CLINICAL IMPACT RATING

GM ★★★★★★☆

# In adults with overweight or obesity, weekly subcutaneous cagrilintide–semaglutide increased weight loss at 68 wk

ACP Journal Club Editorial Team at McMaster University

**Question:** In adults with overweight or obesity and no diabetes, what are the efficacy and safety of weekly subcutaneous cagrilintide–semaglutide?

**Design:** Randomized placebo- and active-controlled trial (REDEFINE 1).

**Blinding:** Treatment allocation concealed; blinded (participants, investigators, center staff, adjudicators of selected adverse events and deaths, and sponsor).*

**Setting:** Multiple centers across 22 countries.

**Participants:** 3417 adults (mean age, 47 y; 68% women; 72% White, 18% Asian, and 5.5% Black or African American; mean body mass index [BMI], 38 kg/m$^2$) who had BMI ≥30 kg/m$^2$ or ≥27 kg/m$^2$ with ≥1 obesity-related complication (e.g., hypertension, cardiovascular disease, dyslipidemia), and ≥1 self-reported unsuccessful attempt to lose weight using diet. Key exclusions: diabetes; surgical treatment other than specified interventions done >1 year before screening; or use of a glucose-lowering drug, glucagon-like peptide-1 (GLP-1) receptor agonist, or antiobesity drug in the past 90 days.

**Interventions:** Fixed-dose combination of weekly subcutaneous cagrilintide, 2.4 mg, and semaglutide, 2.4 mg ($n$ = 2108); cagrilintide, 2.4 mg ($n$ = 302); semaglutide, 2.4 mg ($n$ = 302); or placebo ($n$ = 705). All participants received a lifestyle intervention including diet and physical activity counseling.

*See Glossary.

**Results:** Cagrilintide–semaglutide vs. placebo or either drug alone in adults with overweight or obesity

| Outcomes | Mean change from baseline | | Difference (95% CI) at 68 wk |
|---|---|---|---|
| | Cagrilintide–semaglutide | Placebo | |
| **Weight change** | –20.4% | –3.0% | –17.3% (–18.1 to –16.6) |
| | Proportion of participants | | |
| **Weight reduction ≥5%** | 92% | 32% | 60% (56 to 65) |
| Weight reduction ≥25% | 35% | 1.0% | 34% (32 to 36) |

At 68 wk, cagrilintide–semaglutide increased weight loss vs. cagrilintide alone (difference, –8.9% [CI, –10.1 to –7.7]) and semaglutide alone (difference, –5.5% [CI, –6.7 to –4.3]). In the cagrilintide–semaglutide vs. cagrilintide-alone vs. semaglutide-alone vs. placebo groups, AEs occurred in 92% vs. 84% vs. 90% vs. 82% of participants, respectively; serious AEs occurred in 9.8% vs. 8.9% vs. 5.0% vs. 6.1%, respectively.

AE = adverse event; CI defined in Glossary. Primary outcomes indicated by boldface.

**Bottom line:** In adults with overweight or obesity and no diabetes, adding weekly cagrilintide–semaglutide to a lifestyle intervention increased weight loss at 68 weeks.

**Source Citation:** Garvey WT, Blüher M, Osorto Contreras CK, et al; REDEFINE 1 Study Group. **Coadministered cagrilintide and semaglutide in adults with overweight or obesity.** N Engl J Med. 2025;393:635-647.

## Commentary:

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REDEFINE 1 evaluated a combination of semaglutide and cagrilintide, a centrally acting amylin analogue that modulates appetite, and found clinically useful improvements in body weight, waist circumference, blood pressure, lipid and hemoglobin $A_{1c}$ levels, and physical function vs. placebo. The combination resulted in a 20% weight loss at 68 weeks. By comparison, previous trials reported weight loss of 15% with semaglutide at 68 weeks (1), 21% with the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide at 72 weeks (2), and 24% with the triple GLP-1/GIP/glucagon receptor agonist retatrutide at 48 weeks (3).

REDEFINE 1 was rigorously conducted, and enrollment of a large sample of participants across 22 countries enhances generalizability. However, participants were mostly women and White, and adults with diabetes were excluded. Although REDEFINE 1 did not assess cardiovascular outcomes, REDEFINE 3 is enrolling 7000 patients with established cardiovascular disease to evaluate these end points (NCT05669755).

Although most adverse events were mild to moderate in severity, serious adverse events with cagrilintide–semaglutide were nearly twice as common as with semaglutide alone. Hepatobiliary and gastrointestinal events were most common. Less than 60% of cagrilintide–semaglutide users received the maximal dose, underscoring the importance of active monitoring and titration. In the subgroup of participants with body composition measurements, 33% of total weight loss in the combination group was lean soft tissue mass. To minimize sarcopenia, ensuring sufficient protein intake and regular exercise seems prudent and requires further study.

REDEFINE 1 exemplifies the evolution of antiobesity therapies toward combinations of agonists. One may envision a future of truly personalized therapy with individual targeting of appetite, satiety, energy expenditure, and fat metabolism, as needed. However, affordability of the drugs will probably continue to constrain use, limiting benefits to a small proportion of eligible persons.

**Disclosures**: Disclosure forms are available with the article online.

## References

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3. **Jastreboff AM, Kaplan LM, Frías JP, et al; Retatrutide Phase 2 Obesity Trial Investigators.** Triple–hormone-receptor agonist retatrutide for obesity–a phase 2 trial. N Engl J Med. 2023;389:514-526.

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