BIOMOD LABS · RESEARCH PEPTIDE CO.

RESEARCH COMPOUND MONOGRAPH · SERIES 1 · NO. 002

Retatrutide

LY3437943 — a synthetic single-molecule peptide triple agonist at the glucagon, glucose-dependent insulinotropic polypeptide, and glucagon-like peptide-1 receptors, characterised by Coskun and colleagues at Eli Lilly in Cell Metabolism (2022) as the prototype triagonist building on the dual-agonist tirzepatide platform.

DEVELOPMENT CODE	VIAL STRENGTH	CATALOG REFERENCE	CLASS
LY3437943	30 mg / vial	BM-LYO-002	Synthetic peptide · 39 a.a. + C20 diacid

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Retatrutide (development code LY3437943) is a synthetic single-molecule peptide engineered at Eli Lilly and Company to function as a balanced triple agonist at the glucagon receptor (GCGR), the glucose-dependent insulinotropic polypeptide receptor (GIPR), and the glucagon-like peptide-1 receptor (GLP-1R). The defining preclinical characterisation paper by Coskun, Urva, Roell and colleagues (Cell Metabolism, September 2022, PMID 36099897) describes the molecule's receptor-binding affinities in cell-line transfection studies, with balanced GCGR and GLP-1R activity and more prominent GIPR activity. The chemistry approach builds directly on the tirzepatide framework: a 39-residue peptide backbone with strategic residue substitutions, two Aib substitutions for DPP-IV resistance, and a C20 fatty diacid side chain providing reversible non-covalent association with serum albumin. The addition of meaningful GCGR agonism — absent from selective GLP-1R agonists (semaglutide) and dual GIPR/GLP-1R agonists (tirzepatide) — engages hepatic glucagon receptor signalling that contributes to the molecule's effects on hepatic lipid metabolism in preclinical models. ***This monograph summarises published cellular pharmacology and preclinical findings for laboratory research reference only.***

01 Compound Profile

COMMON DESIGNATION	Retatrutide · LY3437943
BACKBONE	39-residue synthetic peptide with selected residue substitutions engineered for balanced GCGR / GIPR / GLP-1R receptor pharmacology; Aib substitutions for DPP-IV resistance
SIDE-CHAIN MODIFICATION	Lys side-chain acylation with γGlu spacer + C20 fatty diacid
PRIMARY MOLECULAR TARGETS	Glucagon receptor (GCGR) · Glucose-dependent insulinotropic polypeptide receptor (GIPR) · Glucagon-like peptide-1 receptor (GLP-1R) — all three Class B GPCRs; balanced triple agonism with more prominent GIPR activity in cell-line in-vitro assays[1]
RECEPTOR SELECTIVITY IN VITRO	Balanced GCGR and GLP-1R activity; comparatively higher GIPR potency in cell-line transfection systems (Coskun 2022)[1]
PHYSICAL FORM	White lyophilised solid
SOLUBILITY (LAB RECONSTITUTION)	Soluble in sterile water for injection; the lipid side chain creates surfactant-like behaviour in solution
STORAGE (RESEARCH HANDLING)	Lyophilised solid: −18 °C, desiccated; reconstituted solution refrigerated 2–8 °C; long-term aliquots at −18 °C with freeze–thaw minimised; siliconized or polypropylene surfaces preferred for dilute concentrations
ANALYTICAL SPECIFICATION	≥ 97 % purity by HPLC (BIOMOD Labs internal release specification)

02 Origin and Chemistry

Retatrutide emerged from the Eli Lilly research programme exploring multi-receptor incretin agonist peptides. The chemistry strategy extends the dual GIP/GLP-1 architecture of tirzepatide (Monograph 022) by introducing balanced glucagon receptor agonism — a deliberate addition motivated by preclinical evidence that GCGR agonism, calibrated to avoid hyperglycaemia, can contribute to weight loss through energy expenditure and to hepatic lipid metabolism through direct hepatic GCGR engagement. The peptide backbone of retatrutide is engineered with sequence elements drawn from across the GLP-1, GIP, and glucagon scaffolds, with Aib substitutions for DPP-IV resistance and a C20 fatty diacid side chain providing reversible non-covalent association with serum albumin (paralleling the tirzepatide chemistry).[1]

A particular chemistry challenge for triagonist design is achieving balanced rather than dominant receptor pharmacology — a peptide that engages all three receptors with similar functional potency, rather than behaving primarily as a GLP-1R agonist with weak secondary activity. The Coskun et al. 2022 paper documents the in-vitro receptor-binding and functional assay results that characterise retatrutide's pharmacology as "balanced GCGR and GLP-1R activity but more GIPR activity" — a profile distinct from selective and dual agonists.[1]

03 Molecular Targets and Cellular Signalling

Retatrutide is a full agonist at three Class B G-protein-coupled receptors, each with distinct tissue distribution and signalling consequences. **GCGR** is expressed primarily in liver and adipose tissue; receptor activation couples to Gαs, elevates cAMP, activates protein kinase A, and drives hepatic glucose production, glycogenolysis, and lipid mobilisation. **GIPR** is expressed on pancreatic β-cells (where it potentiates insulin secretion) and on adipocytes (where it modulates lipid handling); receptor signalling is Gαs-coupled with downstream cAMP and PKA activation. **GLP-1R** is expressed on β-cells, gut enteroendocrine cells, vagal afferents, brain regions involved in appetite regulation, and additional peripheral tissues; receptor signalling is Gαs-coupled with cAMP and downstream effects on insulin secretion, gastric emptying, and central appetite.[1]

The aggregate cellular pharmacology of retatrutide therefore engages three partly overlapping but partly distinct cell populations and signalling architectures. The hepatic GCGR signal contributes effects (notably on liver fat reduction in preclinical and clinical models) that cannot be reproduced by selective GLP-1R agonists or by dual GIPR/GLP-1R agonists. Researchers should be aware that observed cellular and animal-model effects represent the integrated response across three receptor systems rather than activity at a single target.[2] PRECLINICAL · ANIMAL MODEL

04 Preclinical Findings

SYSTEM	PREPARATION	REPORTED OBSERVATION	REF.
Receptor activation	Cell lines transfected with GCGR, GIPR, GLP-1R	Triple full agonism; balanced GCGR / GLP-1R activity; higher GIPR potency	1
Cellular signalling	cAMP assays at each receptor	Gαs → cAMP → PKA architecture at all three receptors	1
Body weight	Diet-induced obese mice	Reduction in body weight greater than dual or single agonists in head-to-head animal preparations	1
Liver fat	Animal models & subsequent clinical data	Substantial reduction in hepatic triglyceride accumulation	3
Glycaemic control	Animal type-2-diabetes preparations	Improved glucose handling without hyperglycaemia from GCGR activity	1

05 Research Synthesis & Limitations

METHODOLOGICAL NOTES

Retatrutide is the most-advanced triagonist peptide and has been characterised in published primary preclinical and early-phase clinical literature. For researchers, the principal considerations are (a) the triple-receptor pharmacology means that observed effects in cells or animals must be interpreted across three receptor systems rather than at a single target; (b) the GCGR agonism, while calibrated to avoid hyperglycaemia in healthy animals and metabolically intact cell preparations, is a meaningful pharmacological action that distinguishes this molecule from selective GLP-1R and dual GIPR/GLP-1R agonists; and (c) the preclinical literature, while growing, remains substantially smaller than for semaglutide or tirzepatide, with most foundational data concentrated in the originating Eli Lilly programme.

06 Laboratory Handling, Reconstitution, and Storage

Lyophilised retatrutide is supplied under research-use specifications and held at −18 °C, desiccated. Reconstitution in sterile water for injection is the standard practice. The lipid side chain creates surfactant-like behaviour; siliconized or polypropylene surfaces are preferred for dilute concentrations to minimise peptide adsorption. Reconstituted solutions are held refrigerated 2–8 °C for short-term work; long-term aliquoted storage at −18 °C with minimised freeze–thaw. Working concentrations are determined by the investigator's experimental design.

07 References

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2. Urva S, Coskun T, Loh MT, Du Y, Thomas MK, Gurbuz S, Haupt A, Benson C, Hernandez-Illas M, D'Alessio DA, Milicevic Z. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. *Lancet.* 2022;400(10366):1869–1881. pubmed.ncbi.nlm.nih.gov/36354042

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4. Finan B, Yang B, Ottaway N, Smiley DL, Ma T, Clemmensen C, Chabenne J, Zhang L, Habegger KM, Fischer K, Campbell JE, Sandoval D, Seeley RJ, Bleicher K, Uhles S, Riboulet W, Funk J, Hertel C, Belli S, Sebokova E, et al. A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents (precursor triagonist chemistry context). *Nat Med.* 2015;21(1):27–36. pubmed.ncbi.nlm.nih.gov/25485909

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