Cagrilintide/semaglutide in type 2 diabetes – REIMAGINE the impact

30-second summary:

In the REIMAGINE series of clinical trials, cagrilintide, a long-acting amylin agonist, when combined with semaglutide, at doses of 2.4 mg/2.4 mg or 1 mg/1 mg, in people with type 2 diabetes, demonstrated greater reductions in HbA_{1c} than placebo or either semaglutide or cagrilintide monotherapy. Adding cagrilintide/semaglutide at either dose to once-daily basal insulin also produced clinically and statistically significant HbA_{1c} reductions compared with placebo. In addition, cagrilintide/semaglutide demonstrated significant weight loss across all three of these studies. Adverse effects were mainly gastrointestinal and mild to moderate in severity. Neither cagrilintide monotherapy nor its combination with semaglutide are currently licensed in the UK.

Pam Brown
GP in Swansea

Citation: Brown P (2026) Diabetes Distilled: Cagrilintide/semaglutide in type 2 diabetes – REIMAGINE the impact. *Diabetes & Primary Care* **28**: [Early view publication]

Amylin is a neuroendocrine peptide hormone secreted alongside insulin that improves insulin sensitivity, reduces postprandial glucagon secretion and increases satiety. GLP-1 receptor agonists have a complementary action, increasing insulin secretion in a glucose-dependent way, decreasing glucagon and working centrally to enhance satiety. Both slow gastric emptying.

Cagrilintide, a long-acting amylin agonist, has been demonstrated to aid weight loss and reduce HbA_{1c} in people with type 2 diabetes at doses up to 2.4 mg. The GLP-1 RA semaglutide is licensed at doses up to 2 mg weekly for glucose lowering in type 2 diabetes, and at doses up to 7.2 mg weekly for weight loss.

Cagrilintide and semaglutide have been studied in clinical trials as a combined, once-weekly, subcutaneous injection – CagriSema – at doses of 1 mg/1 mg and 2.4 mg/2.4 mg. Currently, neither cagrilintide monotherapy nor CagriSema are licensed for weight loss or type 2 diabetes management in the UK.

CagriSema in clinical trials

The REDEFINE series of phase 3 studies are evaluating CagriSema for weight loss in people with overweight and obesity, including the ongoing REDEFINE 3 cardiovascular outcomes trial.

The REIMAGINE series of phase 3 clinical trials comprises, amongst others, the present three studies exploring once-weekly CagriSema in people with type 2 diabetes, with the primary endpoint of HbA_{1c} reduction and multiple prespecified secondary endpoints. Data were presented at the American Diabetes Association 2026 Scientific Sessions and subsequently published in *The Lancet Diabetes & Endocrinology* (Aroda et al, 2026; Buse et al, 2026) and *The Lancet* (Rosenstock et al, 2026). Note that the study data are for the combination product, CagriSema, not for individual dosing of the two constituents.

REIMAGINE 1

This 40-week, randomised, double-blind, parallel-group, phase 3a study was conducted in 189 adults with type 2 diabetes inadequately controlled with diet and exercise (HbA_{1c} 53–81 mmol/mol [7.0–9.5%]). The safety and efficacy of two doses of CagriSema – 1 mg/1 mg and 2.4 mg/2.4 mg – were evaluated versus placebo. Change in body weight from baseline to week 40 was a prespecified secondary endpoint. Overall, 78% of participants were white and 14% Asian.

Using the efficacy estimand (see *Box 1*), mean estimated HbA_{1c} reductions after 40 weeks were significantly greater in CagriSema recipients than placebo recipients (*Table 1*). Additionally, mean relative weight changes were superior with CagriSema. Adverse events were more common in CagriSema recipients; most were gastrointestinal and mild to moderate in severity.

Box 1. Definition of the efficacy estimand used in the REIMAGINE studies (quoted from Aroda et al, 2026).

The efficacy estimand assessed treatment effect regardless of changes in dose, had all participants remained on randomly assigned treatment without initiation of additional glucose-lowering medication, and was based on data from the on-treatment without rescue period (from randomisation to 14 days after the last administration of trial product or initiation of rescue medication, whichever came first).

Table 1. Outcomes at week 40 in the REIMAGINE 1 trial (Aroda et al, 2026).

Treatment group	Mean change in HbA_{1c} (mmol/mol)	Mean change in body weight	Adverse event rate (% of participants)
CagriSema 2.4 mg/2.4 mg	–19.7	–13.8%	79%
CagriSema 1 mg/1 mg	–16.4	–11.8%	75%
Placebo	–1.1	+1.4%	66%

Table 2. Outcomes at week 68 in the REIMAGINE 2 trial (Buse et al, 2026).

Treatment group	Mean change in HbA_{1c} (mmol/mol)	Mean change in body weight	Adverse event rate (% of participants)
CagriSema 2.4 mg/2.4 mg	–20.9	–14.2%	87%
CagriSema 1 mg/1 mg	–19.9	–12.0%	82%
Semaglutide 2.4 mg	–19.1	–10.2%	81%
Semaglutide 1 mg	–16.8	–7.5%	79%
Cagrilintide 2.4 mg	–8.7	–8.4%	82%
Placebo	–1.0	–1.5%	71%

REIMAGINE 2

This 68-week, randomised, double-blind, placebo-controlled study was conducted in people with type 2 diabetes and an HbA_{1c} of 53–91 mmol/mol (7.0–10.5%) whilst receiving metformin with or without an SGLT2 inhibitor. It was the first study to compare the CagriSema combination with the individual drugs. A total of 2713 people (57.1% male, 81.3% White) were enrolled and randomised to:

- CagriSema 2.4 mg/2.4 mg (*n*=603).
- CagriSema 1 mg/1 mg (*n*=595).
- Cagrilintide 2.4 mg (*n*=152).
- Semaglutide 2.4 mg (*n*=605).
- Semaglutide 1.0 mg (*n*=609).
- Placebo (*n*=149).

The primary endpoint was change in HbA_{1c} from baseline comparing CagriSema 2.4 mg/2.4 mg versus semaglutide 2.4 mg. Secondary endpoints included additional HbA_{1c} comparisons and change in body weight from baseline to week 68. A subset of participants used continuous glucose monitoring to provide additional information on the impact on blood glucose levels, but this did not impact HbA_{1c} results.

Results

Overall, 95.7% of those randomised completed the study, and 87.6% remained on treatment at week 68. Using the efficacy estimand, HbA_{1c} was reduced by 20.9 mmol/mol with CagriSema 2.4 mg/2.4 mg, versus 19.1 mmol/mol with semaglutide 2.4 mg (a statistically significant treatment difference of 1.8 mmol/mol). Other comparisons are detailed in *Table 2*.

This study demonstrates the added benefit on HbA_{1c} of CagriSema over semaglutide or cagrilintide alone in people with type 2 diabetes and overweight or obesity. The combination also provided greater weight reduction than either component alone, which the authors suggest may relate to the complementary effects on appetite suppression. CagriSema 2.4 mg/2.4 mg was more effective for both HbA_{1c} and weight reduction than the 1 mg/1 mg combination.

Adverse events occurred in 79–87% of the active treatment groups, compared with 71% of placebo recipients (*Table 2*). Gastrointestinal adverse effects were the most common.

REIMAGINE 3

This was a 40-week, randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of both doses of CagriSema as an add-on to once-daily basal insulin in 274 people (54% male) with type 2 diabetes and a baseline HbA_{1c} of 53–91 mmol/mol (7.0–10.5%). Using the efficacy estimands, both doses of CagriSema met the primary endpoint to produce statistically significant and clinically relevant HbA_{1c} reductions compared with placebo:

- 18.4 mmol/mol with CagriSema 2.4 mg/2.4 mg.
- 15.7 mmol/mol with CagriSema 1 mg/1 mg.

Body weight reductions of 10–12% also occurred compared with placebo. Adverse events were reported in 80% with the higher-strength combination, 71% with the lower-strength combination and 71% with placebo. There was no severe hypoglycaemia reported in either CagriSema group.

Other CagriSema studies

REIMAGINE 4 is an open-label, head-to-head study, as yet unpublished, comparing CagriSema 2.4 mg/2.4 mg versus tirzepatide 15 mg in people with type 2 diabetes not

controlled on metformin with or without an SGLT2 inhibitor over 68 weeks, with primary endpoints of non-inferiority in terms of HbA_{1c} and weight reductions.

Top-line results have been released very recently, demonstrating a 15.2% weight reduction with CagriSema, which was non-inferior to tirzepatide, while the 20.8 mmol/mol HbA_{1c} reduction failed to meet non-inferiority criteria compared with tirzepatide. The full results will be presented at a future conference and published at that time.

REDEFINE 4 compared the impact of CagriSema 2.4 mg/2.4 mg and tirzepatide 15 mg over 85 weeks in people with overweight and obesity and one or more comorbidities. CagriSema achieved 23% weight loss, compared to 25.5% with tirzepatide, failing to meet non-inferiority criteria for weight reduction.

Implications for practice

Neither CagriSema nor cagrilintide alone are licensed for use in the UK for weight reduction or for glycaemic lowering in type 2 diabetes. However, these studies remind us that additional new drugs are in development. They demonstrate that the combination of the long-acting amylin agonist cagrilintide plus the GLP-1 RA semaglutide, when combined as a single injection once weekly in people with type 2 diabetes, offers increased glucose lowering and significant weight reduction compared with semaglutide 2.4 mg (the licensed dose for weight loss) used alone. We are also gaining clarity into comparisons with tirzepatide.

As would be expected, when comparing the REIMAGINE and REDEFINE studies, CagriSema showed lesser weight loss effects in people with type 2 diabetes than in those without, as has also been observed in those treated with other GLP-1 RAs or tirzepatide. Although it is not appropriate to compare studies, as they have different protocols and inclusion criteria, the 14.2% weight loss achieved in REIMAGINE 2 with CagriSema 2.4 mg/2.4 mg was similar to that achieved in REDEFINE 2, (15.7%) and with tirzepatide 15 mg in the SURPASS-3 trial (13.9%) in people with type 2 diabetes (Ludvik et al, 2021).

The recent update to NICE NG28 recommends we consider earlier use of injectable incretin drugs, such as semaglutide and tirzepatide, in some groups. Injectable semaglutide up to 1 mg per week can be considered for those with atherosclerotic cardiovascular disease (ASCVD) as triple therapy, in conjunction with metformin M/R and an SGLT2 inhibitor. In those with a diagnosis of type 2 diabetes before the age of 40 years, semaglutide up to 1 mg or tirzepatide up to 15 mg, along with metformin M/R and an SGLT2 inhibitor, can be considered from diagnosis in view of the very high risk of ASCVD. In people with type 2 diabetes and obesity (BMI ≥30 kg/m^2) who fail to meet their agreed HbA_{1c} target after 3 months of dual therapy with metformin M/R and an SGLT2 inhibitor, semaglutide or tirzepatide can also be considered as part of triple therapy.

Although primary care teams in England have a limited role in delivering injectable weight loss therapies on the NHS, we are all involved in prescribing both oral and injectable incretin therapies for type 2 diabetes. We have an important role in making sure that these drugs are prescribed only to those who are suitable and to ensure that people using these drugs are aware of the safety issues and the importance of reporting abdominal pain, prolonged vomiting, or new visual problems immediately while taking them.

An additional range of drugs, with agonist actions on GLP-1, GIP, amylin and/or glucagon receptors, as dual or triple combinations or as single molecules combining two or three of these different modes of action, are in development at phase 2 and 3. Once these are launched, we will need expert guidance on how to choose between the drugs so that we can individualise or tailor treatments to the specific needs of each patient.

We practise in exciting times. But let's remember the importance of encouraging and supporting lifestyle changes alongside drug therapies to help optimise long-term benefits in diabetes and weight management.

Read the articles in full
(purchase or institutional access required)

- REIMAGINE 1
- REIMAGINE 2
- REIMAGINE 3

References

Aroda VR, Buzzetti R, Dalskov SM et al (2026) Efficacy and safety of once-weekly cagrilintide–semaglutide (CagriSema) in adults with type 2 diabetes inadequately controlled on diet and exercise (REIMAGINE 1): A randomised, double-blind, placebo-controlled, phase 3a study. *Lancet Diabetes Endocrinol* **14**: 649–61

Buse JB, Bajaj HS, Dalskov SM et al; REIMAGINE 2 study group (2026) Cagrilintide–semaglutide (CagriSema) versus semaglutide or cagrilintide in people with type 2 diabetes (REIMAGINE 2): A double-blind, randomised, controlled, phase 3 study. *Lancet Diabetes Endocrinol* **14**: 662–77

Ludvik B, Giorgino F, Jódar E et al (2021) Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): A randomised, open-label, parallel-group, phase 3 trial. *Lancet* **398**: 583–98

Rosenstock J, Billings LK, Gajria R et al (2026) Cagrilintide–semaglutide (CagriSema) as an add-on to basal insulin in adults with type 2 diabetes (REIMAGINE 3): A randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet* **408**: 38–51