CLOSER LOOK

MEMORANDUM

Novo Nordisk submits CagriSema for FDA approval, supporting long-term weight loss maintenance – December 18, 2025

Filing based on phase 3 REDEFINE 1 and REDEFINE 2 trials showing substantial weight loss and flexible dosing titration in people with overweight or obesity, with or without T2D

Novo Nordisk announced today that it has submitted a New Drug Application (NDA) to the FDA for CagriSema (a once-weekly injection of fixed combination cagrilintide 2.4 mg and semaglutide 2.4 mg) as an adjunct to lifestyle intervention for the management of long-term weight loss in adults who are overweight or have obesity and at least one weight-related comorbid condition. The application is based on the phase 3b REDEFINE 1 (n=3,417) and REDEFINE 2 trials (n=1,206).

The FDA is expected to review the CagriSema NDA in 2026. If approved, the therapy would become the first injectable treatment that combines a GLP-1 RA with an amylin analog. On a day that was very busy for incretins – this was tremendous news for the field.

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REDEFINE 1 trial showed 20% weight loss in people who are overweight or have obesity

In the phase 3 REDEFINE 1 trial, CagriSema conferred weight loss of 20.4%, compared to a reduction of 11.5% with cagrilintide 2.4 mg, 14.9% with semaglutide 2.4 mg, and 3.0% with placebo at Week 68. When considering the results if all study participants adhered to treatment, CagriSema achieved superior weight loss of 22.7% compared to a reduction of 11.8% with cagrilintide 2.4 mg, 16.1% with semaglutide 2.4 mg, and 2.3% with placebo. Notably, 40.4% of patients who received CagriSema reached a weight loss of ≥25%, compared to 6.0% with cagrilintide 2.4 mg, 16.2% with semaglutide 2.4 mg, and 0.9% with placebo.

In a subgroup analysis presented during Novo Nordisk's 4Q24 update, participants who completed the trial at a lower dose (average of 1.1 mg CagriSema; 29% of the study population) achieved 25.1% weight loss at 68 weeks, compared to 22.2% in those who ended at the highest dose (2.4 mg; 57% of the study population).

CagriSema demonstrated superior weight loss in people with T2D and obesity or who were overweight in the REDEFINE 2 trial

In the phase 3 REDEFINE 2 trial, CagriSema demonstrated statistically significant and superior weight loss compared to placebo in adults with T2D and overweight or obesity. Participants could modify their dosing flexibly during the trial, and 62% of participants in the CagriSema group reached the highest dose by 68 weeks.

By treatment policy estimand, CagriSema conferred a 13.7% weight loss from a baseline body weight of 102 kg (225

lbs), compared to 3.4% with placebo. By trial product estimand (assuming full treatment adherence), CagriSema conferred 15.7% weight loss from a baseline body weight of 102 kg (225 lbs), compared to 3.1% with placebo. These results compare to 15.7% weight loss from Lilly's tirzepatide at Week 72 in the SURMOUNT-2 trial (n=938).

The trial met its coprimary endpoint with 89.7% of participants on CagriSema achieving a weight loss of ≥5%, compared to 30.3% on placebo. The safety and tolerability profile was consistent with that of the GLP-1 RA class, with the most common adverse events being mild-to-moderate gastrointestinal events.

At EASD 2025, a secondary CGM analysis for REDEFINE 2 also demonstrated that CagriSema was associated with significant improvements in glycemic management. In the CGM subgroup (n=199), CagriSema use increased Time in Range (TIR; 70-180 mg/dL) from 44% at baseline to nearly 90% at Week 68 (corresponding to nearly 11 additional hours per day spent in range), compared to an increase from 41% at baseline to 53% at Week 68 with placebo. Time in Tight Range (TITR; 70–140 mg/dL) increased over 4x with CagriSema (from 15% to 65%). Time Above Range was significantly reduced, and Time Below Range stayed below 1%, despite background sulfonylurea use in around 22% of participants.

Notably, greater weight reduction was associated with more significant improvements in CGM metrics. Still, 84-92% of participants on CagriSema achieved the study's composite endpoint of ≥70% TIR and <4% Time Below Range.

Novo Nordisk previously projected that CagriSema would demonstrate 25% weight loss in people with obesity and 20% weight loss for T2D

Novo Nordisk previously shared expectations that CagriSema would confer around 20% weight loss in people with T2D and 25% weight loss in people with obesity (3Q24, ADA 2023, Capital Markets Day 2024). However, both the REDEFINE 1 and REDEFINE 2 trial results fell short, with REDEFINE 1 demonstrating 20.4% weight loss in people with overweight or obesity and REDEFINE 2 conferring 13.7% weight loss.

Subsequently, management stressed the potential significance of careful dose escalation/re-escalation in long-term weight management. Today's press release noted that the phase 3 REDEFINE 11 trial is underway to assess dose escalation/re-escalation over a longer duration.

Ongoing REDEFINE and REIMAGINE trials evaluate CagriSema in people who are overweight or who have obesity and T2D, respectively

In addition to investigations for weight loss and long-term maintenance, CagriSema is currently being evaluated in the REDEFINE trials for people who are overweight or who have obesity and in the REIMAGINE trials for people with T2D. See below for details and expected completion dates.

REDEFINE trials	Description and results	Completion date
REDEFINE 1 (n=3,400)	68-week trial of CagriSema vs. placebo in adults with obesity or overweight with one or more comorbidities and without T2D; topline results announced in December 2024 and subgroup analysis results shared in 4Q24.	October 2026
REDEFINE 2 (n=1,206)	68-week trial of CagriSema vs. placebo in adults with T2D and either obesity or overweight; topline results announced in March 2025.	January 2025
REDEFINE 3 (n=7,000)	235-week CVOT of CagriSema vs. placebo in adults with established CVD with or	September 2027

	without T2D.	
REDEFINE 4(n=809)	72-week trial of CagriSema vs. tirzepatide 15 mg in adults with obesity.	October 2027
REDEFINE 11	Trial to assess dose escalation/ re-escalation of CagriSema.	Undisclosed; however, today's announcement described the trial as ongoing

REIMAGINE trials	Description and results	Completion date
REIMAGINE 1 (n=180)	40-week trial of CagriSema vs. placebo in people with T2D treated with diet and exercise.	December 2025
REIMAGINE 2(n=2,734)	68-week trial of CagriSema vs. semaglutide, cagrilintide, and placebo in T2D on metformin and with or without SGLT-2 inhibitor.	January 2026
REIMAGINE 3 (n=270)	40-week trial of CagriSema vs. placebo in people with T2D on once-daily basal insulin with or without metformin.	November 2025
REIMAGINE 4 (n=1,000)	68-week trial of CagriSema vs. tirzepatide in people with T2D on metformin and with or without SGLT-2 inhibitor.	April 2026
REIMAGINE 5 (n=1,000)	60-week trial of CagriSema vs. tirzepatide 5 mg in people with T2D on metformin, SGLT-2 inhibitor, or both.	August 2026

Industry momentum for amylin-based obesity therapies

Beyond Novo Nordisk, several pharmaceutical companies are advancing amylin-based therapies for obesity:

- **Lilly.** Eloralintide is a selective long-acting amylin receptor agonist. In a 48-week phase 2 trial (n=263) in people with obesity and without T2D, eloranlintide conferred dose-dependent weight loss ranging from 9.5% to 20.1%, compared to just 0.4% in placebo. Up to 57% of all participants achieved ≥20% weight loss at the highest dose (9 mg).
- **Roche/Zealand.** Petrelintide is a once-weekly long-acting amylin analog. In a 16-week phase 1b trial (n=48), petrelintide demonstrated 8.6% weight loss, compared to 1.7% in placebo, with mostly mild gastrointestinal adverse events. Petrelintide is currently under investigation in the phase 2b ZUPREME-1 trial (n=480).
- **Pfizer (added from its acquisition of Metsera).** MET-233i is an ultra-long-acting amylin analog. In a phase 1 trial (n=80), MET-233i delivered placebo-adjusted weight loss up to 8.4% by Day 36 (following five weekly doses). Rapid titration occurred within the first week, and no serious adverse events were reported. MET-233i continues to be evaluated in monthly maintenance dosing and GLP-1 RA (MET-097i) combination trials.
- **AbbVie/Gubra.** GUB014295 is a long-acting amylin analog. Announced in March 2025, the candidate has advanced to a phase 1 multiple ascending dose study (n=100), following positive single-ascending dose data in 2024.

Close Concerns' Questions

1. How long might patients have to stay on CagriSema for long-term weight maintenance?
2. Does Novo Nordisk plan on initiating head-to-head trials to test the efficacy of CagriSema against other amylin-based treatments?
3. Following potential approval, how might Novo Nordisk prioritize the development CagriSema in its pipeline?

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