generation obesity pharmacotherapy is accompanied by significant healthcare system challenges. Both tirzepatide (approximately \$1,000–1,200 USD/month in the United States) and anticipated CagriSema pricing represent substantial costs that limit access through out-of-pocket expenditure, and insurance coverage for obesity pharmacotherapy remains inconsistent in many healthcare systems, including much of Europe and lower-income countries. The health-economic case for subsidising high-efficacy obesity pharmacotherapy is strengthened by modelling studies demonstrating that even modest weight reductions translate into significant long-term savings through reduced rates of type 2 diabetes, myocardial infarction, and stroke - conditions whose treatment costs dwarf those of preventive pharmacotherapy. Health technology assessment bodies in multiple countries are currently evaluating the cost-effectiveness of tirzepatide and are expected to evaluate CagriSema upon approval.

Manufacturing constraints and supply chain issues have also affected availability of GLP-1-based therapies globally, with semaglutide experiencing significant shortages in 2022–2024. The anticipated demand for CagriSema - should it match or exceed tirzepatide's clinical profile - will require substantial manufacturing scale-up and may face similar supply challenges during its launch period.

Chapter 6 - Future Directions and Emerging Therapies

Triple Hormone Receptor Agonists

The success of dual agonism has naturally prompted investigation of triple receptor agonists. Retatrutide (LY3437943, Eli Lilly), a GIP/GLP-1/glucagon receptor triagonist, demonstrated mean body weight reductions of approximately 24.2% at 48 weeks in Phase 2 trials - potentially exceeding tirzepatide - driven by glucagon receptor-mediated enhancement of energy expenditure and hepatic fat mobilisation complementing the incretin-based food intake suppression. Phase 3 trials for retatrutide are underway. If triple agonism proves both safe and superior to dual agonism in Phase 3, it will further extend the pharmacological frontier. Other pipeline agents include orforglipron, a non-peptide oral GLP-1 RA that could overcome the injection barrier and dramatically expand global access, and efinopeglu-

tide, a GLP-1/glucagon dual agonist with a particular focus on hepatic steatosis. The development of oral formulations - semaglutide oral 25 mg and 50 mg doses are under Phase 3 investigation - represents another transformative direction for patient acceptability and access.

Obesity as a Chronic Disease: Implications for Long-Term Management

The most profound implication of the SURMOUNT-4 and comparable withdrawal trial data is that obesity pharmacotherapy must be conceptualised as long-term or indefinite for most patients - analogous to antihypertensive or statin therapy for cardiovascular risk management. Weight regain upon discontinuation is not a treatment failure but rather the expected biological response of an energy homeostasis system whose adiposity set point has been pharmacologically suppressed rather than fundamentally altered. Future research must therefore focus not only on maximising initial weight reduction but on optimising long-term adherence strategies, developing combination regimens that minimise adverse effects to sustain treatment, identifying patient subgroups most likely to sustain weight loss with finite pharmacotherapy, and understanding the neurobiological basis of durable adiposity set point recalibration.

Paediatric and Adolescent Obesity

The extension of next-generation obesity pharmacotherapy to paediatric and adolescent populations represents an urgent clinical need and an active area of investigation. Adolescent obesity is associated with premature metabolic disease, cardiovascular risk, and psychosocial burden, and effective interventions during this developmental window have potentially outsized long-term benefits. The FDA approved semaglutide 2.4 mg for obesity in adolescents aged 12 and above in 2023. Tirzepatide trials in adolescents are underway. The investigation of CagriSema in paediatric obesity populations is anticipated to follow regulatory approval in adults, though the specific safety and efficacy profile in developing organ systems requires dedicated study.

Conclusions

Tirzepatide and the cagrilintide/semaglutide combination (CagriSema) represent the current vanguard of obesity pharmacotherapy, collectively achieving weight reductions of 20–25% from baseline - a magnitude that,

for the first time, places pharmacological obesity treatment in direct competition with bariatric surgery on an efficacy basis.

Tirzepatide, as the first approved dual GIP/GLP-1 receptor agonist, has established a robust Phase 3 evidence base through the SURMOUNT programme, with superior efficacy to semaglutide 2.4 mg demonstrated in the head-to-head SURMOUNT-5 trial, meaningful cardiometabolic benefits across the programme, and a tolerable adverse event profile. Its ongoing cardiovascular outcomes trial (SURMOUNT-MMO) will address the critical question of whether its weight-reducing efficacy translates into primary prevention of MACE.

CagriSema, combining a once-weekly amylin analogue with semaglutide 2.4 mg in a co-formulated injection, targets mechanistically distinct and complementary satiety circuits. Preliminary Phase 3 data from the REDEFINE programme suggest efficacy potentially comparable to or exceeding tirzepatide, with particular potential advantages in post-prandial glucose management and possibly in lean mass preservation - hypotheses requiring confirmation through full publication. Regulatory submission has been initiated, and approval during 2026 is anticipated.

The critical outstanding questions in this rapidly evolving field include: (1) definitive head-to-head data for CagriSema versus tirzepatide (REDEFINE vs. SURMOUNT cross-trial comparisons are informative but inherently limited); (2) long-term cardiovascular outcomes for tirzepatide and CagriSema; (3) body composition implications of each therapy; (4) optimal duration and sequencing of pharmacotherapy; (5) durability of weight loss and optimal long-term treatment strategies; and (6) health-economic and access considerations that will determine population-level impact. The obesity pharmacotherapy revolution currently underway has the potential to fundamentally alter the natural history of obesity-related cardiometabolic disease at a population level. Realising this potential will require not only continued scientific excellence in drug development but also equitable access policies, integrated clinical management programmes, and long-term patient support frameworks. Both tirzepatide and CagriSema deserve their position at the frontier of this transformation.

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Writing-rough preparation: MT, HRZ, PS, MR

Writing-review and editing: MT, HRZ, PS, MR

Receiving funding: Not applicable.

All authors have read and agreed with the published version of the manuscript.

Funding: The article did not receive any funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: Authors declare no conflicts of interest.

AI Disclosure: AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.