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The next frontier in managing obesity with or without T2D: The role of novel combinations

Fact sheet for obesity with or without type 2 diabetes

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Rationale for GLP-1–based combination strategies

Targeting multiple hormonal pathways at once could lead to greater efficacy[1]

Potential for increased therapeutic efficacy **by opposing compensatory mechanisms** in our natural human biology that defend against weight loss[1]

Potential to use lower doses of each treatment in the combination to **minimize risk of side effects**[1]

Combination of amylin analogues and GLP-1RAs may induce synergistic weight loss effect[2]

Using amylin analogues in obesity

- Amylin affects both homeostatic and reward-related aspects of feeding[3]
- Amylin is a target for weight loss and improvement in blood glucose[4]
- Cagrilintide can be given once-weekly[5]
- Cagrilintide is associated with fewer GI side effects than GLP-1RAs[6]
- Pramlintide, the only currently approved amylin analogue, must be taken with every meal[2,7]
- Amylin analogues are administered by injection and some patients may be reluctant to consider injections[2,5,7]

Phase II trial investigating ascending doses of cagrilintide for weight management in patients without diabetes[5]

BMI ≥30 kg/m^2 or ≥27 kg/m^2 with hypertension or dyslipidaemia (N=706)

Cagrilintide (0.3–4.5 mg) vs liraglutide 3.0 mg and placebo

Weight loss vs liraglutide

- **Greater with 4.5 mg cagrilintide** vs 3.0 mg liraglutide (–10.8% vs –9.0%; p=0.03)

Changes comparable with cagrilintide and liraglutide for

- Reductions in triglycerides and VLDL cholesterol*
- Improvement in TFEQ-R18 scores
- Proportion of patients with AEs

*Cagrilintide 2.4 mg and 4.5 mg vs liraglutide

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Phase II clinical trial data for CagriSema in patients with type 2 diabetes[8]

2 August–18 October 2021

CagriSema: n=31; semaglutide: n=31; cagrilintide: n=30

Change in HbA1c:

Significantly greater reduction from baseline to week 32 with CagriSema vs cagrilintide (p<0.001)

Mean change in body weight at week 32:

CagriSema: –15.6% (–16.3 kg)

Semaglutide: –5.1% (–5.3 kg)

Cagrilintide: –8.1% (–8.4 kg)

Achieved target HbA1c:

A **greater proportion of patients reached target HbA1c** (<7.0% and ≤6.5%) with CagriSema vs cagrilintide or semaglutide

Clinically significant or severe hypoglycaemic episodes:

n=0

Change in fasting plasma glucose from baseline:

CagriSema: –3.3 mmol/L

Semaglutide: –2.5 mmol/L

Cagrilintide: –1.7 mmol/L

Discontinued treatment:

CagriSema: n=4 **(due to AEs n=0)**

Semaglutide: n=3 **(due to AEs n=1)**

Cagrilintide: n=0

Adverse events:

CagriSema: 68%

Semaglutide: 71%

Cagrilintide: 80%

GI adverse events:*

CagriSema: 58%

Semaglutide: 32%

Cagrilintide: 33%

All mild or moderate in severity and the majority began during dose escalation

Serious adverse events:

CagriSema: n=0

Semaglutide: n=2

Cagrilintide: n=4

'CagriSema' refers to co-administered semaglutide with cagrilintide.

*Including nausea, constipation, diarrhoea, vomiting and GORD.

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GLP-1–based combination treatments under investigation in obesity with T2D[9]

	CagriSema in patients with T2D				
Phase	**II** (NCT04982575)	**III**; REDEFINE 2 (NCT05394519)	**III**; REIMAGINE 1 (NCT06323174)	**III**; REIMAGINE 2 (NCT06065540)	**III**; REIMAGINE 3 (NCT06323161)
Estimated primary completion	COMPLETED	December 2024	October 2025	November 2025	September 2025
Treatment arms	1. CagriSema 2. Cagrilintide + placebo 3. Placebo + semaglutide	1. CagriSema 2. Placebo	1. CagriSema 2. Placebo	1. CagriSema 2. Cagrilintide 3. Semaglutide 4. Placebo	1. CagriSema 2. Placebo
Patient criteria	• T2D for ≥180 days • ≥18 years of age • BMI ≥27.0 kg/m^2	• T2D for ≥180 days • ≥18 years of age • BMI ≥27.0 kg/m^2	• T2D for ≥30 days • ≥18 years of age • BMI ≥23.0 kg/m^2	• T2D for ≥180 days • ≥18 years of age • BMI ≥25 kg/m^2	• T2D for ≥180 days • ≥18 years of age • BMI ≥25 kg/m^2
Primary endpoint	• Change in HbA1c	• Relative change in body weight (%) from baseline • Achievement of ≥5% weight reduction from baseline	• Change in HbA1c	• Change in HbA1c • Relative change in body weight	• Change in HbA1c
Key safety endpoints	• Number of TEAEs • Number of clinically significant or severe hypoglycaemic episodes	• Number of TEAEs and TESAEs • Number of clinically significant or severe hypoglycaemic episodes	• Number of TEAEs • Number of clinically significant or severe hypoglycaemic episodes	• Number of TEAEs • Number of clinically significant or severe hypoglycaemic episodes	• Number of TEAEs • Number of clinically significant or severe hypoglycaemic episodes

'CagriSema' refers to co-administered semaglutide with cagrilintide.

Information on clinical trials found at clinicaltrials.gov by searching the NCT number.

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GLP-1–based combination treatments under investigation in obesity with or without T2D[9]

	Eloralintide + tirzepatide	CagriSema in patients with or without T2D		CagriSema in patients without T2D	
Phase	**II** (NCT06603571)	**III**; REDEFINE 3 (NCT05669755)	**III**; NCT05813925 Study in East Asia	**III**; REDEFINE 1 (NCT05567796)	**III**; REDEFINE 4 (NCT06131437)
Estimated primary completion	June 2026	September 2027	January 2025	October 2024 (actual primary completion date)	August 2025
Treatment arms	1. Eloralintide 2. Eloralintide + tirzepatide 3. Tirzepatide 4. Placebo	1. CagriSema 2. Placebo	1. CagriSema 2. Semaglutide + placebo	1. CagriSema 2. Cagrilintide or semaglutide + placebo 3. Placebo	1. CagriSema 2. Tirzepatide
Patient criteria	• T2D • 18–75 years of age • BMI ≥27.0 kg/m^2	• ≥55 years of age • BMI ≥25.0 kg/m2 • Established CVD* • ±T2D	• ≥18 years of age • BMI ≥27.0 kg/m^2 with ≥2 obesity-related complications‡ or BMI ≥35.0 kg/m^2 with ≥1 obesity-related complications‡ • ±T2D	• ≥18 years of age • BMI ≥30.0 kg/m^2 • No history of T2D or T1D	• ≥18 years of age • BMI ≥30.0 kg/m2 • No history of T2D or T1D
Primary endpoint	• % change in body weight from baseline	• Time to first MACE†	• Relative change in body weight	• Relative change in body weight (%) from baseline • Achievement of ≥5% weight reduction from baseline	• Relative change in body weight
Key safety endpoints	• No safety endpoints listed	• Number of TESAEs • Number of severe hypoglycaemic episodes • Number of EAC-confirmed neoplasms	• Number of TEAEs and TESAEs	• Number of TEAEs and TESAEs	• Number of TEAEs and SAEs

'CagriSema' refers to co-administered semaglutide with cagrilintide. **Information on clinical trials found at clinicaltrials.gov by searching the NCT number.**
*As evidenced by ≥1 of prior MI, prior stroke, symptomatic peripheral arterial disease; †consisting of CV death, non-fatal MI, non-fatal stroke; ‡≥1 complication should be hypertension, dyslipidaemia or T2D.

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Abbreviations and references

Abbreviations

AE, adverse event; BMI, body mass index; CV, cardiovascular; CVD, CV disease; EAC, event adjudication committee; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1RA, GLP-1 receptor agonist; GORD, gastro-oesophageal reflux disease; HbA1c, glycated haemoglobin; MACE, major adverse cardiovascular events; MI, myocardial infarction; SAE, serious AE; T1D, type 1 diabetes; T2D, type 2 diabetes; TEAE, treatment emergent AE; TESAE, treatment emergent SAE; TFEQ-R18, three factor eating questionnaire-R18; VLDL, very low-density lipoprotein.

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