CLOSER LOOK

MEMORANDUM

Novo Nordisk to conduct phase 3 trials evaluating CagriSema in children with obesity or who are overweight (n=500) in nearly 100 sites across the US, EU, Asia, Australia, and South America – December 3, 2025

Trial to begin in January 2026 with completion expected in September 2033; follows topline results that did quite not meet extraordinarily high expectations for weight loss in adults with obesity with or without T2D (reached 23% weight loss but not 25%!)

Novo Nordisk posted last week on ClinicalTrials.gov a phase 3 trial (n=460) to investigate CagriSema (fixed combination of cagrilintide 2.4 mg and semaglutide 2.4 mg) in children aged 8 to 18 years with overweight or obesity, as reported by Reuters.

Participants will be randomly assigned to receive CagriSema, cagrilintide alone, semaglutide alone, or placebo, and must meet the following criteria for enrollment:

- For children aged 8 to 11 years, BMI ≥ the 95th percentile;
- For adolescents aged 12 to 18 years, BMI ≥ the 95th percentile or ≥ the 85th percentile with at least one obesity-related complication (T2D, hypertension, dyslipidemia, or obstructive sleep apnea);
- Body weight ≥45 kg (at minimum, 99 lbs);
- A history of at least one unsuccessful effort to lose sufficient body weight after participation in a structured lifestyle modification program for at least three months; and
- For participants with T2D, an A1c ≤10.0%.

The study will consist of two parts, including: (i) an 18-month primary study; and (ii) an up to 40-month extension study that will include participants assigned to the CagriSema and cagrilintide groups only (while there would be nothing to test with placebo, presumably, we wish for the sake of those who take "placebo" for so many years and need medication, that they could get real treatment as they would presumably very much need it and have given up the chance to "get" real medicine by being in the placebo group). The study's primary outcome will be the relative change in BMI from baseline to Week 68. Secondary outcomes will include changes to body weight, body mass, fat volume, muscle volume, and liver stiffness, among other biomarkers (which include A1c values and fasting serum insulin levels). Given all that has been learned from OTC CGM, we are disappointed not to see CGM metrics as a secondary outcome as we think these would be very useful to assessing and interpreting A1c changes.

The trial is set to begin in January 2026 and estimated to complete in September 2033. In total, 97 sites will be included across the US, Australia, Europe, South America, and Asia.

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Study design: Participants to follow flexible dose titration for up to 16 weeks

Novo Nordisk will continue to explore a flexible titration scheme in its pursuit of high dose weight loss therapy with CagriSema for children and adolescents. In the REDEFINE 1 trial, after 68 weeks, approximately 57% of people treated with CagriSema were on the highest dose, compared to nearly 83% with cagrilintide 2.4 mg and 70% with semaglutide 2.4 mg. At ADA 2025, several sessions emphasized the importance of personalizing obesity management, with one panel saying that the heterogenous nature of obesity demands clinicians tailor dosage and titration schedules to achieve individual goals. See the current study structure and dosing scheme below:

Drug	Main Phase Dosing Scheme	Extension Phase Dosing Scheme
CagriSema	Once-weekly dose of CagriSema in a dose escalation regimen for up to 16 weeks maintained for 52 weeks.	Extension phase: Same dose or maximum tolerated dose (MTD) for up to 156 weeks.
Semaglutide	Once-weekly dose of semaglutide in a dose escalation regimen for up to 16 weeks maintained for 52 weeks.	N/A
Cagrilintide	Once-weekly dose of cagrilintide in a dose escalation regimen for up to 16 weeks maintained for 52 weeks.	Same dose or MTD for up to 156 weeks.
Placebo	Once-weekly dose of placebo in same dose escalation regimen as CagriSema for up to 16 weeks maintained for 52 weeks.	Same dose or MTD for up to 140 weeks.

CagriSema previously conferred weight loss below the company's high expectations, prompting an investigation of long-term weight loss

Novo Nordisk announced topline results for CagriSema in people with obesity and without T2D in December 2024 and in people with obesity with T2D in March 2025. Weight loss was slightly below the company's very high expectations: assuming full treatment adherence, CagriSema demonstrated 23% weight loss in obesity without T2D, compared to expectations of 25%, and 16% weight loss in people with T2D and obesity, below the expectations of some of around 20%. Previously, the company had positioned CagriSema as a potentially more potent successor to Wegovy (semaglutide). In response, investor concerns have increased about Novo Nordisk's competitive position in the weight loss market, especially given positive topline phase 3 results for Lilly's oral GLP-1 RA orforglipron. Announced in April 2025, these data demonstrated comparable weight loss efficacy to Ozempic's phase 3 SUSTAIN 1 trial. We would love to see more focus on titration and maintenance rather than reaching 25% vs. 23% weight loss, which is astounding weight loss by any definition.

Subsequently, Novo Nordisk launched a phase 3 study (n=600) in June 2025 to investigate CagriSema for weight loss and long-term maintenance in people with obesity, featuring a similar main- and extension-phase structure. Participants will receive varying doses of CagriSema or placebo in a 2:1 ratio. The study is expected to complete in November 2028.

Ongoing REDEFINE and REIMAGINE trials evaluate CagriSema in overweight or obesity and T2D, respectively

In addition to investigations for weight loss and long-term maintenance for children and adolescents, CagriSema is currently being evaluated in the REDEFINE trials for people with overweight or 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	October 2026

	subgroup analysis results shared in 4Q24.	
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 without T2D.	September 2027
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.	Unknown

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

Close Concerns' Questions

1. What subgroup analyses does Novo Nordisk anticipate to complete in order to assess for response heterogeneity?
2. Does Novo Nordisk anticipate CagriSema to serve as a chronic therapy for children and adolescents as they mature into adulthood?
3. Did those leading clinical trial design consider collecting CGM metrics?
4. Is it surprising that the primary outcome is BMI, given that this can be difficult to interpret for individuals? Or, since population-level data is what is sought, is this the best measure?
5. What starting BMI is most likely to be seen? How much will this vary across populations?
6. How will lifestyle interventions be interwoven into the trial – diet, exercise, stress, sleep, etc.
7. Will Oura rings be used to collect data?

--by Elizabeth Rose, Nour Khachemoune, Jeremy Alkire, and Kelly Close