

RESEARCH MONOGRAPH . COMPOUND PROFILE

Retatrutide

An Eli Lilly investigational triple receptor agonist of GIP, GLP-1, and glucagon receptors with Phase 3 trials in obesity producing 24% weight loss at 48 weeks.

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ABSTRACT

Retatrutide (LY3437943) is an investigational triple agonist of the GIP, GLP-1, and glucagon receptors developed by Eli Lilly and currently in Phase 3 trials for obesity, type 2 diabetes, and metabolic dysfunction-associated steatohepatitis (MASH). The compound builds on the GIP/GLP-1 dual agonist tirzepatide platform by adding glucagon receptor agonism, which contributes additional weight loss through hepatic energy expenditure increases and lipolytic effects. Phase 2 obesity trial results published in 2023 showed approximately 24.2 percent weight loss at 48 weeks at the highest dose, exceeding the magnitude observed with tirzepatide. The compound is not yet FDA approved; Phase 3 program is ongoing. Pharmacokinetics: weekly subcutaneous administration; half-life supports once-weekly dosing. The triple agonist class represents the current frontier of metabolic peptide development.

1. Compound Identification

Retatrutide is described as gip/glp-1/glucagon triple receptor agonist. An Eli Lilly investigational triple receptor agonist of GIP, GLP-1, and glucagon receptors with Phase 3 trials in obesity producing 24% weight loss at 48 weeks.

1.1 Class summary

GIP/GLP-1/glucagon triple receptor agonist

1.2 Subtitle

An Eli Lilly investigational triple receptor agonist of GIP, GLP-1, and glucagon receptors with Phase 3 trials in obesity producing 24% weight loss at 48 weeks.

2. Abstract

Retatrutide (LY3437943) is an investigational triple agonist of the GIP, GLP-1, and glucagon receptors developed by Eli Lilly and currently in Phase 3 trials for obesity, type 2 diabetes, and metabolic dysfunction-associated steatohepatitis (MASH). The compound builds on the GIP/GLP-1 dual agonist tirzepatide platform by adding glucagon receptor agonism, which contributes additional weight loss through hepatic energy expenditure increases and lipolytic effects. Phase 2 obesity trial results published in 2023 showed approximately 24.2 percent weight loss at 48 weeks at the highest dose, exceeding the magnitude observed with tirzepatide. The compound is not yet FDA approved; Phase 3 program is ongoing. Pharmacokinetics: weekly subcutaneous administration; half-life supports once-weekly dosing. The triple agonist class represents the current frontier of metabolic peptide development.

3. Mechanism of Action

Triple agonist of GIP, GLP-1, and glucagon receptors. The glucagon component adds hepatic lipolysis and energy expenditure to the GIP/GLP-1 satiety effects.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

2 to 12 mg weekly SC in Phase 2 trials.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Jastreboff AM, et al. Triple-hormone-receptor agonist retatrutide for obesity: a Phase 2 trial. N Engl J Med 2023.

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