Rapporti pubblicati su Tirzepatide

25 ottobre 2026

Gli articoli preclinici e clinici indicizzati descrivono Tirzepatide come agonista duale dei recettori GIP/GLP-1 studiato per letture glicemiche e correlate al peso, distinto dalla letteratura sull'incretina singola, sugli analoghi del GHRH e sui peptidi mitocondriali già

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Corpo:

```markdown Tirzepatide is for laboratory research only. Reporting published human trials is not guidance to use the research material in any specific way.

## Chemical Identity and Catalog Context

Tirzepatide (LY3298176) is a synthetic 39-amino acid linear peptide engineered from the native GIP sequence. It incorporates α-aminoisobutyric acid (Aib) substitutions at positions 2 and 13 for DPP-4 resistance, acylation of Lys20 with a C20 fatty diacid moiety via a γ-glutamic acid and two 8-amino-3,6-dioxaoctanoic acid (AEEA) linker units, and C-terminal amidation. These modifications enable albumin binding that supports once-weekly pharmacokinetics while conferring dual agonism at the glucose-dependent insulinotropic polypeptide receptor (GIPR) and glucagon-like peptide-1 receptor (GLP-1R).

In the Rierink catalog, Tirzepatide sits alongside other incretin-related research materials including Semaglutide, Retatrutide, Cagrilintide, Mazdutide, Survodutide, Liraglutide, and Dulaglutide. It is chemically and mechanistically distinct from GHRH analogs such as Tesamorelin and mitochondrial-derived peptides such as MOTS-c or SS-31.

## Foundational Discovery and In Vitro Dual Receptor Pharmacology Studies (in_vitro and method papers, 2018–2022)

Indexed literature on tirzepatide began with Coskun et al. (2018), who described engineering of the molecule from the GIP backbone to achieve meaningful dual agonism. In HEK293 cells expressing human receptors, tirzepatide displayed potency at the GIPR comparable to native GIP while showing approximately 5- to 13-fold reduced potency at the GLP-1R relative to native GLP-1. It stimulated cAMP accumulation in both receptor systems and enhanced insulin secretion from human islets. 1 2

A pivotal 2020 characterization in JCI Insight established tirzepatide as an *imbalanced and biased* dual agonist. Binding affinity at the GIPR matched native GIP, yet GLP-1R affinity was weaker; at the GLP-1R it exhibited bias toward Gαs-cAMP signaling over β-arrestin recruitment and receptor internalization, potentially contributing to prolonged signaling. Cryo-EM structures (2022) further delineated how the lipid moiety and sequence alterations influence receptor engagement differently at GIPR versus GLP-1R. Subsequent in vitro work in human adipocytes

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and islets confirmed GIPR-mediated effects on nutrient metabolism and glucagon secretion that GLP-1R agonism alone does not fully replicate. 3

These cell-based and structural studies provided the mechanistic rationale for pursuing dual agonism but remain limited to isolated systems that do not capture whole-organism pharmacokinetics or compensatory physiology.

Preclinical Animal Models of Obesity, Insulin Sensitivity, and Organ Protection (animal papers, 2018–2026)

In diet-induced obese (DIO) mice and diabetic db/db models, tirzepatide produced dose-dependent reductions in body weight (primarily fat mass), food intake, and plasma glucose that exceeded those of selective GLP-1R agonists. Receptor knockout studies demonstrated that both GIPR and GLP-1R contribute to acute glucose-lowering, while GIPR agonism mediated weight-independent improvements in insulin sensitivity, partly through enhanced branched-chain amino acid (BCAA) catabolism in brown adipose tissue and modulation of adipocyte lipid handling. 4

Later studies (2021–2026) extended these findings to hepatic steatosis, adipose tissue macrophage inflammation, β-cell preservation, and selected neuroprotective readouts in transgenic models. Tirzepatide reduced liver fat, fibrosis markers, and tumor incidence in certain MASLD/HCC mouse models. Effects on energy expenditure, lipoprotein triglyceride clearance, and neuroinflammation were reported as additive or superior to GLP-1R mono-agonism in some contexts. However, translation from rodent to human metabolism is imperfect; mice require higher doses for comparable GIPR engagement, and some metabolic benefits appear more pronounced in rodents than observed clinically. Null or modest effects on certain lean-mass preservation or long-term energy expenditure parameters have also been noted in selected DIO cohorts. 5

Pivotal Randomised Clinical Trials in Type 2 Diabetes (SURPASS program, clinical trials, 2021–2025)

The SURPASS phase 3 program evaluated tirzepatide (5, 10, or 15 mg once weekly) across the spectrum of type 2 diabetes. In SURPASS-1 (monotherapy), HbA1c reductions reached –2.07% (15 mg) versus +0.04% with placebo at 40 weeks, with 20–68% of participants achieving 10% body-weight loss. Head-to-head trials demonstrated superiority to semaglutide 1 mg (SURPASS-2), titrated basal insulin (SURPASS-3, -4), and insulin lispro (SURPASS-5) for both glycemic control and weight reduction. Normoglycemia (HbA1c <5.7%) was attained by up to 62% of participants on the highest dose in selected studies. 6

Gastrointestinal adverse events (nausea, vomiting, diarrhea) were the most common, generally mild-to-moderate, dose-dependent, and attenuated with titration. Hypoglycemia rates were low when not combined with insulin or sulfonylureas. These trials were industry-sponsored and enrolled predominantly middle-aged adults with established disease; generalizability to broader populations or very long-term use remains constrained.

SURMOUNT Program, Head-to-Head, and Broader Cardiometabolic

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Trials (clinical trials and meta-analysis papers, 2022–2026)

The SURMOUNT trials focused on adults with obesity or overweight with comorbidities. SURMOUNT-1 reported mean weight losses of –15.0%, –19.5%, and –20.9% at 5, 10, and 15 mg versus –3.1% with placebo at 72 weeks; >85% of participants on 10 or 15 mg achieved □ 5% loss. SURMOUNT-5 (2025/2026 publication) provided the first direct comparison with semaglutide 2.4 mg, demonstrating superior weight reduction (–20.2% vs –13.7%) and waist circumference change. Maintenance trials showed substantial regain upon withdrawal, underscoring the need for continued therapy. 7 7

Additional studies reported benefits in obstructive sleep apnea (SURMOUNT-OSA), obesity-related HFpEF (SUMMIT), and liver fat. SURPASS-CVOT (published 2025) established noninferiority of tirzepatide to dulaglutide for 3-point MACE in participants with type 2 diabetes and atherosclerotic cardiovascular disease; post-hoc analyses suggested favorable signals for expanded cardiorenal composites and heart-failure hospitalization. Meta-analyses (2023–2026) consistently rank tirzepatide among the most efficacious agents for weight loss and glycemic improvement, with dose-dependent effects but increased odds of gastrointestinal events (nausea OR ~4–7, vomiting higher). Null or smaller effects on certain lipid subfractions or blood-pressure endpoints have been reported in subgroup analyses. 8 9

Recent Reviews, Meta-Analyses, Regulatory Context, and Recurrent Limitations (review and meta-analysis papers, 2022–2026)

Systematic reviews and network meta-analyses (2023–2026) synthesize superior short-to-medium-term weight loss (11–21% at 15 mg) and HbA1c reduction relative to selective GLP-1R agonists and insulin, with favorable trends in cardiometabolic risk markers. Regulatory approvals followed (Mounjaro for type 2 diabetes in 2022; Zepbound for chronic weight management shortly thereafter in major jurisdictions). Safety syntheses highlight class effects including gastrointestinal intolerance, gallbladder-related events, and a boxed warning for medullary thyroid carcinoma risk based on rodent data. Questions persist regarding long-term durability, impact on skeletal muscle and bone health, nutrient malabsorption, cost-effectiveness, and real-world adherence. Many trials were manufacturer-funded; independent long-term data are still maturing. 10

Evidence Context and Recurrent Limitations

Collectively, indexed records position tirzepatide as the most extensively studied dual GIP/GLP-1 receptor agonist, with robust evidence of superior glycemic and weight outcomes compared with single-incretin agents in head-to-head randomised trials. Preclinical mechanistic work supports complementary roles of GIPR agonism in insulin sensitization and adipocyte function that are not fully recapitulated by GLP-1R agonism alone. Clinical benefits extend to cardiometabolic comorbidities in selected populations.

Recurrent limitations include predominant industry sponsorship, relatively short trial durations for a chronic condition, under-representation of certain demographic groups, reliance on surrogate endpoints in many studies, and the transient nature of gastrointestinal tolerability during dose escalation. Weight regain upon discontinuation is well-documented. No

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independent large-scale confirmatory trials of the exact research-grade material exist, and translation of preclinical receptor bias or adipocyte-specific effects to long-term human outcomes remains theoretical. Future independent studies and extended follow-up will further clarify positioning relative to emerging triple agonists and non-incretin modalities.

Sources - Coskun T et al. (2018). Mol Metab. PMID: 30473097. - Willard FS et al. (2020). JCI Insight. doi:10.1172/jci.insight.140532, PMID: 32730231. - Rosenstock J et al. (2021). Lancet (SURPASS-1). - Jastreboff AM et al. (2022). NEJM (SURMOUNT-1). - Nauck MA et al. (2022). Cardiovasc Diabetol. doi:10.1186/s12933-022-01604-7. - Multiple 2023–2026 meta-analyses in Int J Obes, Expert Opin Drug Discov, and NEJM family journals. - Structural and mechanistic papers (PNAS 2022, Nat Commun 2022, Cell Metab 2024). (Full reference lists available via PubMed/Europe PMC searches for “tirzepatide SURPASS” or “tirzepatide SURMOUNT”.)

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