

Ecnoglutide

A long-acting, fatty acid-conjugated GLP-1 analog developed at Sciwind Biosciences as the first cAMP signaling-biased GLP-1 receptor agonist, distinguished from semaglutide and other marketed incretin mimetics by selective activation of the Gs/adenylyl cyclase/cAMP cascade with markedly reduced beta-arrestin recruitment and GLP-1 receptor internalization, yielding sustained receptor surface availability and enhanced glycemic and weight-reducing efficacy in clinical populations.

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ABSTRACT

Ecnoglutide (XW003; CAS 2459531-73-6; molecular formula C₁₉₄H₃₀₄N₄₈O₆₁; molecular weight 4284.84 g/mol) is a lipopeptide analog of human glucagon-like peptide-1 (GLP-1) (7-37) engineered with an alanine-to-valine substitution at position 8 and a C18 fatty diacid conjugated to the epsilon-amino group of lysine 30 through a gamma-glutamate and dual 2-(2-(2-aminoethoxy)ethoxy)acetic acid linker. Designed and developed at Sciwind Biosciences (Hangzhou, China), ecnoglutide is the first GLP-1 receptor agonist intentionally optimized for cAMP signaling bias: it activates the Gs/adenylyl cyclase/cAMP cascade with an EC₅₀ of 0.018 nM (comparable to semaglutide at 0.012 nM) while producing substantially reduced beta-arrestin recruitment (E_{max} approximately 54 to 60 percent of semaglutide, EC₅₀ approximately 1300 nM) and negligible GLP-1 receptor internalization (EC₅₀ greater than 10 micromolar versus 0.093 micromolar for semaglutide) [1]. The biased signaling profile preserves receptor surface density and downstream insulin secretion while reducing the desensitization, tachyphylaxis, and gastrointestinal adverse events theoretically attributable to beta-arrestin-mediated receptor endocytosis. In surface plasmon resonance binding studies, ecnoglutide demonstrates a dissociation constant (K_D) of 1.45 nanomolar at the human GLP-1 receptor, approximately 10- to 30-fold higher affinity than semaglutide (K_D 17.0 nanomolar) [1]. The compound consists exclusively of natural amino acids, simplifying the manufacturing process relative to semaglutide (which incorporates alpha-aminoisobutyric acid at position 8). Pharmacokinetics in healthy human volunteers support once-weekly subcutaneous dosing: the

terminal elimination half-life at steady state ranges from 124 to 138 hours, with median time to peak concentration (T_{max}) of 12 to 72 hours and dose-proportional plasma exposure across the studied dose range [1]. In the Phase 2 randomized, double-blind, placebo-controlled trial in 145 adults with type 2 diabetes, ecnoglutide at 0.4, 0.8, and 1.2 mg weekly for 20 weeks produced HbA_{1c} reductions of 1.81, 1.90, and 2.39 percentage points, respectively, versus 0.55 points on placebo [2]. In the Phase 3 EECOH-1 trial of ecnoglutide monotherapy (0.6 mg and 1.2 mg weekly) in 211 patients with type 2 diabetes, up to 76.1 percent of patients in the 1.2 mg cohort achieved HbA_{1c} targets of 6.5 percent or less [3]. In the Phase 3 EECOH-2 active-comparator trial, ecnoglutide 0.6 mg and 1.2 mg weekly demonstrated non-inferiority to dulaglutide 1.5 mg weekly on HbA_{1c} reduction over 52 weeks, with the 1.2 mg dose achieving statistically significantly greater reduction [4]. In the Phase 3 SLIMMER trial in 664 adults with overweight or obesity without diabetes, ecnoglutide at 1.2, 1.8, and 2.4 mg weekly produced mean body weight reductions of 9.1, 10.9, and 13.2 percent, respectively, at 40 weeks versus 0.1 percent on placebo; at 48 weeks, the 2.4 mg dose achieved 15.4 percent mean weight loss, with 92.8 percent of participants achieving 5 percent or greater weight loss [5]. The safety profile is consistent with the GLP-1 receptor agonist class: the principal adverse events are gastrointestinal (nausea, diarrhea, decreased appetite), predominantly mild to moderate in severity, concentrated during the dose-escalation period, and diminishing over time. Hypoglycemia risk is low. China's National Medical Products Administration (NMPA) approved ecnoglutide injection for chronic weight management in January 2026, making it the first approved cAMP-biased GLP-1 receptor agonist worldwide [6]. The compound is not approved by the United States Food and Drug

Administration or by the European Medicines Agency as of the most recent monograph revision. This monograph reviews the chemistry, biased-agonist pharmacology, comprehensive pharmacokinetics, the clinical evidence base across type 2 diabetes and obesity indications, sourcing and quality considerations, reconstitution and handling, stack-interaction implications, adverse-event signal, and a comparative assessment of five GLP-1 receptor agonist and incretin mimetic candidates against ecnoglutide on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Ecnoglutide.

Development codes: XW003 (Sciwind Biosciences, injectable formulation), XW004 (Sciwind Biosciences, oral tablet formulation). The development code XW003 is the canonical identifier in the discovery and Phase 1 pharmacology literature and the identifier under which the seminal Guo et al. (2023) characterization of cAMP-biased agonism was published [1].

Chemical Abstracts Service registry number: 2459531-73-6.

PubChem CID: 162625103.

DrugBank accession: DB19019.

ChemSpider: 129306901.

UNII: KM6YM7L8LH.

Marketed names: Ecnoglutide injection (Sciwind Biosciences; approved in China for chronic weight management, January 2026) [6]. No other marketed names have been registered as of the monograph revision date.

1.2 Structural class and chemistry

Ecnoglutide is a lipopeptide analog of human glucagon-like peptide-1 (7-37), a 31-amino-acid incretin hormone secreted by enteroendocrine L-cells in the distal ileum and colon. The structural class places it within the fatty acid-acylated GLP-1 peptide family, which includes liraglutide (C16 palmitoyl conjugation at Lys26 via gamma-glutamate linker), semaglutide (C18 fatty diacid conjugation at Lys26 via a dual mini-PEG linker with an alpha-aminoisobutyric acid substitution at position 8), and dulaglutide (immunoglobulin Fc fusion rather than fatty acid conjugation) [7, 8].

Molecular formula: C₁₉₄H₃₀₄N₄₈O₆₁.

Molecular weight: 4284.84 g/mol.

Peptide backbone: Human GLP-1 (7-37), consisting of 31 amino acids (His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-amide in the native sequence, numbered positions 7 through 37). Ecnoglutide incorporates two engineered modifications: (a) an alanine-to-valine substitution at position 8 (Ala8Val), conferring resistance to dipeptidyl peptidase-4 (DPP-4) cleavage and introducing the cAMP signaling bias that distinguishes the compound from semaglutide and other unbiased GLP-1 analogs; and (b) a C18 fatty diacid (octadecanedioic acid) conjugated to the epsilon-amino group of lysine at position 30 through a gamma-glutamate-2xAEEA linker (where AEEA denotes 2-(2-(2-aminoethoxy)ethoxy)acetic acid), enabling non-covalent albumin binding and consequent extension of the plasma half-life to support once-weekly subcutaneous dosing [1].

Physical properties: White to off-white lyophilized powder. Freely soluble in water and in physiological saline at concentrations suitable for subcutaneous injection. The compound is supplied as a clear, colorless to slightly yellow solution in prefilled injection devices for clinical use.

Stereochemistry: All amino acid residues are in the L-configuration. The compound does not contain non-natural amino acids; this distinguishes ecnoglutide from semaglutide, which incorporates the achiral alpha-aminoisobutyric acid (Aib) at position 8 and requires specialized peptide chemistry for its synthesis.

1.3 Synthesis

Ecnoglutide is manufactured by solid-phase peptide synthesis (SPPS) using standard Fmoc (9-fluorenylmethyloxycarbonyl) chemistry on a resin support, followed by on-resin or solution-phase conjugation of the C18 fatty diacid-gamma-glutamate-2xAEEA linker to the lysine 30 side chain [1]. The exclusive use of natural amino acids in the peptide backbone simplifies the synthesis relative to semaglutide and reduces the manufacturing cost, as the alpha-aminoisobutyric acid coupling step in semaglutide synthesis requires specialized reagents and conditions to achieve adequate coupling efficiency. After cleavage from the resin and global side-chain deprotection, the crude peptide-lipid conjugate is purified by preparative reversed-phase high-performance liquid chromatography (RP-HPLC) and characterized by mass spectrometry, analytical RP-HPLC, and amino acid analysis. The final drug substance is lyophilized or formulated directly in the injectable solution at the tar-

get concentration. Industrial-scale production achieves purity greater than 95 percent by HPLC, with identity confirmed by electrospray ionization mass spectrometry and peptide mapping.

2. Abstract

Ecnoglutide (XW003) is a long-acting, cAMP signaling-biased glucagon-like peptide-1 (GLP-1) receptor agonist developed by Sciwind Biosciences (Hangzhou, China) and distinguished from the marketed GLP-1 receptor agonists (semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide) by deliberate engineering of biased agonism at the GLP-1 receptor [1]. The compound activates the canonical Gs/adenylyl cyclase/cyclic adenosine monophosphate (cAMP) intracellular signaling cascade with potency comparable to semaglutide (EC₅₀ 0.018 nM versus 0.012 nM) but produces markedly reduced recruitment of beta-arrestin (E_{max} approximately 54 to 60 percent of the semaglutide maximum, EC₅₀ approximately 1300 nM) and negligible GLP-1 receptor internalization (EC₅₀ greater than 10 micromolar versus 0.093 micromolar for semaglutide). The biased signaling profile is conferred principally by the alanine-to-valine substitution at position 8 of the GLP-1 (7-37) backbone, which alters the receptor-ligand conformational ensemble to favor the Gs-coupled conformation over the beta-arrestin-coupled conformation [1].

The pharmacological consequence of cAMP-biased agonism is sustained GLP-1 receptor surface availability. In unbiased agonism (semaglutide, liraglutide), beta-arrestin recruitment drives receptor internalization, endosomal signaling, and receptor degradation, reducing surface receptor density and potentially contributing to both tachyphylaxis on chronic dosing and the acute gastrointestinal adverse events (nausea, vomiting, diarrhea) that are the principal tolerability limitation of the class. By reducing receptor internalization, ecnoglutide maintains receptor surface density and may produce more sustained insulin-secretory and appetite-suppressing signals per unit of receptor activation.

In preclinical studies in db/db diabetic mice, ecnoglutide at 0.15 mg/kg suppressed blood glucose to a significantly greater extent than semaglutide at equivalent doses at 99 and 147 hours post-dose, and produced more pronounced body weight reduction than semaglutide over 42-day daily dosing [1]. In a diet-induced obesity rat cross-over study, animals switching from semaglutide to ecnoglutide maintained stable body weight reduction, while animals switching from ecnoglutide to semaglutide began to regain weight [1].

Clinical development has progressed through Phase 1 (healthy volunteers), Phase 2 (type 2 diabetes), Phase 1c/2a (overweight and obesity), and four Phase 3 trials. The EECOH-1 trial demonstrated superior HbA1c reduction versus placebo as monotherapy in type 2 diabetes [3]. The EECOH-2 trial demonstrated non-inferiority and, at the 1.2 mg dose, superiority to dulaglutide 1.5 mg on HbA1c reduction over 52 weeks [4]. The SLIMMER trial demonstrated dose-dependent weight loss of 9.1 to 15.4 percent at 40 to 48 weeks in adults with overweight or obesity [5]. China's National Medical Products Administration approved ecnoglutide injection for chronic weight management in January 2026, making it the first approved cAMP-biased GLP-1 receptor agonist worldwide [6].

The compound is not approved by the United States Food and Drug Administration or by the European Medicines Agency. An oral tablet formulation (XW004), co-formulated with an oral absorption enhancer for once-daily or potentially once-weekly dosing, has completed Phase 1 clinical evaluation in Australia with body weight reductions of up to 6.8 percent at 30 mg daily for 6 weeks in overweight participants [9].

3. Discovery and Development History

3.1 Origin

Ecnoglutide was designed at Sciwind Biosciences, a biotechnology company founded in Hangzhou, China, with a proprietary biased-agonist discovery platform, long-acting peptide delivery platform, and oral peptide delivery platform [1, 6]. The discovery rationale was the hypothesis that cAMP signaling bias at the GLP-1 receptor, achieved by reducing beta-arrestin recruitment and receptor internalization while maintaining full cAMP potency, would produce improved efficacy and tolerability relative to the existing unbiased GLP-1 receptor agonists. The medicinal chemistry strategy centered on systematic evaluation of amino acid substitutions at position 8 of GLP-1 (7-37), the DPP-4 cleavage site, combined with fatty acid conjugation at position 30 for albumin binding and half-life extension.

3.2 Selection of the Ala8Val modification

The alanine-to-valine substitution at position 8 was identified as the principal determinant of cAMP signaling bias [1]. Semaglutide incorporates alpha-aminoisobutyric acid (Aib) at position 8, which confers DPP-4 resistance but does not introduce signaling bias; the semaglutide-GLP-1 receptor complex recruits beta-arrestin and internalizes with full efficacy. The valine substitution at position 8 in ecnoglutide produces a subtly different receptor-ligand interaction geometry that favors the Gs-coupled conformation over the conformation required for beta-arrestin engagement. The substitution simultaneously confers DPP-4 resistance (the valine side chain sterically occludes the DPP-4 catalytic cleft) and cAMP bias, achieving two design objectives with a single conservative amino acid change [1].

3.3 Fatty acid conjugation and linker engineering

The C18 fatty diacid conjugation at lysine 30 through the gamma-glutamate-2xAEAA linker was optimized for albumin binding affinity and pharmacokinetic half-life. The linker design is similar to the semaglutide linker architecture (which also employs a gamma-glutamate and mini-PEG spacer to a C18 fatty diacid) but differs in the specific spacer chemistry (AEAA versus OEG) and in the conjugation position

(Lys30 for ecnoglutide versus Lys26 for semaglutide) [1, 8]. The albumin binding extends the plasma half-life from minutes (native GLP-1) to approximately 124 to 138 hours at steady state (ecnoglutide), comparable to semaglutide (approximately 165 hours).

3.4 Preclinical development

Preclinical pharmacology and toxicology studies in rodent (mouse, rat) and non-human primate (cynomolgus monkey) species demonstrated a favorable potency, pharmacokinetic, and tolerability profile. In cynomolgus monkeys, single subcutaneous doses produced pharmacokinetic parameters consistent with once-weekly dosing, with dose-proportional plasma exposure [1]. Chronic toxicology studies supported advancement to human clinical trials.

3.5 Clinical development timeline

Phase 1 (healthy volunteers): Conducted in China; results published in the Guo et al. (2023) Molecular Metabolism report. Single ascending dose (SAD) cohorts at 0.03 to 1.0 mg and multiple ascending dose (MAD) cohorts at 0.2 to 0.6 mg weekly for 6 weeks demonstrated safety, tolerability, and dose-proportional pharmacokinetics [1].

Phase 2 (type 2 diabetes): Randomized, double-blind, placebo-controlled trial in 145 adults with type 2 diabetes; 0.4, 0.8, and 1.2 mg weekly for 20 weeks. Published in Nature Communications (2024) [2].

Phase 1c/2a (overweight and obesity): 1.8 mg and 2.4 mg weekly in non-diabetic overweight and obese adults; mean weight loss of 9.6 percent and 9.0 percent, respectively, over 14 weeks [10].

Phase 3 EECOH-1 (type 2 diabetes monotherapy): Multicenter, randomized, double-blind, placebo-controlled trial in 211 patients. Published in Nature Communications (2025) [3].

Phase 3 EECOH-2 (type 2 diabetes, active comparator): 52-week, multicenter, open-label, non-inferiority trial of ecnoglutide 0.6 mg and 1.2 mg versus dulaglutide 1.5 mg in patients on metformin. Published in The Lancet Diabetes and Endocrinology (2025) [4].

Phase 3 SLIMMER (overweight and obesity): Multicenter, randomized, double-blind, placebo-controlled trial in 664 participants; 1.2, 1.8, and 2.4 mg weekly. Published in The Lancet Diabetes and Endocrinology (2025) [5].

3.6 Regulatory approval

China's National Medical Products Administration (NMPA) approved ecnoglutide injection for chronic weight management in Chinese adults with overweight (body mass index 24 kg/m² or greater with at least one weight-related comorbidity) or obesity (body mass index 28 kg/m² or greater) in January 2026 [6]. Ecnoglutide injection is the first approved cAMP-biased GLP-1 receptor agonist for any indication worldwide. Regulatory submissions in other jurisdictions have not been publicly announced as of the monograph revision date.

4. Mechanism of Action

Ecnoglutide is a GLP-1 receptor agonist with deliberately engineered cAMP signaling bias. Its principal molecular activity is activation of the GLP-1 receptor with preferential engagement of the Gs/adenylyl cyclase/cAMP intracellular cascade and reduced engagement of the beta-arrestin/receptor internalization pathway. This biased-agonism profile is the defining pharmacological characteristic that distinguishes ecnoglutide from all other clinically developed GLP-1 receptor agonists.

4.1 GLP-1 receptor pharmacology

The GLP-1 receptor (GLP-1R) is a class B1 G protein-coupled receptor expressed at high density on pancreatic beta cells, on hypothalamic neurons of the arcuate nucleus and paraventricular nucleus, on vagal afferent neurons, on gastric parietal and enteric neurons, and at lower density in the heart, kidney, lung, and central nervous system [7, 8]. Activation of the GLP-1R by native GLP-1 or by exogenous agonists produces multiple downstream effects through two principal signaling branches:

Gs/cAMP branch: Agonist binding stabilizes the receptor in a Gs protein-coupled conformation. Gs activation stimulates adenylyl cyclase, producing cyclic adenosine monophosphate (cAMP). In pancreatic beta cells, cAMP activates protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac2), which potentiate glucose-stimulated insulin secretion through closure of ATP-sensitive potassium channels, calcium influx, and exocytotic granule mobilization. In hypothalamic neurons, cAMP-dependent signaling mediates appetite suppression and satiety. The cAMP branch is considered the principal effector pathway for the therapeutic effects of GLP-1 receptor agonists: insulin secretion, glucagon suppression, appetite reduction, and gastric emptying delay [7].

Beta-arrestin branch: Following Gs activation, G protein-coupled receptor kinases (GRKs) phosphorylate the intracellular domains of the GLP-1R, recruiting beta-arrestin-1 and beta-arrestin-2. Beta-arrestin recruitment desensitizes the receptor to further Gs activation and scaffolds the receptor for clathrin-mediated endocytosis (internalization). The internalized receptor-ligand complex can signal from endosomes (producing sustained but distinct cAMP signals) or can be sorted

to lysosomes for degradation, reducing surface receptor density. Beta-arrestin recruitment and receptor internalization are associated with receptor desensitization, tachyphylaxis on chronic dosing, and may contribute to the acute gastrointestinal adverse events (nausea, vomiting) that are the principal tolerability limitation of the GLP-1 receptor agonist class [1, 11].

4.2 cAMP signaling bias of ecnoglutide

Ecnoglutide activates the Gs/cAMP branch with an EC₅₀ of 0.018 nM, comparable to semaglutide (0.012 nM), confirming full potency on the therapeutically relevant signaling cascade. However, ecnoglutide produces markedly reduced beta-arrestin recruitment: the maximum beta-arrestin recruitment (E_{max}) is approximately 54 to 60 percent of the semaglutide maximum, with an EC₅₀ of approximately 1300 nM (approximately 10,000-fold right-shifted relative to the cAMP EC₅₀). Most strikingly, ecnoglutide does not produce measurable GLP-1 receptor internalization at concentrations up to 10 micromolar (EC₅₀ greater than 10 micromolar), compared to semaglutide, which drives receptor internalization with an EC₅₀ of 0.093 micromolar [1].

The composite signaling profile is therefore: full cAMP potency, substantially reduced beta-arrestin recruitment, and essentially absent receptor internalization. This profile preserves the insulin-secretory and appetite-suppressive therapeutic effects (which are cAMP-dependent) while reducing the receptor desensitization and surface density loss (which are beta-arrestin-dependent) that may limit the chronic efficacy and tolerability of unbiased agonists.

4.3 Structural basis of the signaling bias

The Ala8Val substitution at position 8 of the GLP-1 backbone is the principal determinant of the cAMP bias [1]. Position 8 is the P1 residue of the DPP-4 cleavage site and is located at the N-terminal helix-receptor interface in the agonist-bound GLP-1R structure. The valine side chain, larger and more hydrophobic than alanine but smaller than the Aib residue used in semaglutide, produces a subtle reorientation of the N-terminal helix relative to the transmembrane domain that favors the Gs-coupled receptor conformation over the conformation required for GRK phosphorylation and beta-arrestin engagement. The effect is a conformational selection mechanism: ecnoglutide stabilizes a receptor state that is fully competent for Gs coupling but conformationally unfavorable for beta-arrestin binding [1].

4.4 Receptor binding affinity

Surface plasmon resonance (SPR) binding studies demonstrate that ecnoglutide binds the human GLP-1 receptor extracellular domain with a dissociation constant (KD) of 1.45 nanomolar, approximately 10- to 30-fold higher affinity than semaglutide (KD 17.0 nanomolar) [1]. The higher binding affinity is consistent with the slow dissociation kinetics that contribute to the sustained pharmacological effect and may partially explain the enhanced glucose-lowering efficacy observed in preclinical head-to-head comparisons with semaglutide at equivalent doses.

4.5 Downstream therapeutic effects

The GLP-1R-cAMP signaling axis mediates the following downstream therapeutic effects relevant to the clinical indications of ecnoglutide:

Glucose-dependent insulin secretion: cAMP/PKA/Epac2 potentiation of glucose-stimulated insulin granule exocytosis in pancreatic beta cells. The glucose-dependence of the effect provides intrinsic protection against hypoglycemia, as the cAMP potentiation requires a threshold glucose concentration for KATP channel closure and calcium entry.

Glucagon suppression: cAMP-dependent reduction of glucagon secretion from pancreatic alpha cells, reducing hepatic glucose output.

Gastric emptying delay: Vagal afferent-mediated reduction in gastric motility, prolonging satiety and reducing postprandial glucose excursions.

Appetite suppression and satiety: Hypothalamic GLP-1R activation in the arcuate and paraventricular nuclei suppresses orexigenic neuropeptide Y and agouti-related peptide signaling and activates pro-opiomelanocortin neurons, reducing caloric intake.

Beta-cell preservation: Chronic GLP-1R activation has been associated with beta-cell proliferation, reduced apoptosis, and maintenance of beta-cell mass in rodent models, mediated by cAMP-dependent transcriptional programs [7].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Ecnoglutide is administered by subcutaneous injection. Absorption from the subcutaneous depot is slow, consistent with the C18 fatty diacid-albumin binding mechanism that retards diffusion from the injection site. In healthy volunteers receiving multiple ascending doses (0.2, 0.4, and 0.6 mg weekly for 6 weeks), the median time to peak plasma concentration (T_{max}) at steady state ranged from 12 to 72 hours across dose cohorts [1]. The slow absorption and albumin binding produce a flat pharmacokinetic profile with modest peak-to-trough fluctuation, supporting consistent receptor exposure over the once-weekly dosing interval.

5.2 Distribution

The fatty acid conjugation to the C18 diacid enables non-covalent binding to serum albumin (the same distribution mechanism as semaglutide and liraglutide), which serves as a circulating depot that protects the peptide from proteolytic degradation, extends the plasma half-life, and restricts the volume of distribution. The albumin-bound fraction circulates in the central and peripheral plasma compartments; the unbound (free) fraction is the pharmacologically active species that engages the GLP-1 receptor on target tissues. Protein binding is expected to be greater than 99 percent based on the fatty acid-albumin interaction, analogous to semaglutide (greater than 99 percent protein binding) [8].

5.3 Plasma pharmacokinetic parameters

At steady state (Day 36 of once-weekly dosing in healthy volunteers), the following pharmacokinetic parameters were observed [1]:

0.2 mg weekly: C_{max} 25.3 ng/mL, T_{max} 72 hours, half-life 124 hours, AUC_{0-infinity} 6611.5 hour-ng/mL.

0.4 mg weekly: C_{max} 46.7 ng/mL, T_{max} 39 hours, half-life 138 hours, AUC_{0-infinity} 11658.2 hour-ng/mL.

0.6 mg weekly: C_{max} 84.7 ng/mL, T_{max} 12 hours, half-life 129 hours, AUC_{0-infinity} 21604.9 hour-ng/mL.

Plasma exposure increased dose-proportionally across the studied range. The terminal elimination half-life of 124 to 138 hours (approximately 5.2 to 5.8 days) supports once-weekly dosing, with steady-state achieved by approximately 4 to 5 weeks of weekly administration.

5.4 Metabolism and elimination

Ecnoglutide is a peptide and is expected to be eliminated by proteolytic degradation rather than by hepatic cytochrome P450-mediated metabolism. The metabolic pathway is analogous to other GLP-1 peptide analogs: endopeptidase and exopeptidase cleavage of the peptide backbone, with the fatty acid-linker conjugate separated and metabolized through beta-oxidation. Renal excretion of intact peptide is negligible. No clinically significant drug-drug interactions through CYP450 inhibition or induction are expected [12].

5.5 Routes of administration

Subcutaneous injection (XW003): The registered route. Ecnoglutide is supplied in prefilled injection pens for once-weekly self-administration. The dose-escalation protocol follows the standard GLP-1 agonist paradigm: initiation at a low dose (typically 0.3 mg weekly) with stepwise escalation over 8 to 16 weeks to the target maintenance dose (1.2, 1.8, or 2.4 mg weekly for the obesity indication) to mitigate gastrointestinal adverse events during the early treatment period [5].

Oral tablet (XW004): An oral formulation co-formulated with an oral absorption enhancer (analogous to the SNAC technology used in oral semaglutide) has completed Phase 1 evaluation. In a randomized, double-blind, placebo-controlled multiple ascending dose study in 56 participants (42 healthy and 14 healthy obese) in Australia, once-daily oral ecnoglutide at 7, 15, and 30 mg for 2 weeks produced weight reductions of 3.6, 3.4, and 6.6 percent, respectively; in the 6-week 30 mg cohort in obese participants, weight reduction reached 6.8 percent [9]. The oral formulation is in earlier development than the injectable and has not entered Phase 3 trials as of the monograph revision date.

5.6 Special populations

Specific pharmacokinetic studies in renal impairment, hepatic impairment, and pediatric populations have not been published in the peer-reviewed literature as of the monograph revision date. The mechanism of elimination (proteolytic degradation rather than hepatic or renal clearance) suggests that mild to moderate renal or hepatic impairment is unlikely to substantially alter ecnoglutide pharmacokinetics, consistent with the pharmacokinetic profiles of semaglutide and liraglutide in these populations. The approved indication in China is for adults aged 18 years and older; pediatric use has not been studied.

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

The Guo et al. (2023) characterization in cell-based assay systems established the biased-agonism profile of ecnoglutide [1]:

cAMP accumulation in CHO cells expressing the human GLP-1R: EC₅₀ 0.018 nM (semaglutide 0.012 nM). Maximum cAMP production was comparable between the two compounds.

Beta-arrestin-2 recruitment (PathHunter assay): Ecnoglutide E_{max} approximately 54 to 60 percent of semaglutide maximum; EC₅₀ approximately 130 nM for ecnoglutide versus 0.15 micromolar for semaglutide. The reduced E_{max} indicates that ecnoglutide is a partial agonist of the beta-arrestin pathway relative to semaglutide.

GLP-1 receptor internalization (imaging-based): Ecnoglutide EC₅₀ greater than 10 micromolar (essentially inactive); semaglutide EC₅₀ 0.093 micromolar. This is the most dramatic pharmacological difference between the two compounds and is the molecular basis for the sustained receptor surface availability hypothesis.

Surface plasmon resonance binding: K_D 1.45 nM for ecnoglutide versus 17.0 nM for semaglutide, indicating approximately 12-fold higher affinity for the GLP-1R extracellular domain.

6.2 In vivo rodent efficacy

Acute glucose-lowering in db/db mice: A single subcutaneous dose of ecnoglutide (0.15 mg/kg) produced glucose suppression comparable to semaglutide at equivalent dose at early time points (24 to 48 hours) but significantly greater glucose suppression at 99 and 147 hours post-dose, consistent with the sustained receptor activation predicted by the reduced internalization profile [1].

Chronic body weight reduction in db/db mice: Daily subcutaneous dosing at 0.05 mg/kg for 42 days produced significantly more pronounced body weight reduction for ecnoglutide compared to semaglutide at the same dose [1].

Diet-induced obesity rat cross-over study: Animals maintained on semaglutide for an initial period and then switched to ecnoglutide maintained stable body weight reduction from baseline; conversely, animals switched from ecnoglutide to semaglutide began to regain body weight [1]. This cross-over result is consistent with the hypothesis that reduced receptor internalization by ecnoglutide preserves receptor surface density and downstream weight-reducing signaling to a greater extent than semaglutide on chronic administration.

6.3 Non-human primate pharmacokinetics

Single subcutaneous dose pharmacokinetic studies in cynomolgus monkeys confirmed dose-proportional plasma exposure, slow absorption consistent with the albumin-binding mechanism, and a pharmacokinetic profile supporting once-weekly dosing in humans [1].

7. Clinical Evidence Base

7.1 Phase 1: Healthy volunteers

The Phase 1, double-blind, randomized, placebo-controlled study enrolled 64 healthy participants in single ascending dose (SAD; 0.03 to 1.0 mg subcutaneous, 6 cohorts) and multiple ascending dose (MAD; 0.2 to 0.6 mg weekly for 6 weeks, 3 cohorts) arms. Ecnoglutide was safe and well tolerated through the studied dose range. The most common treatment-emergent adverse events in the MAD cohorts were decreased appetite, headache, nausea, hypoglycemia, constipation, and injection site pain. One Grade 3 adverse event (severe decreased appetite) occurred at the highest single dose (1.0 mg). No serious treatment-related adverse events occurred, and no adverse events led to study discontinuation [1].

7.2 Phase 2: Type 2 diabetes

A Phase 2, randomized, double-blind, placebo-controlled trial enrolled 145 adults with type 2 diabetes inadequately controlled by diet and exercise, randomized to ecnoglutide 0.4, 0.8, or 1.2 mg weekly or placebo for 20 weeks [2]. The primary endpoint was change in HbA1c from baseline to week 20.

HbA1c reductions from baseline: 1.81 percentage points (0.4 mg), 1.90 percentage points (0.8 mg), 2.39 percentage points (1.2 mg), and 0.55 percentage points (placebo); all ecnoglutide doses were statistically significantly superior to placebo.

Body weight reductions from baseline: 1.57 kg (0.4 mg), 1.65 kg (0.8 mg), and 2.26 kg (1.2 mg), versus minimal change on placebo. Between 11 and 33 percent of ecnoglutide-treated participants achieved the American Diabetes Association recommended weight loss target of 5 percent or greater, versus 3 percent on placebo.

The HbA1c reduction of 2.39 percentage points at 1.2 mg is notable in the context of the GLP-1 receptor agonist class: comparable to tirzepatide at 5 to 15 mg weekly (2.01 to 2.30 percentage points) and to semaglutide 1.0 mg weekly (approximately 1.5 to 1.8 percentage points), suggesting that the cAMP signaling bias may confer an efficacy advantage on HbA1c reduction [2].

7.3 Phase 1c/2a: Overweight and obesity

A Phase 1c/2a study in non-diabetic Chinese adults with overweight or obesity evaluated ecnoglutide at 1.8 mg and 2.4 mg weekly (with dose escalation from 0.3 mg) over a 14-week core treatment period [10]. Mean body weight losses were approximately 8.32 kg (9.6 percent) at 1.8 mg and 7.27 kg (9.0 percent) at 2.4 mg, compared to minimal change in the placebo group. The results supported advancement to Phase 3 in the obesity indication.

7.4 Phase 3 EECOH-1: Type 2 diabetes monotherapy

The EECOH-1 trial was a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial of ecnoglutide monotherapy in approximately 211 patients with type 2 diabetes inadequately controlled by lifestyle intervention alone [3]. Patients were randomized to ecnoglutide 0.6 mg or 1.2 mg weekly or placebo.

Treatment-emergent adverse events occurred in 78.3 percent of the 0.6 mg group, 77.5 percent of the 1.2 mg group, and 63.4 percent of the placebo group. The most commonly reported treatment-emergent adverse events by system organ class were gastrointestinal disorders (diarrhea, nausea) and metabolic and nutritional disorders. Other adverse events with greater than 5 percent incidence included decreased appetite, increased lipase, upper respiratory tract infection, urinary tract infection, and asthenia. Gastrointestinal adverse events were predominantly mild to moderate in severity, occurred principally during the dose-escalation period, and diminished over time.

Up to 76.1 percent of patients in the 1.2 mg cohort achieved HbA1c targets of 6.5 percent or less. Serious treatment-emergent adverse events were reported in 2.9 percent of the 0.6 mg group, 4.2 percent of the 1.2 mg group, and 5.6 percent of the placebo group. Treatment-emergent adverse events led to premature discontinuation in 1 (1.4 percent) participant in each treatment group. No deaths occurred [3].

7.5 Phase 3 EECOH-2: Active comparator (dulaglutide)

The EECOH-2 trial was a 52-week, multicenter, open-label, non-inferiority, randomized Phase 3 trial conducted at 52 hospitals in China [4]. Adults aged 18 to 75 years with type 2 diabetes and elevated glucose concentrations on metformin monotherapy were randomized 1:1:1 to ecnoglutide 0.6 mg, ecnoglutide 1.2 mg, or dulaglutide 1.5 mg weekly.

Both ecnoglutide doses demonstrated non-inferior HbA1c reductions versus dulaglutide 1.5 mg. The 1.2 mg dose achieved statistically significantly greater HbA1c reduction from baseline than dulaglutide 1.5 mg, although the difference was characterized as not clinically meaningful by the investigators. Both ecnoglutide doses achieved statistically significant weight reductions relative to dulaglutide. The safety profile was consistent with the GLP-1 receptor agonist class, with low risk of hypoglycemia [4].

7.6 Phase 3 SLIMMER: Overweight and obesity

The SLIMMER trial was a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial conducted at 36 medical centers across China, enrolling 664 adults with overweight or obesity (without diabetes) between April 2023 and June 2024 [5]. Participants were randomized to ecnoglutide 1.2 mg, 1.8 mg, or 2.4 mg weekly or matching placebo.

At week 40, the least-squares mean percentage change in body weight from baseline was: Ecnoglutide 1.2 mg: minus 9.1 percent. Ecnoglutide 1.8 mg: minus 10.9 percent. Ecnoglutide 2.4 mg: minus 13.2 percent. Placebo: minus 0.1 percent. All ecnoglutide doses were statistically significantly superior to placebo (P less than 0.0001).

At week 48, the 2.4 mg dose achieved 15.4 percent mean body weight loss, with 92.8 percent of participants achieving 5 percent or greater weight loss and 87 percent of participants in the 2.4 mg group achieving this threshold at week 40 [5].

Adverse events were reported in 93 percent of ecnoglutide-treated participants and 84 percent of placebo-treated participants. The principal adverse events were mild to moderate gastrointestinal symptoms, consistent with the GLP-1 receptor agonist class.

8. Sourcing and Quality Verification

Ecnoglutide is available from the following principal sources:

Pharmaceutical-grade (approved product): Ecnoglutide injection is approved for marketing in China for chronic weight management (NMPA, January 2026) and is supplied in prefilled injection pens at the registered strengths. Pharmaceutical sourcing is currently limited to China; regulatory submissions in other jurisdictions have not been publicly announced [6].

Research-grade: Ecnoglutide (XW003) is available from multiple research chemical suppliers, including MedChemExpress, Cayman Chemical, and other specialty peptide suppliers, at research-grade purity (typically greater than 95 percent by HPLC). Supply is in milligram quantities as the trifluoroacetate or acetate salt; pricing reflects the complexity of the 31-amino-acid lipopeptide synthesis.

Investigators should confirm compound identity and purity on every research-grade lot through:

- Reversed-phase high-performance liquid chromatography area-percent purity, ideally greater than 95 percent
- Electrospray ionization mass spectrometry or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ consistent with C₁₉₄H₃₀₄N₄₈O₆₁)
- Amino acid analysis to confirm the composition and the Ala8Val substitution
- Peptide content determination (net peptide weight, typically 70 to 85 percent of gross weight for lyophilized peptides, accounting for residual moisture, counterion, and salt)
- Endotoxin testing (Limulus amoebocyte lysate assay) for any preparation intended for in vivo research

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Given the structural complexity and the cost of the compound, on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Ecnoglutide is supplied as a lyophilized powder (research-grade) or as a ready-to-use solution in prefilled pens (pharmaceutical-grade). For research applications:

Reconstitution: Reconstitute the lyophilized powder in sterile water for injection, bacteriostatic water for injection, or phosphate-buffered saline to a stock concentration of 1 to 10 mg/mL. Gentle swirling is recommended to dissolve the peptide; avoid vigorous vortexing, which can cause aggregation and surface denaturation at the air-liquid interface. The compound is freely soluble in aqueous solutions at neutral pH.

Storage of solid: Store lyophilized powder at minus 20 degrees Celsius, protected from moisture. The compound is stable under these conditions for at least 24 months (per vendor certificates of analysis).

Storage of reconstituted solution: Store reconstituted solutions at 2 to 8 degrees Celsius (refrigerated) for up to 14 days (sterile water) or up to 30 days (bacteriostatic water). For longer-term storage, aliquot and freeze at minus 20 degrees Celsius or minus 80 degrees Celsius. Minimize freeze-thaw cycles; single-use aliquoting is recommended.

Light protection: Not strictly required for short-term handling, but light protection during extended storage is reasonable practice for peptide compounds.

In-use stability for pharmaceutical-grade product: The prefilled injection pen should be stored at 2 to 8 degrees Celsius and used within the manufacturer-specified expiry period. The pen should be protected from freezing and from direct sunlight.

DMSO stock solutions: For in vitro cell-based assays where higher stock concentrations are required, ecnoglutide can be dissolved in dimethyl sulfoxide (DMSO) at concentrations up to 10 mM. DMSO stocks should be stored at minus 20 degrees Celsius and diluted into aqueous assay media immediately before use, with final DMSO concentration in the assay kept below 0.1 percent to avoid solvent effects on cell viability and receptor pharmacology.

10. Stack Interactions and Combinations

Ecnoglutide interacts with several drug classes through its GLP-1 receptor pharmacology and its effects on gastric emptying. Investigators conducting research with ecnoglutide, especially in chronic dosing regimens or in combination with other compounds, should consider:

Gastric emptying effects: Ecnoglutide delays gastric emptying, which can alter the absorption kinetics of orally co-administered drugs. Drugs with narrow therapeutic indices (warfarin, levothyroxine, oral contraceptives, certain antibiotics) should be monitored for altered absorption. However, the Chen et al. (2026) drug-drug interaction study demonstrated that coadministration of ecnoglutide did not clinically alter the total systemic exposure (AUC) of warfarin (both S- and R-enantiomers) or metformin; modest reductions in C_{max} and delays in T_{max} were observed but lacked clinical significance, and no dose adjustment was required for either drug [12].

Insulin and insulin secretagogues: Combination with insulin, sulfonylureas, or meglitinides increases the risk of hypoglycemia, as the additive insulin-secretory or insulin-supplementing effects can exceed the glucose-dependent protective mechanism of the GLP-1 receptor. Dose reduction of the concomitant insulin or secretagogue is standard clinical practice when initiating GLP-1 receptor agonist therapy.

Other GLP-1 receptor agonists: Concurrent use with another GLP-1 receptor agonist (semaglutide, liraglutide, dulaglutide, tirzepatide) is pharmacologically redundant and may produce additive gastrointestinal adverse events. The combination is not recommended in clinical practice.

Metformin: The combination of ecnoglutide and metformin is well characterized in the EECOH-2 trial and is a standard clinical combination. No pharmacokinetic interaction requiring dose adjustment has been identified [4, 12].

SGLT2 inhibitors: The combination of GLP-1 receptor agonists with sodium-glucose cotransporter 2 (SGLT2) inhibitors (empagliflozin, dapagliflozin, canagliflozin) produces complementary mechanisms of glycemic control and weight loss. The combination has not been specifically studied with ecnoglutide but is well established in the broader GLP-1 receptor agonist class and is expected to produce additive efficacy without additive safety concerns.

Oral medications with pH-dependent absorption: The delay in gastric emptying may alter the absorption of drugs requiring acidic gastric conditions for dissolution. Proton pump inhibitors and H2 receptor antagonists should be considered for potential interaction with ecnoglutide through the shared pathway of gastric acid and motility modulation.

Pancreatitis risk medications: Concurrent use with other agents associated with pancreatitis risk (didanosine, valproic acid, azathioprine) should be approached with caution, given the background class-associated signal for acute pancreatitis with GLP-1 receptor agonists.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events across all clinical trials are consistent with the GLP-1 receptor agonist class:

- Nausea (the most common gastrointestinal event; incidence approximately 15 to 30 percent across trials, dose-dependent, typically mild to moderate, predominantly during dose escalation)
- Diarrhea (10 to 20 percent; the most common gastrointestinal event in the EECOH-1 trial)
- Decreased appetite (10 to 20 percent; consistent with the appetite-suppressive mechanism)
- Vomiting (5 to 15 percent; dose-dependent)
- Constipation (5 to 10 percent)
- Injection site reactions (pain, erythema; 5 to 10 percent)
- Headache (5 to 10 percent)
- Asthenia (greater than 5 percent in the EECOH-1 trial)
- Upper respiratory tract infection (greater than 5 percent in the EECOH-1 trial)

Gastrointestinal adverse events are the principal tolerability limitation. They occur predominantly during the dose-escalation period and diminish substantially with continued treatment, consistent with adaptation to the GLP-1 receptor-mediated gastric emptying delay [3, 5]. The stepwise dose-escalation protocol used in all Phase 3 trials (starting at 0.3 mg and escalating over 8 to 16 weeks) is designed to mitigate the severity and incidence of gastrointestinal symptoms.

11.2 Laboratory abnormalities

- Increased lipase (greater than 5 percent incidence in the EECOH-1 trial). Lipase elevation is a class effect of GLP-1 receptor agonists and is generally asymptomatic. The clinical significance of asymptomatic lipase elevation in the absence of pancreatitis symptoms is uncertain.

- Increased amylase (observed at lower frequency than lipase elevation)

11.3 Serious adverse events

Serious treatment-emergent adverse events in Phase 3 trials were infrequent and were not more common in ecnoglutide groups than in placebo groups. In the EECOH-1 trial, serious adverse events were reported in 2.9 percent (0.6 mg), 4.2 percent (1.2 mg), and 5.6 percent (placebo) of participants [3]. No deaths occurred in any ecnoglutide clinical trial reported as of the monograph revision date.

11.4 Hypoglycemia

The risk of hypoglycemia with ecnoglutide monotherapy is low, consistent with the glucose-dependent mechanism of GLP-1 receptor-mediated insulin secretion. In the EECOH-2 trial comparing ecnoglutide to dulaglutide in patients on metformin, the risk of hypoglycemia was low across all treatment groups [4]. The risk increases with concurrent insulin or sulfonylurea use.

11.5 Pancreatitis signal

Acute pancreatitis is a class-associated safety signal for GLP-1 receptor agonists. No cases of acute pancreatitis have been reported in the published Phase 3 ecnoglutide trials. The lipase and amylase elevations observed in some participants are monitored as potential precursors but have not been associated with clinical pancreatitis events in the published data. Ongoing pharmacovigilance in the post-marketing setting will continue to monitor for this signal [3, 5].

11.6 Thyroid C-cell signal

GLP-1 receptor agonists produce thyroid C-cell tumors in rodents at supratherapeutic exposures, a class effect attributed to GLP-1 receptor expression on rodent thyroid C-cells (which express the GLP-1 receptor at much higher density than human C-cells). The clinical relevance to humans is uncertain; no excess of medullary thyroid carcinoma has been detected in human postmarketing surveillance of semaglutide or liraglutide. Ecnoglutide prescribing information in China includes a precautionary statement regarding this class signal, and the compound is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

11.7 Pregnancy and lactation

Reproductive and developmental toxicology data in humans are not available. GLP-1 receptor agonists are generally not recommended during pregnancy or lactation. Animal reproduction studies have not been published for ecnoglutide specifically. The prescribing information advises discontinuation of ecnoglutide at least 2 months before planned conception, consistent with the long elimination half-life.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five GLP-1 receptor agonists and incretin mimetics against ecnoglutide, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal GLP-1-based agents with substantive clinical evidence in glycemic control and weight management, with priority on those with advanced regulatory status and large clinical datasets.

12.1 Semaglutide (Ozempic, Wegovy, Rybelsus)

Mechanism: Unbiased GLP-1 receptor agonist. Full agonism of both the Gs/cAMP and beta-arrestin/internalization pathways. Fatty acid-acylated GLP-1 (7-37) analog with Aib8 substitution and C18 fatty diacid at Lys26 [8].

Development trajectory: Novo Nordisk. Approved by the FDA for type 2 diabetes (Ozempic, 2017; 0.5, 1.0, 2.0 mg weekly), for chronic weight management (Wegovy, 2021; 2.4 mg weekly), and as an oral formulation (Rybelsus, 2019; 3, 7, 14 mg daily). Approved globally in more than 100 jurisdictions.

Novelty: Moderate at time of introduction. The first GLP-1 receptor agonist with once-weekly dosing at the potency level required for robust weight loss. The oral formulation (Rybelsus) was novel in demonstrating oral peptide bioavailability. However, the mechanism is unbiased GLP-1 receptor agonism, representing a refinement of existing pharmacology rather than a mechanistic advance.

Effect size: Large. In the STEP program for obesity, semaglutide 2.4 mg weekly produced approximately 15 to 17 percent mean body weight loss at 68 weeks [13]. In the SUSTAIN program for type 2 diabetes, HbA1c reductions of 1.5 to 1.8 percentage points were observed [8]. These are the benchmark effect sizes against which ecnoglutide is evaluated.

Promising potential: Very high. Semaglutide is the market-leading GLP-1 receptor agonist with extensive clinical evidence across multiple indications (type 2 diabetes, obesity, cardiovascular risk reduction, MASH, Alzheimer's disease). Ongoing trials span a broad range of metabolic and non-metabolic indications.

Side-effect profile: The principal limitation is gastrointestinal: nausea (approximately 20 to 44 percent), vomiting (approximately 10 to 25 percent), diarrhea, and constipation. These are the class-defining adverse events that limit dose escalation and reduce patient adherence. The gastrointestinal burden has been hypothesized to relate in part to beta-arrestin-mediated receptor internalization and endosomal signaling, the pathway that ecnoglutide was designed to reduce.

Overall validation: Very high. The most extensively validated GLP-1 receptor agonist in clinical medicine, with multiple Phase 3 programs, cardiovascular outcome trials (SELECT), and real-world evidence.

Comparison to ecnoglutide: Semaglutide is the principal benchmark for ecnoglutide. The compounds share the same receptor target, the same fatty acid-albumin binding mechanism, and similar pharmacokinetic profiles. The critical difference is signaling bias: semaglutide is an unbiased full agonist of both cAMP and beta-arrestin pathways, while ecnoglutide is a cAMP-biased agonist with reduced beta-arrestin recruitment and negligible receptor internalization. In preclinical head-to-head studies, ecnoglutide demonstrated superior glucose suppression at late time points and superior weight reduction on chronic dosing [1]. The clinical weight-loss efficacy of ecnoglutide 2.4 mg at 48 weeks (15.4 percent) approaches semaglutide 2.4 mg at 68 weeks (approximately 15 to 17 percent), but the comparison is limited by differences in trial duration, population (Chinese versus global), and trial design. Ecnoglutide has the advantage of the biased-agonism mechanism, exclusive use of natural amino acids, and higher receptor binding affinity; semaglutide has the advantage of extensive global clinical validation, multiple approved indications, oral and injectable formulations at scale, and cardiovascular outcome data.

12.2 Tirzepatide (Mounjaro, Zepbound)

Mechanism: Dual GLP-1/GIP (glucose-dependent insulintropic polypeptide) receptor agonist. Activates both the GLP-1 receptor and the GIP receptor, producing complementary incretin effects [14].

Development trajectory: Eli Lilly. Approved by the FDA for type 2 diabetes (Mounjaro, 2022; 5, 10, 15 mg weekly) and for chronic weight management (Zepbound, 2023; 5, 10, 15 mg weekly). Approved globally.

Novelty: High. The dual GLP-1/GIP mechanism is a genuinely distinct pharmacological approach. GIP receptor agonism adds a second incretin axis that potentiates insulin secretion and may directly promote adipose tissue browning and lipid metabolism.

Effect size: Very large. In the SURMOUNT-1 trial for obesity, tirzepatide 15 mg weekly produced approximately 22.5 percent mean body weight loss at 72 weeks, the largest weight reduction reported for any pharmacotherapy in a Phase 3 trial [14]. HbA1c reductions of 2.0 to 2.3 percentage points in type 2 diabetes exceed semaglutide at comparable doses. Tirzepatide demonstrated superiority to semaglutide on both weight loss and HbA1c endpoints in the SURPASS-2 and head-to-head obesity trials.

Promising potential: Very high. Active development in multiple indications; regulatory approvals expanding.

Side-effect profile: Gastrointestinal adverse events are the principal limitation, similar in character to semaglutide (nausea, vomiting, diarrhea, constipation). Rates are broadly similar to semaglutide at equivalent efficacy levels.

Overall validation: Very high. Extensive Phase 3 data across diabetes and obesity indications; the current benchmark for maximum pharmacotherapy-induced weight loss.

Comparison to ecnoglutide: Tirzepatide has a fundamentally different mechanism (dual-receptor) and currently produces greater weight loss than ecnoglutide at the highest studied doses. Ecnoglutide is a single-target GLP-1 receptor agonist and does not engage the GIP receptor. The comparison is therefore primarily one of single versus dual receptor pharmacology. Ecnoglutide's biased-agonism approach represents an optimization within the GLP-1 receptor agonist class, while tirzepatide represents a class expansion through dual-receptor engagement. The two approaches are not mutually exclusive; a cAMP-biased dual GLP-1/GIP agonist is a theoretically conceivable next-generation compound.

12.3 Liraglutide (Victoza, Saxenda)

Mechanism: Unbiased GLP-1 receptor agonist. Fatty acid-acylated GLP-1 (7-37) analog with Arg34Lys substitution and C16 palmitic acid at Lys26 [7].

Development trajectory: Novo Nordisk. Approved for type 2 diabetes (Victoza, 2010; 1.2, 1.8 mg daily) and for chronic weight management (Saxenda, 2014; 3.0 mg daily). Once-daily dosing reflects the shorter half-life (approximately 13 hours) relative to semaglutide and ecnoglutide.

Novelty: Low (at current date). The first fatty acid-acylated GLP-1 analog; novel at introduction but now superseded by once-weekly agents.

Effect size: Moderate. In the SCALE program for obesity, liraglutide 3.0 mg daily produced approximately 8 percent mean body weight loss at 56 weeks. HbA1c reductions of approximately 1.0 to 1.5 percentage points at 1.8 mg daily for type 2 diabetes.

Promising potential: Moderate. Established product with declining market share as once-weekly agents (semaglutide, tirzepatide) demonstrate superior efficacy and convenience.

Side-effect profile: Gastrointestinal adverse events (nausea approximately 39 percent, vomiting approximately 15 percent at the 3.0 mg obesity dose). Once-daily dosing produces daily fluctuations in GLP-1 receptor occupancy that may contribute to recurrent nausea.

Overall validation: High. Extensive Phase 3 and real-world evidence; the LEADER cardiovascular outcome trial demonstrated cardiovascular benefit.

Comparison to ecnoglutide: Ecnoglutide has substantially greater weight-loss efficacy (13 to 15 percent versus approximately 8 percent), once-weekly versus once-daily dosing, and the cAMP-biased signaling profile. Liraglutide has the advantage of an established global regulatory footprint, cardiovascular outcome data (LEADER), and a longer post-marketing safety record.

12.4 Dulaglutide (Trulicity)

Mechanism: GLP-1 receptor agonist; GLP-1 analog fused to a modified immunoglobulin G4 (IgG4) Fc fragment rather than fatty acid-acylated. The Fc fusion extends the half-life to approximately 5 days, supporting once-weekly dosing [7].

Development trajectory: Eli Lilly. Approved for type 2 diabetes (Trulicity, 2014; 0.75, 1.5, 3.0, 4.5 mg weekly). Not separately approved for chronic weight management, though weight loss is observed at higher doses.

Novelty: Low. The Fc-fusion approach is mechanistically conventional; the principal contribution was demonstrating the viability of once-weekly GLP-1 receptor agonism as a clinical concept.

Effect size: Moderate. HbA1c reductions of approximately 1.3 to 1.6 percentage points at 1.5 mg weekly. Weight loss of approximately 3 to 5 percent at registered doses. In the EECO-2 head-to-head trial, ecnoglutide 1.2 mg weekly demonstrated non-inferiority to dulaglutide 1.5 mg on HbA1c reduction, with the ecnoglutide 1.2 mg dose achieving statistically significantly greater reduction and significantly greater weight loss [4].

Promising potential: Moderate. Established product with stable market position in type 2 diabetes; the REWIND cardiovascular outcome trial demonstrated cardiovascular benefit.

Side-effect profile: Gastrointestinal adverse events similar to the class; nausea approximately 12 to 21 percent at 1.5 mg, lower than semaglutide at efficacy-equivalent doses.

Overall validation: High. Extensive Phase 3 data and the REWIND cardiovascular outcome trial.

Comparison to ecnoglutide: Ecnoglutide 1.2 mg demonstrated non-inferiority to dulaglutide 1.5 mg on glycemic control and significantly greater weight loss in the head-to-head EECO-2 trial [4]. Ecnoglutide has the advantages of the cAMP-biased mechanism and greater weight-loss efficacy; dulaglutide has the advantages of established global regulatory approval, cardiovascular outcome data (REWIND), and a longer post-marketing safety record.

12.5 Orforglipron (Eli Lilly, LY3502970)

Mechanism: Small-molecule, non-peptide, oral GLP-1 receptor agonist. Full agonism of the GLP-1 receptor through a binding site distinct from the orthosteric peptide-binding site, enabling oral bioavailability without absorption enhancers [15].

Development trajectory: Eli Lilly. Phase 3 development for type 2 diabetes and obesity. Phase 2 results in obesity (GZGI trial) demonstrated dose-dependent weight loss of up to approximately 14.7 percent at 36 mg daily at 36 weeks [15]. Phase 3 trials are in progress; results have not been reported as of the monograph revision date.

Novelty: Very high. The first non-peptide, small-molecule GLP-1 receptor agonist to reach Phase 3 development. Oral administration without absorption enhancers represents a fundamental advance in drug delivery for the incretin class.

Effect size: Encouraging in Phase 2. The 14.7 percent weight loss at 36 weeks at the highest dose is competitive with injectable semaglutide and ecnoglutide, though the Phase 3 confirmation is awaited.

Promising potential: High. If Phase 3 results confirm Phase 2 efficacy and safety, orforglipron would represent a paradigm shift from injectable to oral GLP-1 receptor agonist therapy. The small-molecule format eliminates the cold-chain requirement, the injection burden, and the manufacturing cost constraints of peptide synthesis.

Side-effect profile: Phase 2 data showed gastrointestinal adverse events (nausea, vomiting, diarrhea) broadly consistent with the GLP-1 receptor agonist class, with dose-dependent incidence. The gastrointestinal burden at efficacious doses was substantial and is a potential limitation for clinical adoption.

Overall validation: Moderate. Phase 2 data are robust but Phase 3 confirmation is pending. The compound has not been approved by any regulatory authority.

Comparison to ecnoglutide: Orforglipron and ecnoglutide represent different strategic approaches to GLP-1 receptor optimization. Ecnoglutide optimizes signaling quality (cAMP bias) within the peptide agonist paradigm; orforglipron optimizes drug delivery (oral small molecule) within the unbiased full-agonist paradigm. The two approaches are not mutually exclusive; a cAMP-biased small-molecule GLP-1 receptor agonist is a conceivable future direction. Ecnoglutide has the advantage of approved regulatory status (NMPA, China) and Phase 3 clinical validation; orforglipron has the advantage of the oral small-molecule format and the potential for lower manufacturing cost and broader patient acceptability.

12.6 Comparator summary

The five comparators occupy distinct positions in the GLP-1 receptor agonist and incretin mimetic landscape. **Semaglutide** is the benchmark unbiased GLP-1 receptor agonist with the largest clinical evidence base and global regulatory footprint. **Tirzepatide** produces the largest weight-loss effect through dual GLP-1/GIP receptor agonism but is a fundamentally different mechanism from single-target GLP-1 agonism. **Liraglutide** is the first-generation fatty acid-acylated GLP-1 analog, now largely superseded by once-weekly agents. **Dulaglutide** is the Fc-fusion once-weekly GLP-1 agonist against which ecnoglutide has demonstrated non-inferiority and superior weight loss in a head-to-head Phase 3 trial. **Orforglipron** is the most mechanistically novel comparator through its small-molecule oral format, pending Phase 3 confirmation.

Ecnoglutide occupies a unique position in this comparator landscape: it is the only compound with deliberately engineered cAMP signaling bias at the GLP-1 receptor, the only compound that produces negligible receptor internalization, and the first cAMP-biased GLP-1 receptor agonist approved by any regulatory authority worldwide. Its clinical evidence base is currently concentrated in Chinese populations and in type 2 diabetes and obesity indications; the absence of cardiovascular outcome data, of global regulatory approval, and of data in non-East Asian populations are the principal limitations relative to semaglutide and tirzepatide. The biased-agonism mechanism is a testable pharmacological hypothesis with strong pre-clinical support: if sustained receptor surface availability translates to improved chronic efficacy or tolerability at scale, ecnoglutide or next-generation biased agonists could materially alter the competitive positioning of the GLP-1 receptor agonist class.

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