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Short Communication

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Cagrilintide-Semaglutide (CagriSema): A Novel Combination Therapy for Obesity and Type 2 Diabetes Mellitus – Results from REDEFINE 1 and REDEFINE 2

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Abstract

Obesity and type 2 diabetes mellitus (T2DM) represent major global health challenges requiring novel therapeutic strategies. Cagrilintide, a long-acting amylin analogue, and semaglutide, a GLP-1 receptor agonist, have been co-developed as a dual-incretin–based therapy (CagriSema) to enhance weight loss, glycemic control, and cardiometabolic outcomes. Recent phase 3 trials—REDEFINE 1 in adults with obesity without diabetes and REDEFINE 2 in individuals with obesity and T2DM—have demonstrated robust efficacy of CagriSema. In REDEFINE 1, patients achieved a mean weight reduction of –20.4% versus –3.0% with placebo, while in REDEFINE 2, weight loss reached –13.7% compared to –3.4% with placebo ($p < 0.001$ for both). Additionally, 73.5% of patients in REDEFINE 2 achieved HbA1c ≤ 6.5% versus 15.9% in the placebo group. Beyond weight and glycemic benefits, improvements in waist circumference, blood pressure, lipid profiles, and inflammatory markers were observed. The most common adverse events were gastrointestinal, predominantly mild-to-moderate and transient, with no unexpected safety signals. Together, these findings establish CagriSema as a promising therapeutic advance for obesity and T2DM, offering synergistic efficacy with an acceptable safety profile.

Keywords: REDEFINE 1, REDEFINE 2, CagriSema, Cagrilintide, semaglutide, obesity

Introduction

Obesity and type 2 diabetes mellitus (T2DM) represent major global health challenges, often requiring innovative therapeutic approaches. Cagrilintide, an amylin analogue, in combination with semaglutide, a GLP-1 receptor agonist, forms a dual-incretin–based therapy (CagriSema) that targets weight reduction, glycemic control, and cardiometabolic improvement. Recent phase 3 clinical trials (REDEFINE 1 and REDEFINE 2) have provided robust evidence on the efficacy and safety of this combination.

Mechanism of Action

Semaglutide, a GLP-1 analogue, binds to GLP-1 receptors and controls appetite by acting on brain regions that regulate food intake [1-3]. Cagrilintide, a long-acting amylin analogue, mimics the action of amylin, a peptide co-secreted with insulin from pancreatic β-cells in response to nutrients and glucose, and regulates satiety by acting on amylin-sensitive brain regions [4-5]. Cagrilintide acts by slowing gastric emptying, suppressing appetite, and enhancing satiety, while semaglutide augments insulin secretion, reduces glucagon, and supports weight reduction. Together, CagriSema exerts synergistic effects on both weight loss and glycemic control.

Clinical Evidence

REDEFINE 1 Trial

The REDEFINE 1 phase 3a trial evaluated the efficacy of co-administered cagrilintide and semaglutide (CagriSema) in adults without diabetes who were overweight or obese. A total of 3417 participants with a BMI ≥30, or ≥27 with comorbidities, were randomized to receive CagriSema, semaglutide alone, cagrilintide alone, or placebo, along with lifestyle interventions. At 68 weeks, the treatment-policy estimand (intention-to-treat) showed a mean weight reduction of –20.4% with CagriSema versus –3.0% with placebo (difference: –17.3 percentage points; $p < 0.001$). Under the trial-product estimand (adherence-based), weight loss reached –22.7% for CagriSema compared to –2.3% with placebo. Refer Table 1) [3].

Table 1: Efficacy Results: Change in Body Weight from Baseline to Week 68

Estimand	Treatment	Mean Weight Reduction (%) (Mean body weight at baseline: 106.9 kg)
Treatment-policy (intention-to-treat)	CagriSema	–20.4
Treatment-policy (intention-to-treat)	Placebo	–3.0
Trial-product (adherence-based),	CagriSema	–22.7
Trial-product (adherence-based),	Placebo	–2.3

Patients on CagriSema achieved higher proportions of clinically meaningful weight-loss thresholds (≥5%, ≥20%, ≥25%, and ≥30%)

than placebo (P<0.001 for all). Gastrointestinal adverse events such as nausea, vomiting, diarrhea, constipation, and abdominal pain occurred in 79.6% of the CagriSema group, versus 39.9% with placebo, but were generally mild-to-moderate and transient. Improvements were also observed in BMI category, waist circumference, and cardiometabolic markers like blood pressure and inflammatory markers.

Overall, the trial demonstrated that cagrilintide–semaglutide provided substantial, clinically relevant weight reductions in this population.

REDEFINE 2 Trial

The REDEFINE-2 trial, a phase 3a double-blind, randomized, placebo-controlled study, evaluated the efficacy of once-weekly coadministration of cagrilintide and semaglutide (CagriSema) in adults with overweight or obesity and type 2 diabetes. Conducted across 12 countries, the trial enrolled 1206 participants with BMI ≥ 27 kg/m² and HbA1c between 7–10%, assigning them in a 3:1 ratio to CagriSema (2.4 mg each) or placebo for 68 weeks, alongside lifestyle intervention [6].

Under the treatment-policy estimand (intention-to-treat), CagriSema led to a mean weight loss of –13.7%, compared to –3.4% with placebo (difference: –10.4 percentage points; p < 0.001). With the trial-product estimand (if fully adherent), weight loss was even greater: –15.7% with CagriSema versus –3.1% for placebo (statistically significant). (Refer Table 2)

Table 2: Efficacy Results: Change in Body Weight from Baseline to Week 68

Estimand	Treatment	Mean Weight Reduction (%) (Mean body weight at baseline: 102.2 kg)	Difference vs Placebo (percentage points)	p-value
Treatment-policy (intention-to-treat)	CagriSema	–13.7	–10.4	<0.001
Treatment-policy (intention-to-treat)	Placebo	–3.4	–	–
Trial-product (if fully adherent),	CagriSema	–15.7	–12.6	<0.001
Trial-product (if fully adherent),	Placebo	–3.1	–	–

Significantly more patients in the active arm achieved ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20% weight loss compared to placebo (all p<0.001).

Glycemic outcomes also improved, with 73.5% of CagriSema recipients reaching HbA1c ≤ 6.5% compared to 15.9% in the placebo group. (Figure 1)

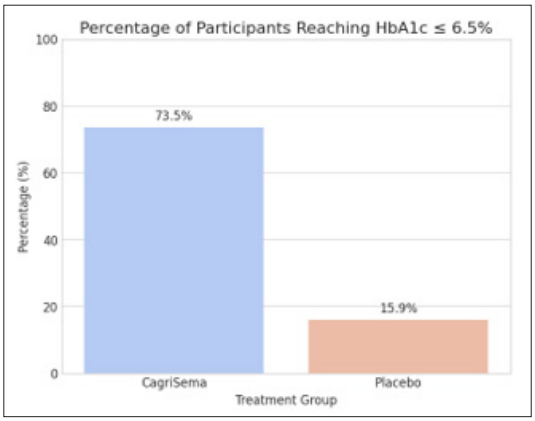

Figure 1: Glycemic Outcomes: A1c Reduction at 68 Weeks

Gastrointestinal adverse events, mainly nausea and constipation, occurred in 72.5% of treated patients versus 34.4% on placebo, though most were mild to moderate and transient. Overall, the findings confirm that CagriSema provides clinically meaningful weight reduction and improved glycemic control in patients with obesity and type 2 diabetes, with a safety profile consistent with GLP-1–based therapies.

Across both trials, improvements were noted in cardiovascular risk parameters, blood pressure, and lipid profiles, underscoring the potential cardiometabolic advantages of CagriSema.

REDEFINE 1 and REDEFINE 2 Safety Results Summary

The most common adverse events were related to gastro-intestinal system. Nausea, vomiting, and constipation were more common in the treatment arm vs placebo. AEs leading to discontinuation were uncommon GI AEs were mostly mild to moderate, peaked during dose escalation, and decreased over time, as seen in other GLP-1 therapies. The treatment was reasonably tolerated No unexpected safety signals were observed.

Conclusion

CagriSema represents a promising therapeutic advance for patients with obesity and T2DM. The dual action of cagrilintide and semaglutide provides enhanced weight loss, improved glycemic control, and favorable cardiometabolic outcomes. Safety analyses revealed a tolerability profile consistent with GLP-1 receptor agonists, with gastrointestinal events being the most common adverse effects. Future real-world studies and long-term follow-up will further define its clinical role.

References

1. Drucker DJ (2018) Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metab 27: 740-756.
2. Kalra S, Sahay R (2020) A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus. Diabetes Ther 11: 1965-1982.
3. Garvey WT, Blüher M, Osorto Contreras CK, Davies MJ, Lehmann EW, et al. (2025) Co-administered cagrilintide and semaglutide in adults with overweight or obesity. N Engl J Med 393: 635-647.
4. Cao J, Belousoff MJ, Johnson RM, Keov P, Mariam Z, et al. (2025) Structural and dynamic features of cagrilintide binding to calcitonin and amylin receptors. Nat Commun DOI: https://doi.org/10.1038/s41467-025-58680-y.
5. Hay DL, Chen S, Lutz TA, Parkes DG, Roth JD (2015) Amylin: Pharmacology, Physiology, and Clinical Potential. Pharmacol Rev 67: 564-600.
6. Davies MJ, Bajaj HS, Broholm C, Eliasen A, Garvey WT, et al. (2025) REDEFINE 2 Study Group. Cagrilintide-Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes. N Engl J Med 393: 648-659.