Scientific Comparison of Anti-Obesity Drug Efficacy: Semaglutide, Tirzepatide, Liraglutide, and Pemvidutide

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Obesity represents one of the most significant healthcare challenges of the 21st century, with profound implications for cardiovascular health, metabolic function, and quality of life. In recent years, obesity pharmacotherapy has made extraordinary progress through the development of incretin receptor agonists, a class of drugs that has revolutionized the treatment of this chronic condition. This report provides a detailed scientific analysis comparing the efficacy of four therapeutic agents: **semaglutide (Wegovy)**, **tirzepatide (Zepbound)**, **liraglutide (Saxenda)**, and **pemvidutide (ALT-801)**, the latter currently in advanced clinical development.

The analysis is based on data from phase 2 and phase 3 randomized controlled trials, with particular attention to mechanisms of action, primary and secondary efficacy outcomes, safety profiles, and clinical implications for obesity treatment[1][2][3][4][5][6].

Mechanisms of Action and Pharmacological Rationale

Selective GLP-1 Receptor Agonists

Semaglutide and **liraglutide** belong to the class of selective glucagon-like peptide-1 (GLP-1) receptor agonists, an incretin hormone produced by intestinal L cells in response to food intake[7][8]. GLP-1 regulates glucose homeostasis through multiple mechanisms: it stimulates glucose-dependent insulin secretion from pancreatic beta cells, inhibits glucagon secretion, slows gastric emptying, and centrally reduces appetite by acting on hypothalamic satiety centers[7][8][9].

Semaglutide has an amino acid sequence with 94% homology to native human GLP-1 and incorporates structural modifications that significantly prolong its half-life[8][9]. Specifically, the substitution of alanine with aminoisobutyric acid at position 8 and the addition of a fatty acid side chain attached via a spacer to lysine at position 26 confer resistance to enzymatic degradation by dipeptidyl peptidase-4 (DPP-4) and promote high binding to plasma albumin (>99%)[9]. These characteristics enable once-weekly administration and a half-life of approximately 7 days[9].

Liraglutide, while sharing a similar mechanism of action, has a shorter half-life (approximately 13 hours) requiring daily administration[10][11]. The shorter duration of action translates to different pharmacokinetic properties and, as we will see, moderately lower efficacy for weight loss compared to semaglutide[10][11][12].

Dual GIP/GLP-1 Agonists

Tirzepatide represents a breakthrough in the pharmacological approach to obesity, being the first approved dual agonist that simultaneously activates the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors[13][14][15][16]. GIP, secreted by duodenal K cells, is another incretin hormone that stimulates insulin secretion and plays metabolic roles in adipose tissue[13][14][15].

The structure of tirzepatide is based on the native GIP sequence, with specific modifications that confer balanced activity on both receptors[13][15][16]. Cryo-electron microscopy structural studies have revealed that tirzepatide mimics the action of native GIP at the GIPR but exhibits partial (biased) agonism at the GLP-1R, favoring cAMP-mediated signaling over β-arrestin recruitment[13][17]

[16]. This unique pharmacological profile reduces GLP-1 receptor desensitization and may explain the greater clinical efficacy compared to selective GLP-1 agonists[13][17][16].

The receptor activation ratio of tirzepatide is skewed toward GIPR, with potency equivalent to native GIP but approximately 5-fold lower than GLP-1 at GLP-1R[13][16]. However, preclinical studies demonstrate that GIPR agonism contributes independently of weight to insulin sensitization, increasing glucose uptake in white adipose tissue and influencing fatty acid metabolism[14][18]. Additionally, GIPR expression in specific brain areas involved in metabolic control suggests that the GIP component contributes to tirzepatide's anorectic effects[13][16].

Dual GLP-1/Glucagon Agonists

Pemvidutide (ALT-801) adopts a distinct pharmacological strategy, combining GLP-1 receptor agonism with glucagon receptor agonism[19][20][21]. Unlike pure GLP-1 agonists, which promote weight loss primarily through appetite reduction and gastric emptying delay, the addition of the glucagon component provides complementary mechanisms that act directly on hepatic metabolism[19][20].

Glucagon stimulates fatty acid oxidation and inhibits de novo lipogenesis in the liver, reducing hepatic fat content more effectively than GLP-1 agonists alone[19]. This characteristic is particularly relevant for patients with obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH)[19][20]. Additionally, glucagon increases energy expenditure and promotes thermogenesis, potentially contributing to greater fat loss relative to lean mass[22][23][19].

Pemvidutide is designed as a balanced 1:1 agonist of the GLP-1 and glucagon receptors, distinguishing itself from other dual agonists in development that exhibit different activity ratios[19][20]. Preclinical studies have demonstrated significant effects on LDL cholesterol reduction (-26-28%), triglycerides (-38%), and pro-atherogenic lipid species, suggesting a favorable cardiovascular profile[22][20].

Clinical Efficacy: Results from Major Trials

Semaglutide (Wegovy) - STEP and SELECT Trials

The clinical development program for semaglutide in obesity includes the **STEP (Semaglutide Treatment Effect in People with obesity)** trial series, which enrolled over 5,000 participants in phase 3 studies[24][25][26][27].

In the pivotal **STEP 1 trial**, a randomized, double-blind, placebo-controlled study, 1,961 adults with obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with at least one weight-related comorbidity were treated with semaglutide 2.4 mg subcutaneously weekly for 68 weeks[24][25][27]. Results demonstrated a mean body weight reduction of **15.0%** in the semaglutide group compared to 2.4% in the placebo group (treatment difference -12.6%; $p<0.001$)[24][25][27]. Additionally, 86.6% of participants treated with semaglutide achieved weight loss ≥5%, 69.1% achieved ≥10%, and 50.5% achieved ≥15%[25][27].

Subgroup analysis revealed that women lost more weight on average than men (treatment difference vs. placebo: -11.1% vs -7.5%), while Asian patients showed slightly lower but still clinically significant weight loss (-7.3% vs. placebo)[24]. Importantly, patients with higher baseline BMI showed greater absolute percentage weight loss, although the relative percentage was lower[24].

The **SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity)** trial provided crucial evidence on the cardiovascular benefits of semaglutide[24][28][29][30]. This cardiovascular outcomes study enrolled 17,604 patients with overweight or obesity and pre-existing cardiovascular disease but without diabetes, followed for a mean of 40 months[30]. Semaglutide reduced the risk of major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) by 20% compared to placebo (6.5% vs 8.0%; HR 0.80, 95% CI 0.72-0.90; $p<0.001$)[24][30].

Long-term analysis of SELECT at 208 weeks demonstrated that weight loss with semaglutide was sustained for 4 years, with a mean body weight reduction of -10.2% compared to -1.5% with placebo[24]. In the "on-treatment" analysis (excluding patients who discontinued treatment), weight loss reached -11.7%[24].

Tirzepatide (Zepbound) - SURMOUNT Trials

The **SURMOUNT** program represents the clinical development of tirzepatide for obesity, with phase 3 trials enrolling over 5,000 participants[31][32][33][34][35][36][37][38][39][40][41][42][43][44].

In the pivotal **SURMOUNT-1** trial, a double-blind, randomized, placebo-controlled study, 2,539 adults with obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with weight-related comorbidities (excluding diabetes) were randomized to receive tirzepatide 5 mg, 10 mg, 15 mg, or placebo weekly for 72 weeks[33][44][45]. The results were remarkable: mean body weight reduction was 15.0%,

19.5%, and 20.9% in the groups treated with 5 mg, 10 mg, and 15 mg respectively, compared to 3.1% with placebo (all p<0.001)[33][44][45].

89% of patients treated with tirzepatide 15 mg achieved weight loss ≥5%, 73% achieved ≥10%, 57% achieved ≥15%, and 40% achieved ≥20% weight loss[33][44]. These results significantly exceed those observed with selective GLP-1 agonists[32][34][46].

In **SURMOUNT-2**, which enrolled 938 adults with obesity or overweight and type 2 diabetes, tirzepatide demonstrated mean body weight reductions of 12.8% (10 mg) and 14.7% (15 mg) compared to 3.3% with placebo at 72 weeks[33][23]. Although weight loss was lower than in SURMOUNT-1, likely due to greater metabolic resistance associated with diabetes, the results remain clinically significant[33].

The **SURMOUNT-4** trial evaluated weight loss maintenance[47][48]. After an initial 36-week open-label treatment period with tirzepatide, which produced a mean weight loss of 20.9%, patients were randomized to continue tirzepatide or switch to placebo for another 52 weeks[47][48]. The group that continued tirzepatide lost additional weight (-5.5%), while the placebo group regained weight (+14%), demonstrating the need for continuous treatment to maintain benefits[47][48].

Meta-analyses and network meta-analyses have confirmed tirzepatide's superiority over GLP-1 agonists[32][34][36][37][38][46]. A meta-analysis of 6 RCTs with 6,266 participants showed that tirzepatide produces significantly greater weight reductions compared to placebo and GLP-1 agonists, with a clear dose-dependent profile[34]. Direct comparisons with semaglutide demonstrated that tirzepatide produces an average additional weight loss of 4-6 kg[46].

Liraglutide (Saxenda) - SCALE Trials

The **SCALE (Satiety and Clinical Adiposity−Liraglutide Evidence)** program evaluated liraglutide 3.0 mg for weight management[10][11][12].

In the **SCALE Obesity and Prediabetes** trial, 3,731 adults with obesity or overweight were randomized to liraglutide 3.0 mg daily or placebo for 56 weeks[10][12]. Mean body weight reduction was 8.0% with liraglutide compared to 2.6% with placebo (difference -5.4%; p<0.001)[10][12]. 63.2% of patients treated with liraglutide achieved weight loss ≥5%, 33.1% achieved ≥10%, and approximately 15% achieved ≥15%[10][12].

In the **SCALE Diabetes** trial, which enrolled 635 adults with type 2 diabetes and obesity or overweight, mean weight reduction was 6.0% with liraglutide compared to 2.0% with placebo[10]. As observed with other drugs, the presence of type 2 diabetes reduces weight loss efficacy, likely due to alterations in incretin sensitivity[10].

Although liraglutide's efficacy is lower than semaglutide and tirzepatide, the drug has demonstrated sustained benefits over time and a well-established safety profile, having been the first GLP-1 agonist approved for obesity in 2014[10][11][12].

Pemvidutide (ALT-801) - MOMENTUM and IMPACT Trials

Pemvidutide is currently in advanced clinical development, with promising results from phase 2 studies[49][50][51][22][52][23][53][54][55][56][57][58].

In the phase 2 **MOMENTUM** trial, a randomized, double-blind, placebo-controlled study conducted over 48 weeks, adults with obesity or overweight were treated with pemvidutide 1.2 mg, 1.8 mg, 2.4 mg, or placebo weekly[22][23][54]. Results at 48 weeks showed mean body weight reductions of 10.3%, 11.2%, and 15.6% in the 1.2 mg, 1.8 mg, and 2.4 mg groups respectively, compared to 2.2% with placebo (all p<0.001)[22][23][54]. Importantly, 78.1% of total weight loss was from fat mass loss, suggesting better lean mass preservation compared to other anti-obesity incretin-based drugs[22][23].

The phase 2b **IMPACT** trial evaluated pemvidutide in patients with metabolic steatohepatitis (MASH) and fibrosis[52][56][57][58]. This study enrolled 212 participants with biopsy-confirmed MASH and stage F2/F3 fibrosis[52][56][57]. At 24 weeks, pemvidutide achieved the primary endpoint of MASH resolution without worsening of fibrosis in 59.1% (1.2 mg) and 52.1% (1.8 mg) of participants compared to 19.1% with placebo (p<0.0001 for both doses)[52][56][57][58].

Additionally, pemvidutide significantly reduced hepatic fat content by 46.6%, 68.5%, and 57.1% at doses of 1.2 mg, 1.8 mg, and 2.4 mg respectively, compared to 4.4% with placebo in a phase 2 study of MASLD[19]. Body weight reduction at 24 weeks in IMPACT was 5.0% (1.2 mg) and 6.2% (1.8 mg) compared to 1.0% with placebo, with no evidence of plateau, suggesting that greater losses could be achieved with longer treatment[52][56][57][58].

A notable aspect of pemvidutide is its superior tolerability profile, with less than 1% of participants discontinuing treatment due to adverse events in the MOMENTUM and IMPACT trials, compared to discontinuation rates of 4-7% with semaglutide and tirzepatide[22][52][56][57][58].

Comparative Analysis of Efficacy Endpoints

Mean Weight Loss

The primary endpoint in obesity trials is typically the percentage change in body weight from baseline. Based on results from major trials:

- **Tirzepatide 15 mg**: 20.9% weight reduction at 72 weeks (SURMOUNT-1)[33][44]
- **Pemvidutide 2.4 mg**: 15.6% weight reduction at 48 weeks (MOMENTUM)[22][23]
- **Semaglutide 2.4 mg**: 15.0% weight reduction at 68 weeks (STEP 1)[24][25][27]
- **Liraglutide 3.0 mg**: 8.0% weight reduction at 56 weeks (SCALE)[10][12]

Tirzepatide clearly emerges as the most effective currently approved drug, with weight loss 30-40% greater than semaglutide[32][34][46]. Pemvidutide, although still in development, shows efficacy comparable to semaglutide at 48 weeks, with the potential for even better results with longer treatment, given that no plateau was observed in the weight loss curve[22][23][54].

Percentage of Patients Achieving Clinically Significant Weight Loss

Standardized secondary endpoints include the percentage of patients achieving weight losses of ≥5%, ≥10%, ≥15%, and ≥20%, thresholds associated with progressive metabolic and cardiovascular benefits[24][33][44][12].

Weight loss ≥5%:

- Tirzepatide 15 mg: 89-91%[33][44]
- Semaglutide 2.4 mg: 86.6%[24][25][27]
- Liraglutide 3.0 mg: 63.2%[10][12]
- Pemvidutide 2.4 mg: 78.1%[22][23]

Weight loss ≥10%:

- Tirzepatide 15 mg: 73-79%[33][44]
- Semaglutide 2.4 mg: 44-69%[24][25]
- Liraglutide 3.0 mg: 33%[10][12]

Weight loss ≥15%:

- Tirzepatide 15 mg: 40-57%[33][44]
- Semaglutide 2.4 mg: 22.9-40%[24][25]
- Liraglutide 3.0 mg: 10-15%[10][12]

Weight loss ≥20%:

- Tirzepatide 15 mg: 30-40%[33][41][44]
- Semaglutide 2.4 mg: 11%[24]
- Liraglutide 3.0 mg: 4-5%[10]

These data demonstrate a clear efficacy hierarchy: tirzepatide > semaglutide > pemvidutide ≈ semaglutide > liraglutide. However, direct comparison is complex due to differences in study designs, enrolled populations, and treatment durations.

Weight Loss Composition: Fat vs Lean Mass

A critical consideration in evaluating anti-obesity drugs is the composition of weight loss. Preservation of lean mass (muscle and bone) is desirable to maintain metabolic function, mobility, and quality of life[22][23].

Pemvidutide has demonstrated a particularly favorable profile, with 78.1% of total weight loss consisting of fat in the MOMENTUM trial[22][23]. This represents superior lean mass preservation compared to what has been historically reported with diet and exercise programs and greater than publicly reported with other weight loss incretin-based drugs[22].

Tirzepatide has shown superior lean mass preservation compared to pure GLP-1 agonists, likely due to the GIP component that influences adipose tissue metabolism[33][35][39]. However, precise quantitative data on weight loss composition in SURMOUNT trials have not been widely reported in primary publications.

Semaglutide and liraglutide, as pure GLP-1 agonists, tend to produce weight loss with a greater proportion of lean mass, although visceral fat reduction remains significant[24][10].

Visceral Fat and Waist Circumference Reduction

Visceral fat, the intra-abdominal adipose depot, is strongly associated with cardiometabolic risk, insulin resistance, and systemic inflammation[24]. Waist circumference (WC) reduction is a surrogate marker of visceral fat reduction.

In the SELECT trial, semaglutide reduced waist circumference by -7.7 cm compared to -1.3 cm with placebo at 208 weeks[24]. The waist-to-height ratio (WHtR) decreased by -6.9% with semaglutide compared to -1.0% with placebo[24]. Importantly, 43.4% of patients treated with semaglutide achieved WC values below sex- and race-specific thresholds associated with increased cardiometabolic risk[24].

Tirzepatide has demonstrated superior waist circumference reductions, with data from SURMOUNT showing mean reductions of 10-15 cm depending on dose[33][35][38][39].

Pemvidutide significantly reduced visceral adipose tissue measured by magnetic resonance imaging, with significant correlations between non-invasive central adiposity tests and reductions in visceral adipose tissue mass measured by MRI[59].

Metabolic and Cardiometabolic Effects

Beyond weight loss, anti-obesity drugs produce significant metabolic benefits that contribute to cardiovascular risk reduction.

Glycemic control: All drugs under review reduce HbA1c in patients with type 2 diabetes. Tirzepatide has demonstrated HbA1c reductions up to -2.1% from baseline in patients with diabetes[33][35][23], superior to semaglutide (-1.5-1.8%)[24][23] and liraglutide (-1.0-1.3%)[10].

Lipid profile: Semaglutide in the SELECT trial modestly reduced LDL cholesterol and triglycerides[24][29]. Tirzepatide has demonstrated significant reductions in triglycerides, total cholesterol, and LDL-C across several trials[33][35][23]. Pemvidutide has produced particularly impressive reductions: -28% total cholesterol, -26% LDL-C, -38% triglycerides at 12 weeks in the phase 1 trial[22][23][20]. Additionally, pemvidutide significantly reduced pro-atherogenic lipids such as lysophosphatidylcholines, sphingomyelins, and ceramides[20].

Blood pressure: All drugs have demonstrated reductions in systolic and diastolic blood pressure, with tirzepatide and pemvidutide showing particularly marked reductions[24][33][22][52].

Cardiovascular outcomes: The SELECT trial provided definitive evidence that semaglutide reduces major cardiovascular events by 20% in patients with obesity and pre-existing cardiovascular disease[24][28][29][30]. Tirzepatide is currently being evaluated in the SURMOUNT-MMO cardiovascular outcomes trial, with results expected in coming years[33]. For pemvidutide, integrated cardiac data analyses have shown systolic and diastolic blood pressure reductions without clinically relevant effects on QTc or heart rate, and no imbalance in cardiac adverse events[59].

Safety and Tolerability Profiles

Gastrointestinal Adverse Events

Gastrointestinal adverse events (nausea, vomiting, diarrhea, constipation) represent the most common category of side effects of incretin agonists, derived primarily from gastric emptying delay and effects on the gastrointestinal tract[24][33][35][38][39][10][12].

Semaglutide: In STEP trials, nausea was reported in 20-30% of patients treated with semaglutide 2.4 mg, vomiting in 9-13%, and diarrhea in 30%[24]. Most events were of mild-to-moderate severity and occurred predominantly during the dose titration phase[24].

Tirzepatide: In SURMOUNT trials, gastrointestinal events were more frequent: nausea in 25-35%, vomiting in 10-15%, diarrhea in 20-25% of patients[33][35][38][39][40]. However, a post-hoc analysis demonstrated that weight loss with tirzepatide was significant even in patients who did not report nausea, vomiting, or diarrhea, suggesting that metabolic effects do not depend exclusively on gastrointestinal side effects[40].

Liraglutide: Gastrointestinal events with liraglutide 3.0 mg are similar to semaglutide, with nausea in 25-40% and vomiting in 10-15% of patients[10][12].

Pemvidutide: A distinctive aspect of pemvidutide is its superior tolerability. In the MOMENTUM trial, gastrointestinal adverse events were significantly less frequent compared to historical comparators[22][52][54]. In the IMPACT trial, less than 1% of participants treated with pemvidutide discontinued treatment due to adverse events, compared to 9% total discontinuations (for any reason)[52]

[56][57][58]. This superior tolerability profile has been attributed to the balanced GLP-1/glucagon mechanism, which may mitigate some of the gastrointestinal effects associated with pure GLP-1 agonists[22][19].

Treatment Discontinuation Rates

Treatment discontinuation rates due to adverse events provide an indicator of real-world tolerability:

- **Pemvidutide:** <1% (IMPACT)[52][56][57][58]
- **Semaglutide:** 4-7% (STEP)[24]
- **Tirzepatide:** 4.6-6% (SURMOUNT)[33][35]
- **Liraglutide:** 6-9% (SCALE)[10][12]

Serious Adverse Events

Pancreatitis: Acute pancreatitis is a rare but serious adverse event associated with GLP-1 agonists. Incidence is low (<0.5%) and similar across drugs, without statistically significant differences compared to placebo in most trials[24][33][35][42][10].

Gallbladder disease: Rapid weight loss increases the risk of cholelithiasis. In trials, the incidence of gallbladder events was higher with active drugs compared to placebo (1.5-2.5% vs 0.7-1.0%)[24][33][10][12].

Hypoglycemia: The risk of hypoglycemia is low in patients without diabetes and not treated with insulin secretagogues or insulin, given the glucose-dependent mechanism of incretins[24][33][35][10].

Serious cardiovascular events: No negative cardiovascular safety signals have been observed. On the contrary, semaglutide demonstrated cardiovascular benefits in the SELECT trial[24][28][29][30].

Approved Indications and Regulatory Status

Approved Drugs

Semaglutide (Wegovy) was approved by the FDA in June 2021 for chronic weight management in adults with obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with at least one weight-related comorbidity[24][25][27]. It is indicated as adjunctive therapy to a reduced-calorie diet and increased physical activity. Approval was extended in 2020 to adolescents aged ≥12 years with obesity[10][27]. The European Medicines Agency (EMA) approved Wegovy in 2021[27].

Tirzepatide (Zepbound) received FDA approval for chronic weight management in obesity in November 2023[60][45]. Indications are similar to those of semaglutide: adults with BMI ≥30 kg/m² or BMI ≥27 kg/m² with weight-related comorbidities[60][45]. In January 2025, the FDA approved Zepbound as the first drug for moderate-to-severe obstructive sleep apnea in patients with obesity, based on results from the SURMOUNT-OSA trials demonstrating reductions in apnea-hypopnea events of 25-29 per hour and remission of apnea in 42-50% of patients[61].

Liraglutide (Saxenda) was the first GLP-1 agonist approved for obesity by the FDA in December 2014[10][11][12]. Indications include adults with obesity or overweight with comorbidities. In 2020, approval was extended to adolescents aged ≥12 years with obesity[10][11][12].

Drugs in Development

Pemvidutide (ALT-801) is currently in phase 2b clinical development for multiple indications[22][52][53][54][55][56][57][58][62][63]:

- **MASH (Metabolic Steatohepatitis):** The IMPACT phase 2b trial in 212 patients with biopsy-confirmed MASH achieved the primary endpoint at 24 weeks[52][56][57][58]. Altimmune has announced that 48-week data will be presented in the fourth quarter of 2025[62][63]. The FDA has granted Fast Track designation to pemvidutide for MASH treatment[53][54][55].
- **Obesity:** The MOMENTUM phase 2 trial over 48 weeks was successfully completed[22][23][54][55].
- **Alcohol Use Disorder (AUD):** Altimmune has completed enrollment in the RECLAIM phase 2 trial, ahead of schedule, with results expected in 2026[53][62][63]. The FDA has granted Fast Track designation for pemvidutide in AUD treatment[53][62].
- **Alcohol-Associated Liver Disease (ALD):** The RESTORE phase 2 trial was initiated in the third quarter of 2025[53][62][63].

Altimmune has scheduled an end-of-phase 2 meeting with the FDA for the fourth quarter of 2025 to discuss the phase 3 trial design for MASH[62][63]. The company plans to advance rapidly to phase 3 in 2026[62].

Viking Therapeutics VK2735 is another dual GIP/GLP-1 agonist in advanced development[64][65][66][67][68][69][70][71][72]. In 2024, Viking announced positive results from the phase 2 VENTURE trial, with weight losses up to 14.7% after 13 weeks of weekly subcutaneous treatment[64][68][69]. Viking initiated the phase 3 VANQUISH program in June 2025, bypassing phase 2b after discussions with the FDA[69][71][72][73].

The VANQUISH program includes two trials:

- **VANQUISH-1:** approximately 4,650 adults with obesity or overweight, with enrollment completion announced in November 2025, ahead of schedule[64][69][72][73].
- **VANQUISH-2:** adults with obesity or overweight and type 2 diabetes, with enrollment completion expected in the first quarter 2026[64][69][72][73].

Both trials evaluate subcutaneous VK2735 weekly at doses of 7.5 mg, 12.5 mg, 17.5 mg vs placebo for 78 weeks[64][69][72][73]. Viking is also developing an oral formulation of VK2735, with a phase 2 trial ongoing[66][67][68][69].

Clinical Implications and Practice Considerations

Drug Selection

The choice of appropriate anti-obesity drug should consider multiple factors:

Required efficacy: For patients requiring more aggressive weight loss (e.g., very high BMI, severe metabolic complications), tirzepatide represents the most effective currently available option[32][33][34][46][44]. Semaglutide offers intermediate efficacy with a well-established safety profile and robust cardiovascular data[24][25][27][28][30]. Liraglutide, although less effective, may be appropriate for patients with more modest weight loss goals or who prefer daily treatment[10][12].

Tolerability: Patients with a history of gastrointestinal intolerance or high sensitivity may benefit from pemvidutide, when available, given its superior tolerability profile[22][52][56][57][58]. Gradual dose titration is essential with all incretin agonists to minimize gastrointestinal events[24][33][10].

Comorbidities: For patients with pre-existing cardiovascular disease, semaglutide has demonstrated cardiovascular benefits in the SELECT trial[24][28][29][30]. For patients with MASH or MASLD, pemvidutide has shown particularly promising results in liver fat reduction and hepatic inflammation resolution[52][56][57][58][19].

Cost and access: Currently, high costs and limitations in access represent significant barriers. The future availability of biosimilar formulations may improve accessibility[74][75].

Treatment Duration

Data from the SURMOUNT-4 and SELECT trials clearly demonstrate that treatment discontinuation leads to weight regain[47][48]. Therefore, obesity should be conceptualized as a chronic condition requiring long-term therapy, analogous to hypertension or diabetes[75][76]. Patients must be informed about the need for continuous treatment to maintain weight loss benefits[47][48].

Lifestyle Interventions

All trials combined pharmacotherapy with lifestyle interventions (reduced-calorie diet, increased physical activity)[24][33][10][12]. Although drugs produce significant weight loss, the adoption of healthy eating and physical activity habits remains fundamental for optimizing results and improving overall metabolic health[24][33][10][12].

Monitoring and Adverse Event Management

Patients should be informed about potential gastrointestinal adverse events and their management[24][33][10]. Healthcare professionals should monitor for signs of pancreatitis (persistent severe abdominal pain), gallbladder disease, and, in patients with diabetes, hypoglycemia[24][33][10][45]. Regular monitoring of weight, blood pressure, glucose, and lipid profile is recommended[24][33][10].

Future Perspectives and Emerging Developments

The obesity pharmacotherapy landscape is rapidly evolving, with numerous agents in development promising to further expand therapeutic options[77][23][78][76].

Triagonists: Molecules like retatrutide, which simultaneously activate GLP-1, GIP, and glucagon receptors, have demonstrated in phase 2 studies even greater weight losses than tirzepatide (up to 24% at 48 weeks)[79][23]. These agents represent the frontier of rational polypharmacology in obesity[78][76].

Oral formulations: Oral semaglutide is already approved for type 2 diabetes, and high-dose formulations are in development for obesity[23]. Viking Therapeutics is developing an oral formulation of VK2735[66][67][68][69]. Oral formulations could improve adherence and acceptability for some patients[66][67].

Maintenance regimens: Viking is exploring monthly dosing regimens after achieving target weight loss, potentially improving long-term convenience and adherence[68][69][71].

Therapeutic combinations: Combining incretin agonists with other metabolic agents (e.g., thyroid receptor beta agonists like VK2809, SGLT2 inhibitors) could produce synergistic benefits[80][81].

Personalized approaches: Inter-individual variability in response to anti-obesity drugs suggests the need for precision medicine strategies[75][41]. Predictive biomarkers of response could guide optimal drug selection for each patient[41].

Conclusions

Incretin agonist drugs represent a transformative advancement in obesity treatment, offering clinically significant and sustained weight loss with associated metabolic and cardiovascular benefits. Based on current evidence:

Tirzepatide is confirmed as the most effective currently approved anti-obesity drug, with mean weight losses of 15-21% at 72 weeks and with 40-57% of patients achieving losses ≥15%[31][32][33][34][35][36][37][44]. Its dual GIP/GLP-1 mechanism of action confers superior metabolic advantages compared to pure GLP-1 agonists, with better lean mass preservation and greater visceral fat reductions[33][39][13][15][18][16].

Semaglutide offers robust efficacy (mean loss of 15-16% at 68 weeks) with the unique advantage of definitive cardiovascular outcome data from the SELECT trial, demonstrating a 20% reduction in major cardiovascular events[24][25][27][28][29][30]. It represents an excellent choice for patients with obesity and pre-existing cardiovascular disease[24][28][30].

Liraglutide, although less effective (mean loss of 8% at 56 weeks), maintains a role in obesity treatment thanks to its well-established safety profile and decade of clinical experience[10][11][12]. It may be appropriate for patients with more modest weight loss goals or as an initial step in obesity pharmacotherapy[10][12].

Pemvidutide emerges as a promising agent in advanced development, with efficacy comparable to semaglutide (15.6% weight loss at 48 weeks) but with a superior tolerability profile, characterized by discontinuation rates <1% and exceptional lean mass preservation (78% of weight loss from fat)[22][52][23][56][57][58]. Its dual GLP-1/glucagon mechanism confers unique benefits on liver fat reduction and lipid metabolism, potentially positioning it as a treatment of choice for patients with obesity and MASH[52][56][57][58][19].

All drugs require long-term treatment to maintain weight loss, underscoring the need to conceptualize obesity as a chronic condition requiring continuous management[47][48][76]. Integration of pharmacotherapy with lifestyle interventions remains fundamental for optimizing results[24][33][10][12].

The next generation of anti-obesity drugs, including triagonists and oral formulations, promises to further expand therapeutic options and potentially achieve even greater weight losses[79][23][78][76]. However, challenges related to cost, access, and long-term adherence remain significant obstacles that must be addressed to maximize the public health impact of these transformative agents[74][75][76].

Appendix: Regulatory Updates Altimmune and Viking (November 2025)

Altimmune (Ticker: ALT) - Pemvidutide Status

End-of-Phase 2 Meeting with FDA:
Contrary to initial speculation, **the End-of-Phase 2 meeting between Altimmune and the FDA has NOT yet occurred as of November 25, 2025**. The meeting is scheduled for **fourth quarter 2025** (by December 2025), but according to the most recent official communications it has not yet taken place[62][63][82].

Primary SEC sources:

- Altimmune 8-K filing dated November 5, 2025: https://www.sec.gov/Archives/edgar/data/1326190/000132619025000031/
- Q3 2025 Press Release: https://www.globenewswire.com/news-release/2025/11/06/3182413/0/en/Altimmune-Announces-Third-Quarter-2025-Financial-Results-and-Business-Updates.html

IMPACT 48-week data:
Altimmune has announced that **48-week data from the IMPACT Phase 2b trial** will be released **by the end of 2025** (Q4)[62][63][82]. The 24-week data, published in November 2025, demonstrated:

- MASH resolution without worsening of fibrosis: 59.1% (1.2mg) and 52.1% (1.8mg) vs 19.1% placebo ($p<0.0001$)[52][56][57][58]
- Liver fat reduction: 68.5% (1.8mg dose)[52][58]
- Weight loss at 24 weeks: 6.2% (1.8mg) with no plateau[52][58]
- Exceptional tolerability: <1% discontinuations due to adverse events[52][58]

Phase 3 Timeline:
After the FDA meeting (Q4 2025), Altimmune intends to finalize the phase 3 trial design for MASH and initiate the study in **2026**[62][63]. Phase 3 will use traditional endpoints (liver biopsy) and potentially new non-invasive imaging and AI-pathology endpoints, in line with new FDA guidance[62][63].

Other Indications in Development:

- **RECLAIM trial (Alcohol Use Disorder):** enrollment completed ahead of schedule, results expected 2026; FDA Fast Track designation granted[53][62][63]
- **RESTORE trial (Alcohol-associated Liver Disease):** initiated Q3 2025[62][63]

Financial position:
As of September 30, 2025, Altimmune had $211.3 million in cash, equivalents, and marketable securities, sufficient to fund operations through **fourth quarter 2027**[62][63][82].

Viking Therapeutics (Ticker: VKTX) - VK2735 Status

VANQUISH-1 Enrollment Completion:
Viking announced on **November 19, 2025** the completion of enrollment in the Phase 3 **VANQUISH-1** trial, ahead of schedule[64][69][72][73][83].

Primary source:

- Press Release dated November 18, 2025: https://www.prnewswire.com/news-releases/viking-therapeutics-announces-completion-of-enrollment-in-phase-3-vanquish-1-trial-of-vk2735-in-adults-with-obesity-or-overweight-302088664.html
- Viking IR: https://ir.vikingtherapeutics.com/news-releases

VANQUISH-1 Details:

- **Population:** ~4,650 adults with obesity (BMI ≥30) or overweight (BMI ≥27) with comorbidities
- **Design:** randomized, double-blind, placebo-controlled
- **Doses:** VK2735 subcutaneous weekly at 7.5 mg, 12.5 mg, 17.5 mg vs placebo
- **Duration:** 78 weeks of treatment
- **Primary endpoint:** percentage change in body weight from baseline at 78 weeks
- **Expected results:** second half of 2026[64][69][72][73][83]

VANQUISH-2 (Obesity + Type 2 Diabetes):
The second Phase 3 trial, **VANQUISH-2**, had completed approximately 95% of enrollment as of November 2025, with completion expected in **first quarter 2026**[64][69][72][73][83]. Design similar to VANQUISH-1 but with a type 2 diabetes population.

Oral VK2735 Formulation:
Viking is developing in parallel an **oral once-daily formulation** of VK2735, currently in a Phase 2 trial. Preliminary results have shown weight losses up to **12.1%** after 28 days of treatment at the highest dose tested[66][67][68][69]. A larger Phase 2 trial (VENTURE-Oral) is ongoing with results expected in 2025-2026[69][83].

Regulatory Strategy:
Viking obtained FDA alignment to bypass additional phase 2b studies and proceed directly to Phase 3 after positive results from the phase 2 VENTURE trial[69][71][72]. The strategy includes:

1. Complete VANQUISH-1 and VANQUISH-2 (subQ) for obesity approval
2. Develop oral formulation in parallel
3. Explore monthly maintenance regimens post-target weight loss[68][69][71]

Estimated Approval Timeline:
Based on enrollment completion in November 2025 and 78-week trial duration, **topline results from VANQUISH-1 are expected in the second half of 2026**. Assuming positive results, NDA submission could occur in **2027**, with potential FDA approval in **2028**[64][69][72][83].

Competitive Position:
VK2735, as a dual GIP/GLP-1 agonist, competes directly with tirzepatide (Zepbound) but with potential advantages:

- Oral formulation in development (vs injectable-only tirzepatide)
- Possibility of monthly maintenance regimens
- Proprietary IP profile
  However, it arrives on the market 4-5 years after tirzepatide, requiring demonstration of superiority or significant differentiation to gain market share[64][69][71].

Regulatory Timeline Comparison: Altimmune vs Viking

Parameter	Altimmune (Pemvidutide)	Viking (VK2735)
Current phase	Phase 2b completed	Phase 3 ongoing
Next milestone	FDA meeting Q4 2025	VANQUISH-1 data H2 2026
Phase 3 start	2026 (estimated)	Already initiated (2025)
Possible NDA filing	2028-2029	2027
Possible approval	2029-2030	2028

Implications for Investors:

- **Viking** is further along in development and could reach the market 1-2 years earlier than Altimmune
- **Altimmune** has demonstrated significant differentiation (superior tolerability, lean mass preservation, MASH efficacy) that could justify a distinct competitive profile
- Both companies face clinical execution risk (Phase 3 failure) and intense competition (Eli Lilly, Novo Nordisk dominate the market with tirzepatide and semaglutide)

SEC and Regulatory Sources:

- Altimmune SEC filings: https://www.sec.gov/cgi-bin/browse-edgar?action=getcompany&CIK=0001326190
- Viking SEC filings: https://www.sec.gov/cgi-bin/browse-edgar?action=getcompany&CIK=0001174940
- FDA Drug Approvals: https://www.fda.gov/drugs/development-approval-process-drugs
- ClinicalTrials.gov: https://clinicaltrials.gov/

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