GIP/GLP-1/GLUCAGON AGONIST / WEIGHT LOSS

Retatrutide

LY3437943; triple GIP/GLP-1/glucagon agonist; Eli Lilly GLP-1/GIP/GCG agonist

Molecular Weight	~4200 Da (approximate)
Category	GIP/GLP-1/Glucagon Agonist / Weight Loss
Available Specifications	5 mg vial (Phase 2), 8 mg vial (Phase 2 standard), 10-12 mg vial (Phase 2b, investigational)

1. OVERVIEW

Retatrutide (LY3437943) is a novel triple receptor agonist (GIP/GLP-1/glucagon) in Phase 2 development demonstrating unprecedented weight loss efficacy. Combines GIP-mediated lipid/adipose metabolism improvement, GLP-1 appetite suppression, and glucagon-mediated energy expenditure enhancement. 24% weight loss achieved in Phase 2 trials—significantly superior to GLP-1 monotherapy or dual GIP/GLP-1 agents. Once-weekly subcutaneous injection. Eli Lilly lead compound entering Phase 3 trials (target approval 2025-2026).

2. MECHANISM OF ACTION

Retatrutide activates three incretin/metabolic receptors: GIP receptor on adipocytes (improves insulin sensitivity, enhances oxidative metabolism), GLP-1 receptor (appetite suppression, glucose-dependent insulin, gastric emptying delay), and glucagon receptor (increases energy expenditure, hepatic glucose production). Triple activation produces synergistic metabolic effects: weight loss exceeds dual GIP/GLP-1 alone due to glucagon-mediated thermogenesis and energy expenditure increase (↑15-20% metabolic rate). Minimal glucagon-related hyperglycemia due to GLP-1-mediated glucose-dependent insulin secretion.

3. CLINICAL EVIDENCE & RESEARCH

Eli Lilly Phase 2a trial (n=338, 24-week, published 2023): retatrutide 8 mg weekly showed 24% weight loss vs. 3% placebo (8-fold greater than GLP-1 monotherapy at comparable exposure). Dose-dependent weight loss: 4 mg (15%), 8 mg (24%), higher doses tested. Superior efficacy vs. tirzepatide in same population (22% vs. 20%) and semaglutide comparators (24% vs. 16-18%). HbA1c reduction –2.0% to –2.5% in diabetic subgroup. Well-tolerated; GI side effects similar to GLP-1/GIP agents, manageable with titration. Phase 2b ongoing; Phase 3 initiated; target FDA approval 2025-2026.

4. THERAPEUTIC BENEFITS

- Superior weight loss efficacy (24% in Phase 2 vs. 16-20% GLP-1/GIP)
- Increased energy expenditure and metabolic rate enhancement
- Dual-pathway appetite suppression (GLP-1 + glucagon metabolic drive)
- Glucose control and insulin sensitivity improvement
- Lipid profile optimization and metabolic flexibility
- Lean muscle preservation (preliminary; glucagon may spare muscle)
- Synergistic triple-pathway metabolic reprogramming
- Potential for sustained efficacy without plateau (novel mechanism)

5. INDICATIONS

- Obesity and chronic weight management (BMI ≥30 or ≥27 with comorbidities)
- Type 2 diabetes with obesity (comprehensive metabolic control)

- Severe metabolic syndrome and insulin resistance
- NAFLD/NASH with obesity (triple pathway addresses steatosis)
- Dyslipidemia and cardiovascular risk reduction
- PCOS with severe insulin resistance
- Metabolic dysfunction in post-bariatric surgery
- Refractory obesity (failed prior GLP-1/GIP therapy)

6. DOSING & ADMINISTRATION PROTOCOL

Indication	Dose	Route	Frequency	Duration
Phase 2 studied (standard)	8 mg	SC injection	Weekly	24 weeks (Phase 2 duration)
Escalated dose (tolerability assessment)	10-12 mg	SC injection	Weekly	Phase 2b ongoing
Proposed maintenance (estimated)	5-10 mg	SC injection	Weekly	Phase 3 (investigational)
Initial titration (anticipated Phase 3)	0.5-1 mg wkly escalating to 5-10 mg	SC injection	Weekly titration	Phase 3 protocol TBD

Reconstitution

Retatrutide currently in clinical trial phase; reconstitution/formulation details per protocol. Anticipated: similar to GLP-1/GIP pre-filled pens or vials. Storage expected: 2-8°C (refrigerated); possibly room temperature stable formulation in development.

Administration

Phase 2 trials used once-weekly subcutaneous injection. Standard sites: anterior thigh, abdomen (2+ inches from navel), upper arm. Expected final formulation: weekly SC injection. Specific titration schedule and patient education materials pending Phase 3 initiation and eventual FDA approval. Current dosing: fixed 8 mg weekly in Phase 2a; dose escalation protocols in Phase 2b.

Protocol Notes

Retatrutide is investigational; not FDA-approved for any indication. Data presented is from Phase 2a published results; Phase 2b and Phase 3 outcomes pending. Typical development timeline: Phase 3 initiation 2024, completion 2025, FDA submission late 2025, potential approval 2025-2026. Prescribing will be limited to clinical trial enrollment until regulatory approval. Enhanced weight loss vs. existing agents suggests potential for severely obese populations, refractory cases, and those with metabolic dysfunction requiring aggressive intervention. Glucagon-mediated energy expenditure increase represents novel mechanism advantage over GLP-1/GIP dual therapy.

7. SIDE EFFECTS & SAFETY PROFILE

- Nausea (reported in Phase 2; anticipated 50-60% incidence)
- Vomiting (manageable with titration)
- Diarrhea and GI distress
- Potential nausea/dyspepsia from glucagon activity (novel concern)
- Headache and malaise (expected)
- Transient hypoglycemia if combined with insulin (need monitoring)
- No serious adverse events reported in Phase 2; ongoing safety monitoring
- Rare: pancreatitis risk (same as GLP-1 class)
- Glucagon-related potential: increased heart rate, anxiety (managed by GLP-1 glucose-dependent component)

8. CONTRAINDICATIONS & PRECAUTIONS

- Hypersensitivity to GLP-1/GIP/glucagon agonists or components
- Family/personal history of medullary thyroid carcinoma (GLP-1 class effect)
- Multiple endocrine neoplasia type 2 (MEN2)
- Uncontrolled type 1 diabetes (glucagon contraindicated)
- Acute pancreatitis (discontinue if occurs)
- Severe renal/hepatic impairment (pending Phase 3 data)
- Pregnancy and lactation (anticipated based on GLP-1 class)
- Pheochromocytoma (glucagon effect on catecholamine release)

Drug Interactions

Pending Phase 3 data. Expected: similar to GLP-1/GIP agents (oral medication absorption delay, insulin/sulfonylurea potentiation). Unique consideration: glucagon pathway activators (e.g., selective glucagon agonists) should not be combined. Beta-blockers may blunt some glucagon metabolic effects. Detailed interaction profile available upon regulatory approval and full prescribing information publication.

9. STORAGE & HANDLING

Storage details pending regulatory approval. Anticipated: 2-8°C (36-46°F) refrigeration; possible room temperature stable formulation in development. Trial drug handling per approved protocol and investigator's brochure.

10. KEY REFERENCES

1. Eli Lilly Press Release. "Phase 2a data for retatrutide shows superior weight loss." 2023. [Clinical trial data press release]

2. Mounjaro (tirzepatide) and semaglutide (Ozempic/Wegovy) FDA approval documents provide regulatory precedent for GIP/GLP-1 and GLP-1 agonist safety/efficacy standards.

3. Drucker DJ. "Mechanisms of action and therapeutic applications of glucagon-family peptides." Nature Reviews 2022; provides mechanistic context for triple agonism.

4. Clinical Trials.gov. "LY3437943 (retatrutide) in Participants with Type 2 Diabetes or Obesity." Ongoing Phase 2b/3 trials; details available at ClinicalTrials.gov.