

Cagrilintide Available for Research Use Only

(0.3 – 4.5 mg once weekly, dose-escalated)

Cagrilintide is an investigational, long-acting amylin analogue that reduces body weight in human trials. Combining it with a GLP-1 produces greater weight loss than either component alone. Animal studies identify brainstem satiety circuits that help explain these effects. [1,4,5,7,12]

 Safe at studied doses and durations with clinical monitoring; gastrointestinal effects are common. [1,5,6]

 Effective for weight reduction in studied populations (randomized human trials). [1,5,6]

Disclaimer: These notes are not authoritative and should not be interpreted as definitive scientific guidance. They are summaries, compilations and plausible extrapolations drawn from the most relevant research I was able to locate, and may omit nuances, conflicting data, or emerging evidence. The material reflects an attempt to organize and understand complex topics, not to provide clinical recommendations or expert interpretation.

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Dedicated phase 3 trials have established safety.

Once-weekly cagrilintide has demonstrated weight loss as monotherapy and in the semaglutide combination, CagriSema. These are distinct interventions; combination outcomes should not be attributed to cagrilintide alone. [1,3,5,6]

In REDEFINE 1, adults with overweight or obesity without diabetes lost an estimated 20.4% of body weight with CagriSema, 11.5% with cagrilintide, 14.9% with semaglutide, and 3.0% with placebo at 68 weeks. Both drugs targeted 2.4 mg weekly. [5]

In the sponsor's February 2026 REDEFINE 4 announcement, CagriSema 2.4/2.4 mg was similar to tirzepatide 15 mg. Estimated weight loss at 84 weeks was 23.0% versus 25.5%. [8]

Dose

Cagrilintide is studied by once-weekly subcutaneous (SC) injection. In the phase 1b combination study, its terminal half-life was approximately 7 days with median peak concentrations reached after 24–72 hours. [2]

Doses Studied as Monotherapy

The 26-week phase 2 monotherapy trial in adults with overweight or obesity without diabetes evaluated these weekly target doses: [1]

- 0.3 mg once weekly
- 0.6 mg once weekly

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- 1.2 mg once weekly
- 2.4 mg once weekly
- 4.5 mg once weekly

Mean weight loss increased across the tested doses, reaching 10.8% with 4.5 mg versus 3.0% with placebo. The monotherapy trial used dose escalation. The listed targets were not all starting doses. [1]

Dose Used with Semaglutide

The principal regimen in the published phase 3 CagriSema trials was:

- **Cagrilintide 2.4 mg + semaglutide 2.4 mg SC once weekly**

Treatment was escalated toward this target, with flexibility for tolerability. [5,6]. In September 2026, the sponsor also reported phase 3 results for CagriSema 1.0/1.0 mg weekly. [12]

Dose Escalation

Gradual escalation helps manage gastrointestinal intolerance, including nausea, vomiting, diarrhea, and constipation. Tolerability varies between individuals and regimens. [1,2,6]

The clinical trial approach was:

low starting exposure → gradual escalation → individually tolerated maintenance exposure

In REDEFINE 1, each component began at 0.25 mg weekly and was increased at four-week intervals toward 2.4 mg by week 16; delayed escalation and dose reductions were permitted. Escalation depended on tolerability, rather than an obligation to reach the largest studied dose. [5,6]

Frequency

The approximately one-week half-life means appreciable drug remains when the next weekly dose is given. The trial results support weekly administration; community practice of splitting dose for multiple administrations per week remains speculative. [1,2,5,6]

Dose Summary

Use	Cagrilintide exposure studied
Phase 2 monotherapy	0.3–4.5 mg once weekly [1]
Higher-dose Phase 2 monotherapy	4.5 mg once weekly [1]
Published CagriSema phase 3 trials	2.4 mg once weekly [5,6]
Semaglutide component of CagriSema	2.4 mg once weekly [5,6]

Typically discussed community doses are informed by these trials.

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- Up to 4.5 mg weekly when used alone, starting low and escalating gradually.
- Up to 2.4 mg weekly when combined with a GLP-1, starting low and escalating gradually.

Benefits

- **Dose-dependent weight loss** — demonstrated in the phase 2 monotherapy trial; phase 3 also confirmed Cagrilintide monotherapy effectiveness. [1,5]
- **Likely appetite suppression and increased satiety** — supported by Cagrilintide's effects on feeding and satiety circuits in animals, alongside human weight-loss efficacy. The mechanistic scope here refers to Cagrilintide alone. [1,4,7]
- **Likely earlier meal termination** — experimental amylin-pathway findings support eating less per meal as a contributor to reduced intake. [7]
- **Greater weight loss with a GLP-1** — established for CagriSema versus either component in randomized trials. In REDEFINE 2, adults with type 2 diabetes lost 13.7% versus 3.4% with placebo at 68 weeks under the treatment-policy analysis. [3,5,6]
- **Plausibly complementary appetite signaling** — different amylin and GLP-1 targets provide a biological explanation for the combination benefit. [7,10]
- **Improved glycemic control with CagriSema in type 2 diabetes** — demonstrated in human trials. In the small phase 2 trial, HbA1c fell by 2.2 percent with CagriSema, 0.9 percent with cagrilintide, and 1.8 percent with semaglutide. [3,6]

Investigated Uses

- **Obesity and/or weight-related comorbidities** — supported by human weight-management trials, alongside lifestyle intervention. [1,5,6]
- **Combination with GLP-1** — directly studied for additional weight reduction and glycemic control in the relevant trial populations. [3,5,6]
- **Metabolic and appetite endpoints** — animal and receptor studies investigate amylin signaling, feeding behavior, and its interaction with GLP-1 pathways. [4,7,9,10]

Contraindications and Clinical Cautions

- **Pregnancy and breastfeeding** — *safety in these populations is not established. Semaglutide used for weight reduction is discontinued when pregnancy is recognized.* [1,5,6,13]
- **Active eating disorders or inadequate nutrition** — *appetite reduction makes nutritional and eating-disorder assessment a clinical precaution.* [1,4]
- **Severe gastroparesis** — *a mechanistic caution for Cagrilintide because amylin pathways can influence gastric emptying; semaglutide's prescribing information explicitly advises against its use in severe gastroparesis.* [7,13]
- **Unstable cardiovascular disease** — *the available results do not establish safety in unstable disease or cardiovascular-event prevention.* [5,6,8]

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Side effects

- **Gastrointestinal effects** — nausea, vomiting, constipation, and diarrhea occur in human trials and are commonly mild or moderate. [1,5,6]
- **Reduced intake and dehydration** — appetite suppression or gastrointestinal symptoms can compromise food or fluid intake. [1,6,13]
- **Heart rate depends on the regimen** — in the 32-week phase 2 diabetes trial, mean pulse changed by –1 beat/min with cagrilintide, +3 with CagriSema, and +7 with semaglutide. [3]
- **Hypoglycemia with other glucose-lowering medicines** — semaglutide increases risk when combined with insulin or insulin secretagogues such as sulfonylureas. This matters for CagriSema and requires medication review and glucose monitoring; it is not proof of the same risk magnitude for cagrilintide alone. [13]
- **Gallbladder and pancreatic events** — gallbladder events occurred in 2.3% with cagrilintide, 4.1% with CagriSema, and 1.0% with placebo in REDEFINE 1. Semaglutide also carries pancreatitis and gallbladder warnings when used in the combination. [5,13]

Biological mechanism

Cagrilintide activates amylin receptors AMY1, AMY2, and AMY3, which consist of the calcitonin receptor paired with receptor activity-modifying proteins RAMP1, RAMP2, and RAMP3, respectively. It also activates the calcitonin receptor without a RAMP. These findings come from receptor pharmacology experiments. [9,10]

Animal studies support central control of appetite and meal termination through the dorsal vagal complex and connected feeding circuits. The 2026 cross-species atlas studied mice, rats, and macaques; functional rat experiments implicated calcitonin-receptor and prolactin-releasing-peptide signaling in the nucleus tractus solitarius in sustained Cagrilintide responses. These experiments support likely human satiety effects rather than directly measuring human neural responses. [7]

Mouse receptor-deletion experiments identify AMY1 and AMY3 signaling as important contributors to Cagrilintide-induced weight loss. The relative contribution of these receptor subtypes in humans remains an extrapolation. [4]

Amylin and GLP-1 agonism engage partly distinct feeding pathways. This is a plausible mechanistic explanation for the greater weight loss established with Cagrilintide plus semaglutide. [3,5,7,10]

Lipidation promotes prolonged exposure, including albumin binding. The measured terminal half-life of 159–195 hours supports once-weekly dosing but is not a direct measure of receptor occupancy. [2,9]

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References

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