Favorable and unfavorable findings on Retatrutide

25 October 2026

Clinical trials of retatrutide (LY3437943), a GIP/GLP-1/glucagon triple receptor agonist, report substantial mean weight loss (18-25% at 80 weeks in phase 3 TRIUMPH studies), glycemic improvements, cardiometabolic benefits, and gains in knee osteoarthritis pain and obstructive sleep apnea. However, dose-dependent gastrointestinal adverse events, dysesthesia, increased heart rate, and higher discontinuation rates are consistently reported alongside inconclusive cardiovascular outcomes and data gaps on long-term safety.

Retatrutide is provided by Rierink Compounds exclusively for laboratory research. Retatrutide is a synthetic unimolecular peptide designed as a balanced agonist of the glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon receptors. Materials on this site are for laboratory research only and are not medicines. Reporting findings from human trials does not constitute guidance to administer the research material to people or animals.

Favorable Reported Findings

A 2023 phase 2 randomised, double-blind, placebo-controlled trial (Jastreboff et al., *New England Journal of Medicine*, PMID 37366315) in adults with obesity without diabetes demonstrated dose-dependent weight reduction reaching a least-squares mean of -24.2% at the 12 mg dose at 48 weeks versus -2.1% with placebo. Categorical responses were high, with 83% of the 12 mg group achieving at least 15% weight loss. Improvements in cardiometabolic markers, including blood pressure, lipids, and insulin sensitivity, were also observed. A phase 2a substudy in participants with metabolic dysfunction-associated steatotic liver disease (Sanyal et al., *Nature Medicine*, 2024, PMID 38858523) reported relative liver fat reductions of up to -82.4% at 24 weeks with the 12 mg dose versus +0.3% with placebo, with 86% achieving normal liver fat levels (<5%).

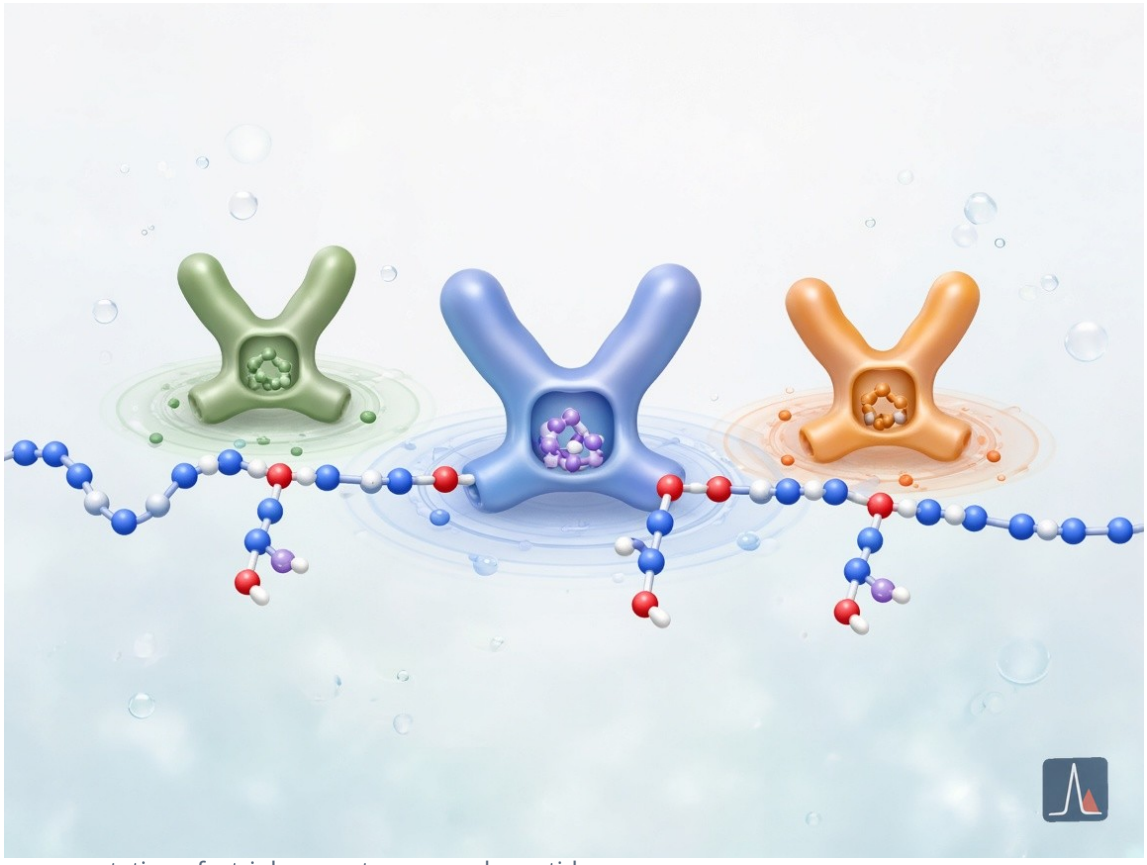
Phase 3 TRIUMPH programme results published in 2026 confirm and extend these findings. In TRIUMPH-1 (Jastreboff et al., *New England Journal of Medicine*, 2026, DOI 10.1056/NEJMoa2604169, PMID 42814954; n=2339 adults with obesity or overweight plus weight-related conditions, no diabetes), the 12 mg dose produced a mean weight change of -25.0% (treatment-regimen estimand) or -28.3% (efficacy estimand) at 80 weeks versus approximately -4% and -2% with placebo. Substantial proportions achieved □ 25%or □ 30% weight loss. Benefits extended to participants with knee osteoarthritis (significant WOMAC pain score reductions) and obstructive sleep apnea (clinically meaningful reductions in apnea-hypopnea index). TRIUMPH-2 (*The Lancet*, 2026) in adults with obesity and type 2 diabetes showed weight loss of approximately 18.8% at 12 mg alongside HbA1c reductions of up to 1.6 percentage points from a baseline of 7.7%. TRIUMPH-3 and TRIUMPH-4 readouts reinforced cardiometabolic improvements, including reductions in triglycerides (up to ~39%), non-HDL cholesterol, systolic blood pressure (~9-11 mmHg), waist circumference, and high-sensitivity C-reactive protein (~51%).

Preclinical and mechanistic studies support these outcomes. In vitro and structural studies (e.g.,

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cryo-EM analyses, *Cell Discovery*, 2024, PMID 39019866) confirm potent, balanced activation of all three receptors. Animal models of diet-induced obesity have shown increased energy expenditure attributable to the glucagon component, alongside fat-specific loss and metabolic protection. A 2025 systematic review and meta-analysis of randomised controlled trials (Baylor University Medical Center Proceedings, DOI 10.1080/08998280.2025.2456441) pooled data confirming statistically significant reductions in body weight (-14.33%), BMI, waist circumference, fasting glucose, HbA1c (-0.91%), and blood pressure, with no statistically significant increase in overall adverse event rates versus placebo (RR 1.11, p=0.24).

These data make it theoretically plausible that triple agonism could offer advantages over dual incretin agonists through combined effects on satiety, insulin secretion, and energy expenditure, although direct head-to-head long-term comparisons remain limited.



Abstract representation of a triple-receptor research peptide.

Unfavorable Reported Findings

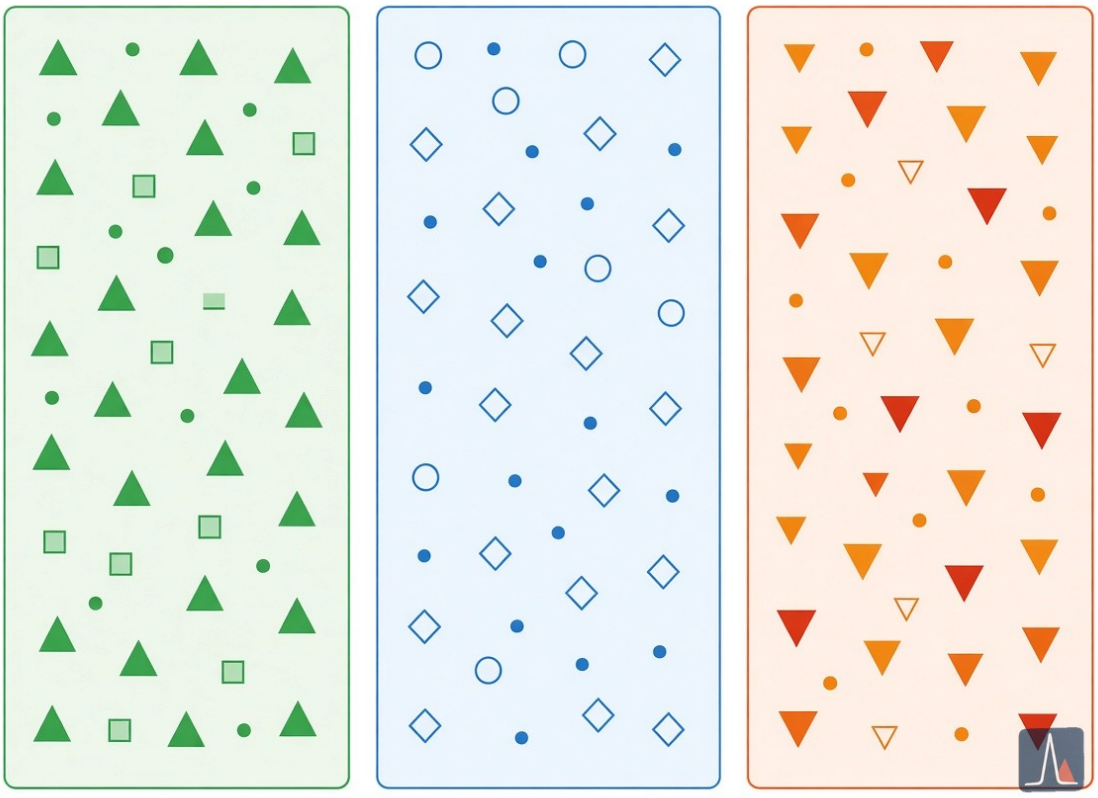
Gastrointestinal adverse events are the most frequently reported across the clinical programme and are dose-dependent. In TRIUMPH-1, nausea occurred in 28.6-42.4% of retatrutide participants (versus 14.8% placebo), diarrhoea in 25.2-34.1% (versus 13.5%), vomiting in up to 25.3% (versus 4.8%), and constipation in ~26% (versus 10.9%). Rates were similar or slightly lower in participants with type 2 diabetes (TRIUMPH-2) but remained substantially elevated versus placebo. Events were generally mild to moderate, peaked during dose escalation, and often attenuated with time; however, they drove higher rates of treatment discontinuation due to adverse events (4.1-11.3% at 4-12 mg versus 4.9% placebo in TRIUMPH-1; up to 18.2% at 12 mg in TRIUMPH-4).

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A distinctive signal is dysesthesia (abnormal skin sensations such as tingling, numbness, or burning), reported in 4.5-12.5% (TRIUMPH-1/2) and up to 20.9% (TRIUMPH-4 12 mg) of participants versus <1% on placebo. This appears dose-related and is thought to be linked to glucagon receptor activity, though events were typically mild and infrequently led to discontinuation.

Phase 2 data documented a transient, dose-dependent increase in resting heart rate that peaked around week 24 (~+9 bpm at 12 mg versus +0.8 bpm placebo) before partial normalisation. Hypotension was also more common in some TRIUMPH trials (up to 6% versus <1%). Class-effect risks observed with other incretin-based therapies, including pancreatitis, gallbladder disease, and dehydration-related acute kidney injury, have been reported at low rates; phase 2 noted a small number of pancreatitis and cholecystitis cases (none in placebo arms, though numbers were small). Meta-analyses published in 2025 noted increased risk of treatment discontinuation due to adverse events (RR ~2.5 in one Bayesian analysis) despite no overall statistically significant increase in adverse events in some pooled analyses.

Real-world reports from unregulated or compounded sources (distinct from pharmaceutical-grade trial material) have described additional or divergent patterns, including fatigue, paradoxical appetite increase, insomnia, and muscle-related complaints, alongside safety concerns such as product contamination or mislabeling. These do not reflect controlled trial conditions.



Separation of favorable, null, and unfavorable reported findings.

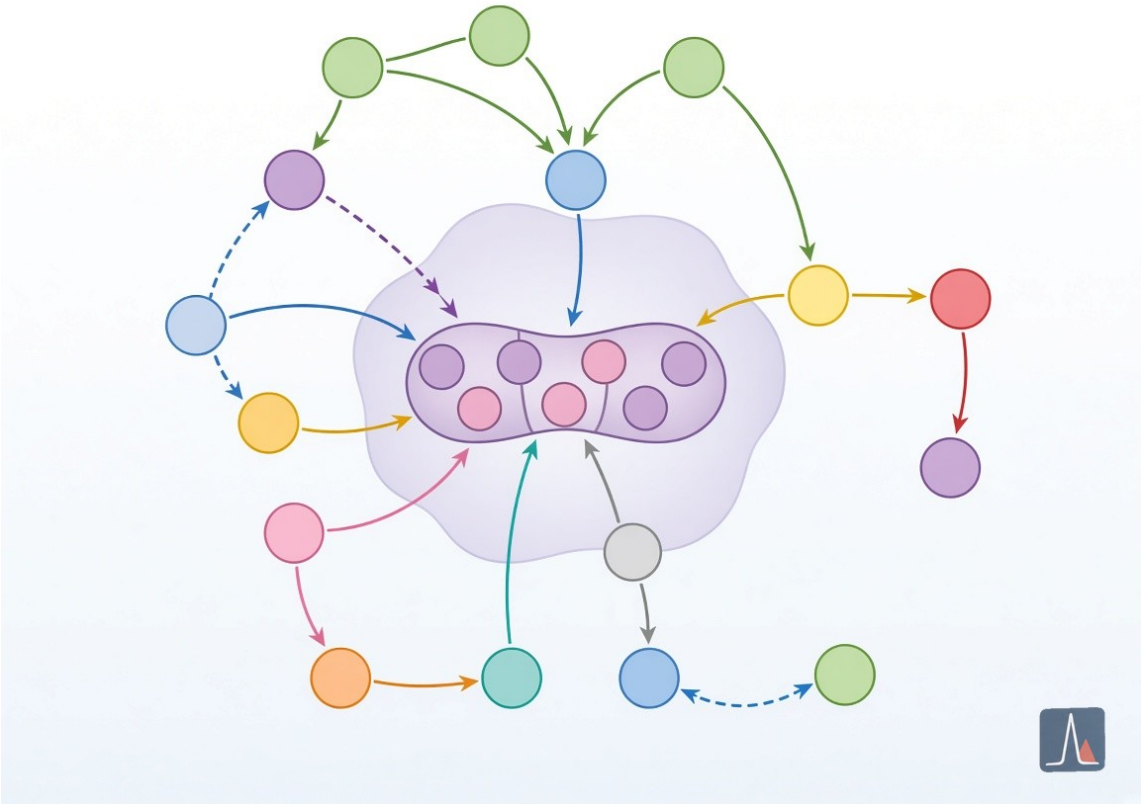
Null, Inconclusive, or Context-Limited Results

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Cardiovascular outcomes in TRIUMPH-3 were inconclusive. The hazard ratio for three-point major adverse cardiovascular events was 1.12 (95% CI 0.64-1.96) and for a broader five-point composite 0.82 (0.55-1.22); event numbers were low and the trial was not powered as a dedicated cardiovascular outcomes trial. Confidence intervals crossed 1.0, precluding firm conclusions of benefit or harm.

Body composition data from phase 2 DXA substudies in participants with type 2 diabetes indicated that fat mass comprised the majority of weight lost (~62-69%), with lean mass loss representing ~31-38%—a proportion broadly similar to other incretin agents. Phase 3 DXA or functional strength data have not been fully detailed in primary publications, leaving the functional impact of lean mass changes during 25%+ weight loss uncertain, particularly in older adults or those without resistance exercise or optimised protein intake.

Weight loss magnitude was attenuated in participants with type 2 diabetes compared with those without diabetes, a pattern seen across the incretin class. Long-term data beyond 80-104 weeks, post-discontinuation weight maintenance, effects on bone health, cancer incidence, and thyroid safety remain limited. No published full head-to-head phase 3 trial versus tirzepatide or semaglutide was available as of October 2026. Meta-analyses have noted heterogeneity, reliance on preliminary data in earlier reviews, and the need for larger, longer trials to characterise rare events and durability.



Conceptual pathway schematic associated with the research compound.

Evidence Context and Recurrent Limitations

The published literature on retatrutide demonstrates clear, dose-dependent efficacy on weight,

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glycemia, and several obesity-related comorbidities that exceeds what has been reported for many prior agents in similar populations. The addition of glucagon receptor agonism appears to contribute to greater energy expenditure and fat utilisation in preclinical systems, potentially explaining aspects of the observed weight loss magnitude. However, the tolerability profile, characterised by prominent gastrointestinal events and the novel dysesthesia signal, results in discontinuation rates that are higher at the top doses than those seen with some approved dual agonists. Real-world use of non-pharmaceutical material introduces additional risks not observed in controlled trials using GMP-grade compound.

Recurrent limitations across the dataset include selected trial populations (often with high BMI and motivated participants), relatively short follow-up for a chronic condition, underpowered assessment of rare or long-latency events, and the absence of mature cardiovascular outcomes data. Systematic reviews emphasise that while efficacy signals are strong, certainty for long-term safety and effectiveness in broader populations is still developing. Future studies, including completed cardiovascular outcomes trials and real-world evidence with approved product (if approved), will be required to refine the benefit-risk profile.

Researchers using retatrutide in laboratory settings should interpret published human data strictly within the context of controlled clinical trial conditions using pharmaceutical-grade material. Findings from animal or in vitro models do not directly translate to human use. Related laboratory research materials in the Rierink catalog include tirzepatide, semaglutide, cagrilintide, mazdutide, and survodutide.



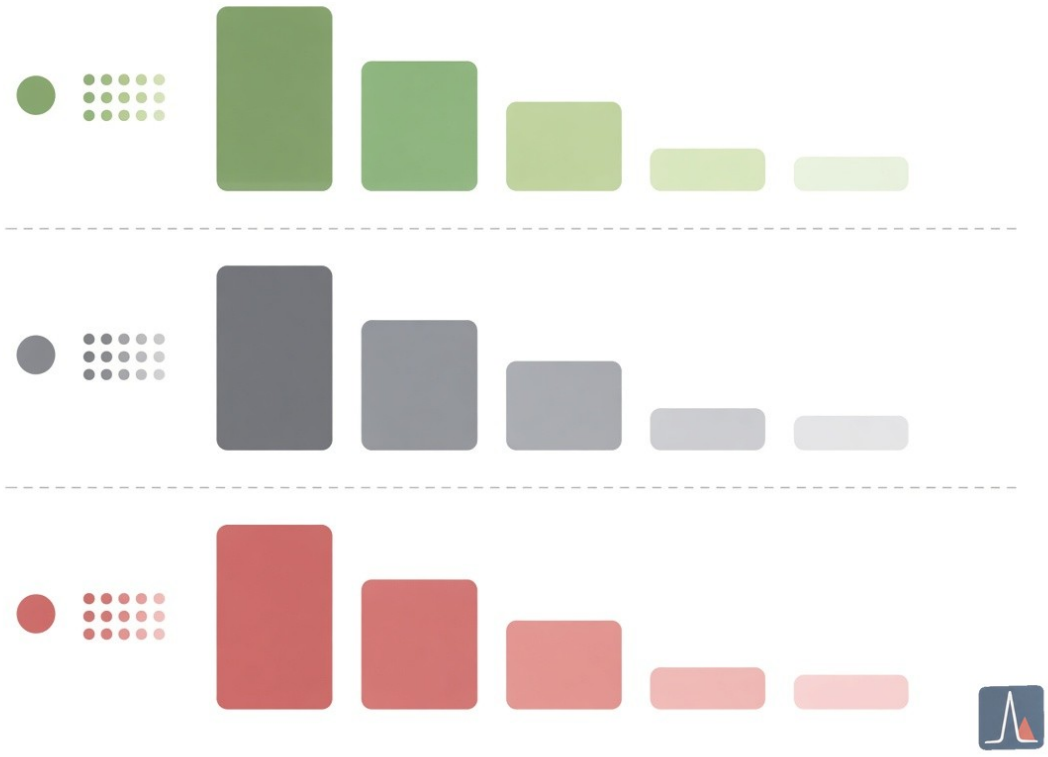
Laboratory instrumentation context for research materials.

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Sources

• Jastreboff AM et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity. *N Engl J Med*. 2023. PMID: 37366315. DOI: 10.1056/NEJMoa2301972 (phase 2).
• Jastreboff AM et al. Retatrutide, a Triple Hormone Receptor Agonist, for Treatment of Obesity. *N Engl J Med*. 2026. DOI: 10.1056/NEJMoa2604169. PMID: 42814954 (TRIUMPH-1).
• Retatrutide in adults with obesity and type 2 diabetes (TRIUMPH-2). *Lancet*. 2026. DOI: 10.1016/S0140-6736(26)01861-1.
• Sanyal AJ et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease. *Nat Med*. 2024. PMID: 38858523.
• 2025 systematic review and meta-analysis. *Baylor University Medical Center Proceedings*. DOI: 10.1080/08998280.2025.2456441.
• Structural insights paper. *Cell Discovery*. 2024. PMID: 39019866.

Additional Lilly press releases, meta-analyses, and safety summaries from 2025–2026 were reviewed for consistency. All claims are tied to indexed publications with DOIs or PMIDs.



Visual balance of favorable, null, and unfavorable outcome categories.

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