# GLP-1 EVOLUTION

*The complete story of metabolic medicine, told honestly.*

# The 2026 Honest Guide to GLP-1 Weight Loss Medications

Semaglutide vs Tirzepatide vs Retatrutide — What the trials actually showed.

16 pages. PMID-cited. No hype.

**Edition: v4 — published 2026-05-11 (with direct provider links)**

# Important Disclaimer

**Educational content only. Not medical advice.**

This guide summarizes published clinical-trial data and the U.S. regulatory framework for GLP-1 receptor agonists as of May 2026. It is intended for educational purposes only and does not constitute medical advice, diagnosis, or treatment. Consult your physician before starting, changing, or stopping any GLP-1 medication.

**Affiliate disclosure (FTC).**

GLP-1 Evolution is reader-supported. We work with several telehealth affiliate partners and may receive a commission at no additional cost to you if you sign up through links on our site. All outbound affiliate links are tagged rel="sponsored nofollow". Editorial assessment is independent — we describe the regulatory framework as we understand it, not as our affiliate partners would prefer it framed.

Individual results from any prescription medication vary. Clinical-trial averages are produced under controlled conditions (defined dose titration, lifestyle counseling, screened populations) and real-world outcomes routinely differ. Side-effect profiles, contraindications, and drug interactions are summarized briefly here and are not comprehensive — consult the full FDA prescribing information and your prescriber.

Compounded products discussed in this guide are not FDA-approved finished products. **Retatrutide is investigational and NOT FDA-approved** as of May 2026. Pricing references are dated; verify current pricing directly with the provider.

# What is GLP-1?

**Short answer:** GLP-1 (glucagon-like peptide-1) is a hormone your gut releases after you eat. It signals the pancreas to release insulin, slows how fast the stomach empties, and acts on appetite centers in the brain to reduce hunger.

GLP-1 is one of several incretin hormones — gut-derived signals that prepare the body to handle incoming nutrients. The other major incretin is GIP (glucose-dependent insulinotropic polypeptide). Modern GLP-1 medications are synthetic peptides engineered to mimic this signal but resist the rapid breakdown that natural GLP-1 undergoes (the natural hormone has a half-life of roughly two minutes; semaglutide's is about a week).

## Three mechanisms relevant to weight

- **Slowed gastric emptying.** Food leaves the stomach more slowly, prolonging satiety.
- **Central appetite reduction.** Receptors in the hypothalamus and brainstem reduce drive to eat.
- **Improved insulin response.** Glucose-dependent insulin secretion improves blood-sugar control, which has metabolic benefits beyond weight.

> **Why generations matter.**
>
> *First-generation GLP-1 agonists (liraglutide, exenatide) target GLP-1 only. Second generation (semaglutide) is GLP-1 only but with longer half-life. Third generation (tirzepatide) targets GLP-1 and GIP. Investigational agents (retatrutide) target GLP-1, GIP, and glucagon. Each added receptor changes the trade-off profile — both for efficacy and side effects.*

# GLP-1: Pharmacology in Plain English

All currently marketed GLP-1 weight-loss medications are injectable peptides. Oral GLP-1 (oral semaglutide / Rybelsus) exists for type-2 diabetes but is not currently approved at weight-loss doses. The injection is subcutaneous (under the skin, typically abdomen, thigh, or upper arm) and is taken once weekly for the products covered here.

## Dose titration is not optional

Every approved GLP-1 weight-loss medication uses a step-up dosing schedule — starting at a low dose and increasing every 4 weeks. This is not a marketing convention; it is the only way to manage gastrointestinal side effects (nausea, vomiting, constipation, diarrhea) which are dose-dependent. Skipping titration steps materially increases the chance of stopping the medication.

## What "mean weight loss" means in trials

When a trial reports "14.9% mean body weight reduction," that figure is the average across all participants who received the active dose. The distribution around the mean is wide: some participants lost much more, some lost very little, and a small fraction did not respond. Trials also include intensive lifestyle counseling that real-world telehealth patients may or may not receive at the same intensity.

**Plain-English regulatory translation.**

*An FDA-approved finished product (Wegovy, Zepbound) means the manufacturer's specific formulation, dosing device, and manufacturing process have been reviewed and approved. A compounded product uses the same active pharmaceutical ingredient but is mixed by a pharmacy under a different regulatory framework (503A or 503B). The active molecule may be the same; the regulatory object is not.*

# Semaglutide

| Status | Brand (weight) | Brand (T2D) | Mechanism |
|---|---|---|---|
| FDA-approved | Wegovy | Ozempic | GLP-1 agonist |

## STEP-1 trial — the headline data

The STEP-1 trial (**PMID 33567185**) randomized 1,961 adults with overweight or obesity (BMI ≥ 30, or ≥ 27 with at least one weight-related condition) and without diabetes to either semaglutide 2.4 mg weekly or placebo, for 68 weeks. Both groups received lifestyle counseling. **Mean body weight reduction was 14.9% in the semaglutide group versus 2.4% in placebo.** About a third of participants in the semaglutide arm achieved ≥20% weight loss.

## Dose schedule (weight-loss indication)

- Weeks 1-4: 0.25 mg weekly
- Weeks 5-8: 0.5 mg weekly
- Weeks 9-12: 1.0 mg weekly
- Weeks 13-16: 1.7 mg weekly
- Week 17 onward: 2.4 mg weekly (maintenance)

**Honest caveat.**

*STEP-1's 14.9% figure assumes adherence to the full titration through week 17 and continued weekly dosing for the full 68 weeks. Drop-out and non-adherence in real-world telehealth settings are higher than in trial settings.*

# Semaglutide (continued)

## Common side effects

Gastrointestinal effects are the dominant side-effect class: nausea (in roughly 40-45% of participants in STEP-1), diarrhea, constipation, vomiting, and abdominal pain. These are typically worst during titration and improve with time. Less common but serious: pancreatitis, gallbladder disease, and a boxed warning for thyroid C-cell tumors based on rodent data (no causal human evidence).

## Who semaglutide may not be appropriate for

- Personal or family history of medullary thyroid carcinoma (MTC).
- Multiple Endocrine Neoplasia syndrome type 2 (MEN-2).
- History of pancreatitis (relative caution).
- Pregnancy or planning pregnancy in the near term.
- Severe gastroparesis (slowed stomach emptying may worsen).

## Discontinuation and weight regain

The STEP-4 extension data showed that participants who stopped semaglutide regained a substantial fraction of lost weight within a year. GLP-1 medications act as ongoing metabolic therapy — weight benefit is maintained while on therapy and largely reverses on discontinuation. This is a clinically important fact to discuss with a prescriber before starting.

**Compounded semaglutide note.**

*Compounded semaglutide is mixed by 503A or 503B pharmacies and is not the same regulatory object as Wegovy. The active pharmaceutical ingredient is semaglutide in both, but the FDA does not review and approve each batch of a compounded product the way it does for branded Wegovy. Whether to use compounded semaglutide is a trade-off between cost and regulatory ambiguity. The trade-off is real and worth understanding.*

# Tirzepatide

| Status | Brand (weight) | Brand (T2D) | Mechanism |
|---|---|---|---|
| FDA-approved | Zepbound | Mounjaro | GLP-1 + GIP |

## SURMOUNT-1 trial — the headline data

SURMOUNT-1 (**PMID 35658024**) randomized 2,539 adults with obesity (or overweight with comorbidity) without type-2 diabetes to tirzepatide 5 mg, 10 mg, 15 mg weekly, or placebo, for 72 weeks, with lifestyle counseling in all arms. **Mean body weight reduction at the 15 mg dose was approximately 20.9% versus 3.1% in placebo.** Approximately 57% of participants on the 15 mg dose achieved ≥20% weight loss — a higher response rate than reported for semaglutide in STEP-1.

## Why dual agonism may produce larger weight loss

Adding GIP-receptor activity to GLP-1 activity appears to amplify weight-loss signal, and may also moderate some GI side effects in some participants. The mechanism by which GIP contributes to weight loss is still actively researched; the trial endpoint is the verified part.

## Dose schedule (weight-loss indication)

- Weeks 1-4: 2.5 mg weekly (starter)
- Weeks 5-8: 5 mg weekly
- Weeks 9-12: 7.5 mg weekly
- Weeks 13-16: 10 mg weekly
- Weeks 17-20: 12.5 mg weekly
- Week 21 onward: 15 mg weekly (maintenance, if tolerated)

# Tirzepatide (continued)

## Common side effects

GI side effects are again dominant: nausea, diarrhea, vomiting, constipation, decreased appetite, and abdominal pain. Boxed warning for thyroid C-cell tumors carries over from the GLP-1 class. Pancreatitis, gallbladder disease, and acute kidney injury are listed in prescribing information.

## Cost and access in 2026

Branded Zepbound list price has historically been the highest-cost option among GLP-1 weight-loss medications. Insurance coverage for the weight-loss indication remains inconsistent across plans. Some telehealth providers offer compounded tirzepatide as a lower-cost alternative; the same 503A/503B regulatory caveats apply as with compounded semaglutide. Verify current pricing directly with any provider you are considering.

> **Trade-off framing.**
> *Among FDA-approved options, current SURMOUNT-1 data places tirzepatide as the higher-efficacy option versus semaglutide on average. Branded Zepbound is also typically the more expensive option per month at list price. Lower price isn't automatically worse, and higher price isn't automatically better — but the trade-offs are real and worth understanding before you choose.*

## Discontinuation pattern

As with semaglutide, weight regain after discontinuation is the typical pattern (see SURMOUNT-4). Tirzepatide is best understood as ongoing metabolic therapy, not a time-limited course.

# Retatrutide

| Status | Trial stage | Manufacturer | Mechanism |
|---|---|---|---|
| **INVESTIGATIONAL**<br>NOT FDA-approved | Phase 3 (TRIUMPH) | Eli Lilly | GLP-1 + GIP + glucagon |

**Status statement (mandatory).**

***Retatrutide is investigational and NOT FDA-approved as of May 2026.*** *It is not legally available for prescription in the United States outside of active clinical trials. Any provider claiming to offer retatrutide outside a registered trial should be regarded as a serious red flag.*

## Phase 2 trial — the headline data

The Phase 2 retatrutide trial was published in NEJM in 2023 (**PMID 37296141**). It randomized 338 adults with obesity (and without diabetes) to retatrutide at multiple doses or placebo, for 48 weeks. **Mean body weight reduction at the highest dose (12 mg) approached approximately 24%.** Roughly a quarter of participants on the highest dose achieved ≥30% weight loss — a magnitude not previously documented in a Phase 2 weight-loss trial of an injectable peptide.

## Why a triple agonist

Adding glucagon-receptor activity to GLP-1 and GIP is a different theoretical bet than adding GIP alone. Glucagon-receptor activation can increase energy expenditure (more calories burned at rest), which is a different mechanism from suppressing appetite. The trade-off is that glucagon also elevates blood glucose and may have cardiovascular implications — questions Phase 3 trials are designed to answer at scale.

# Retatrutide (continued)

## Phase 3 timeline (TRIUMPH program)

Eli Lilly's TRIUMPH Phase 3 program for retatrutide includes multiple parallel trials covering obesity, obstructive sleep apnea, and obesity with type-2 diabetes. Public clinical-trial registry timelines suggest primary completion across the program in 2026 with potential FDA submission in the 2026-2027 window if data support it. This is a projection, not a guarantee. Drug development timelines slip routinely.

## What we do not yet know about retatrutide

- Long-term safety beyond 48 weeks.
- Cardiovascular outcomes data (separate dedicated trials are typical).
- Effect of glucagon-receptor activity on blood-sugar control in non-diabetic populations at scale.
- Comparative real-world tolerability vs tirzepatide.
- Final FDA-approved labeling, indications, contraindications, and dosing.

**Anti-pattern alert.**

*Some online providers and influencers describe retatrutide as if it were available, imminent, or already proven. As of May 2026, none of those framings is accurate. Wait-list signups for "notification when approved access opens" are reasonable. Prescription claims today are not.*

# Side Effects: Side-By-Side

Approximate incidence of the most common side effects across pivotal trials. Figures are rounded; check the full prescribing information (or Phase 2 publication for retatrutide) for exact rates.

| Side effect | Semaglutide 2.4 mg | Tirzepatide 15 mg | Retatrutide 12 mg (Ph2) |
|---|---|---|---|
| Nausea | ~44% | ~29-32% | ~30-35% |
| Diarrhea | ~30% | ~21-23% | ~25-28% |
| Vomiting | ~24% | ~13% | ~16-22% |
| Constipation | ~24% | ~17% | ~10-12% |
| Abdominal pain | ~20% | ~10% | ~10-15% |
| Pancreatitis (serious) | Rare | Rare | Rare (limited data) |
| Gallbladder events | Reported | Reported | Reported |
| Boxed: thyroid C-cell tumors | Yes (rodent data) | Yes (rodent data) | Class effect (TBD) |

**Reading this table.**

*Nausea is the most reliable predictor of who will discontinue. The titration schedule is the single biggest lever for tolerability — do not try to skip steps. If a specific dose level produces side effects you can't live with, your prescriber can hold or reduce dose; this is a normal clinical decision, not a failure.*

# Telehealth Access — Overview

Telehealth providers are the most common access path for GLP-1 weight-loss medication in the United States in 2026, particularly for patients without insurance coverage for the indication. Most operate under one of two models: **branded prescribing** (prescription for FDA-approved Wegovy or Zepbound, fulfilled via a retail or specialty pharmacy) or **compounded prescribing** (prescription for compounded semaglutide or tirzepatide via a 503A or 503B pharmacy partner).

## Affiliate disclosure (FTC)

GLP-1 Evolution maintains affiliate relationships with several telehealth providers. If you sign up through links on our site — or through the clickable provider names in the table below — we may receive a commission at no additional cost to you. **All provider names in the table below are affiliate links** tagged rel="sponsored nofollow". We list current affiliate partners below in editorial order based on the data we have; up-to-date comparison reviews live at glp1evolution.com. **Editorial assessment is independent.**

| Provider | Typical model | Notable for |
|---|---|---|
| Embody (Affiliate link) | Compounded route | Top recommended on current data |
| Eden Health (Affiliate link) | Compounded route | Established telehealth GLP-1 access + 13-tier payout structure |
| SHED (Affiliate link) | Compounded route | Compounded semaglutide / tirzepatide programs |
| SkinnyRx (Affiliate link) | Compounded route | Telehealth-led GLP-1 onboarding |
| GobyMeds (Affiliate link) | Compounded route | Direct affiliate; $25-off via my.gobymeds.com/s/EVOLUTION |

**How we ordered this list.**

*Ranking is based on aggregated performance data and editorial review (not on commission tiers). Provider fit depends on your situation (insurance, state, comfort with compounded products, follow-up cadence). Read the per-provider regulatory posture before deciding. All outbound affiliate links are tagged rel="sponsored nofollow" per FTC guidance.*

# Affiliate Partner Reference

For full per-provider reviews, regulatory posture, and current pricing, visit glp1evolution.com/providers. Each row below lists the canonical affiliate tracker URL we direct readers to. **Click any provider name to open the affiliate link in your browser.** All outbound clicks carry rel="sponsored nofollow" per FTC guidance.

| # | Provider | Affiliate tracker URL |
|---|---|---|
| 1 | Embody GLP1 **(TOP RECOMMENDED)** | track.revoffers.com/aff_c?offer_id=1548&aff_id=12418 |
| 2 | Eden Health GLP-1 | track.revoffers.com/aff_c?offer_id=1435&aff_id=12418 |
| 3 | SHED | track.revoffers.com/aff_c?offer_id=1516&aff_id=12418 |
| 4 | SkinnyRx | track.revoffers.com/aff_c?offer_id=1464&aff_id=12418 |
| 5 | GobyMeds (direct, $25 off) | my.gobymeds.com/s/EVOLUTION |

**FTC affiliate disclosure (repeat).**

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# 503A vs 503B Compounding

"Compounded" is a regulatory category, not a quality grade. Two distinct frameworks exist under the Drug Quality and Security Act of 2013 (DQSA), and the difference matters when you are choosing where your medication actually comes from.

## 503A pharmacies

Traditional compounding pharmacies operating under section 503A of the Federal Food, Drug, and Cosmetic Act. They prepare medications for individual patients pursuant to a valid prescription. They are licensed and inspected at the state level by state boards of pharmacy. They are not registered with the FDA as outsourcing facilities and are not subject to the same federal cGMP (current Good Manufacturing Practice) requirements as 503B facilities.

## 503B outsourcing facilities

Created by the DQSA in 2013 in response to the New England Compounding Center meningitis outbreak. 503B outsourcing facilities register with the FDA, comply with cGMP, and are subject to FDA inspection. They can produce compounded products in larger batches without patient-specific prescriptions. The cGMP and FDA-inspection layer is the primary regulatory difference vs 503A.

**What this means for a buyer.**

*Neither 503A nor 503B compounded products are FDA-approved finished products. Both are legitimate pathways under defined conditions. 503B adds an FDA-inspection layer that 503A does not have. Whether a specific provider uses 503A or 503B is a fair question to ask before you sign up. Either way, request a Certificate of Analysis (COA) for the lot you receive when possible.*

# 10 Questions to Ask Your Provider

Bring this checklist to your telehealth intake or in-person consultation. The goal is not to interrogate — the goal is to know what you are signing up for.

1. Is the medication you are prescribing FDA-approved (Wegovy / Zepbound) or compounded?
2. If compounded, does the dispensing pharmacy operate under 503A or 503B?
3. Can I obtain a Certificate of Analysis (COA) for the lot I receive?
4. What is the full titration schedule, and how do you handle dose holds for side effects?
5. What does the medication actually cost per month at each dose, and how does that change as I titrate up?
6. Is there an additional consultation, membership, or labs fee on top of medication cost?
7. How do I reach a clinician between visits if I have a side-effect concern?
8. What is your protocol for pancreatitis symptoms, severe nausea, or signs of gallbladder issues?
9. If I want to discontinue, how do you taper and what monitoring do you provide afterward?
10. What happens to my data and prescription history if I cancel my membership?

> **Methodical principle.**
> *Three checks — FDA-approved vs compounded, 503A vs 503B, and access to a COA — take two minutes total and give you meaningful regulatory confidence in any compounder. Add the cost-and-access questions and you have most of what matters.*

# Where to Go From Here

This guide is a starting point. The provider landscape, pricing, and regulatory framework all move — sometimes by quarter. We update glp1evolution.com regularly with current comparison reviews, regulatory disclosures, and provider audits.

## On glp1evolution.com you will find

- Side-by-side comparison reviews of telehealth providers, including affiliate disclosure per provider.
- Current pricing references (with date stamps and verify-with-provider notes).
- Long-form articles on the regulatory framework (503A/503B, FDA shortage list status, FTC actions).
- Email updates on retatrutide Phase 3 progress — without hype.
- A Spanish-language section with the same compliance force as English.

**Visit glp1evolution.com**

Latest comparison reviews, provider audits, and PMID-cited analysis.

*Educational use only. Not medical advice.*

## Sources & PMID Reference

| # | Citation | Used for |
|---|---|---|
| 1 | Wilding JPH, et al. NEJM 2021. PMID 33567185 (STEP-1). | Semaglutide 14.9% |
| 2 | Jastreboff AM, et al. NEJM 2022. PMID 35658024 (SURMOUNT-1). | Tirzepatide 20.9% |
| 3 | Jastreboff AM, et al. NEJM 2023. PMID 37296141 (Phase 2). | Retatrutide ~24% |
| 4 | U.S. FDA. Drug Quality and Security Act (2013). | 503A/503B. Compounding framework |
| 5 | Wegovy / Zepbound U.S. Prescribing Information. | Side-effect rates & warnings |
| 6 | ClinicalTrials.gov — TRIUMPH program records. | Retatrutide Phase 3 timeline |

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