Efficacy and safety of co-administered cagrilintide–semaglutide (CagriSema) 1·7 mg each and 1·0 mg each in adults with overweight or obesity (REDEFINE 9): a multicentre, randomised, double-blind within-dose-level, placebo-controlled, parallel-group, phase 3b trial

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Introduction

- CagriSema is a fixed-dose combination of the long-acting amylin receptor agonist cagrilintide and the GLP-1RA semaglutide in development as a treatment for weight management[1,2]
- Although CagriSema 2.4 mg/2.4 mg results in significant weight reduction with an acceptable safety and tolerability profile,[1,2] different dosing options could accommodate individual variations in response and allow greater dosing flexibility in clinical practice
- The aim of the REDEFINE 9 trial was to investigate the efficacy and safety of once-weekly subcutaneous CagriSema 1.7 mg/1.7 mg and 1.0 mg/1.0 mg versus placebo in participants with overweight or obesity and at least one obesity-related complication

GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Garvey WT et al. *N Engl J Med* 2025;393:635–647; 2. Davies MJ et al. *N Engl J Med* 2025;393:648–659.

REDEFINE 9 trial design

Key inclusion criteria

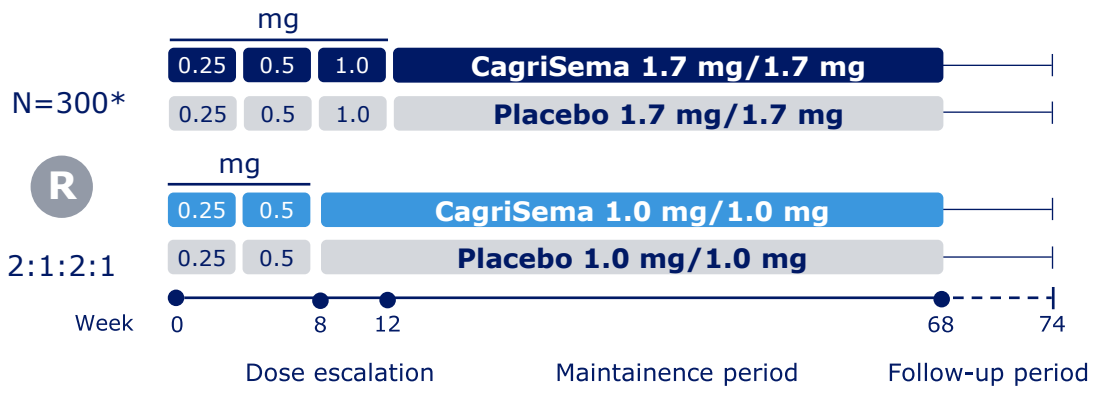
- Age ≥18 years
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 ORC but without diabetes
- ≥1 self-reported unsuccessful dietary effort to lose weight

Key exclusion criteria

- HbA_{1c} level ≥6.5% or a history of diabetes
- Receiving treatment with a glucose-lowering agent, GLP-1RA or weight-management medication within 90 days before screening
- History or presence of chronic pancreatitis or acute pancreatitis within 180 days before screening
- Self-reported change in body weight of >5% in the 90 days prior to screening

Trial design

- Multicentre, randomised, double-blind, parallel-group, phase 3b trial carried out across 24 sites in Canada, France, Germany, the UK and the USA
- Participants were randomised 2:1:2:1 to OW s.c. CagriSema 1.7 mg/1.7 mg, placebo 1.7 mg/1.7 mg, CagriSema 1.0 mg/1.0 mg or placebo 1.0 mg/1.0 mg
- Treatment was initiated at 0.25 mg/0.25 mg and escalated over 8 weeks for CagriSema 1.0 mg/1.0 mg or over 12 weeks for CagriSema 1.7 mg/1.7 mg



*Planned number of participants. Trial treatment was administered as an adjunct to lifestyle intervention (−500 kcal/day diet + 150 min/week physical activity).
This trial was not designed to directly compare the two doses of CagriSema; CagriSema 1.7 mg/1.7 mg and CagriSema 1.0 mg/1.0 mg were evaluated separately versus placebo.
BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; ORC, obesity-related complication; OW, once weekly; R, randomisation; s.c., subcutaneous.
Wharton S et al. *Lancet Diabetes Endocrinol* 2026; doi.org//10.1016/S2213-8587(26)00275-5 [Epub ahead of print].

Endpoints – baseline to week 68

Co-primary endpoints



Relative change in body weight (%)



≥5% body weight reduction

Confirmatory secondary endpoints



≥10%, ≥15% or ≥20% body weight reduction

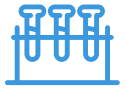


Change in waist circumference

Key supportive secondary endpoints



Change in SBP



Ratio to baseline for lipids

Key exploratory endpoints



Change in DBP



Change in HbA_{1c}



Ratio to baseline for hsCRP

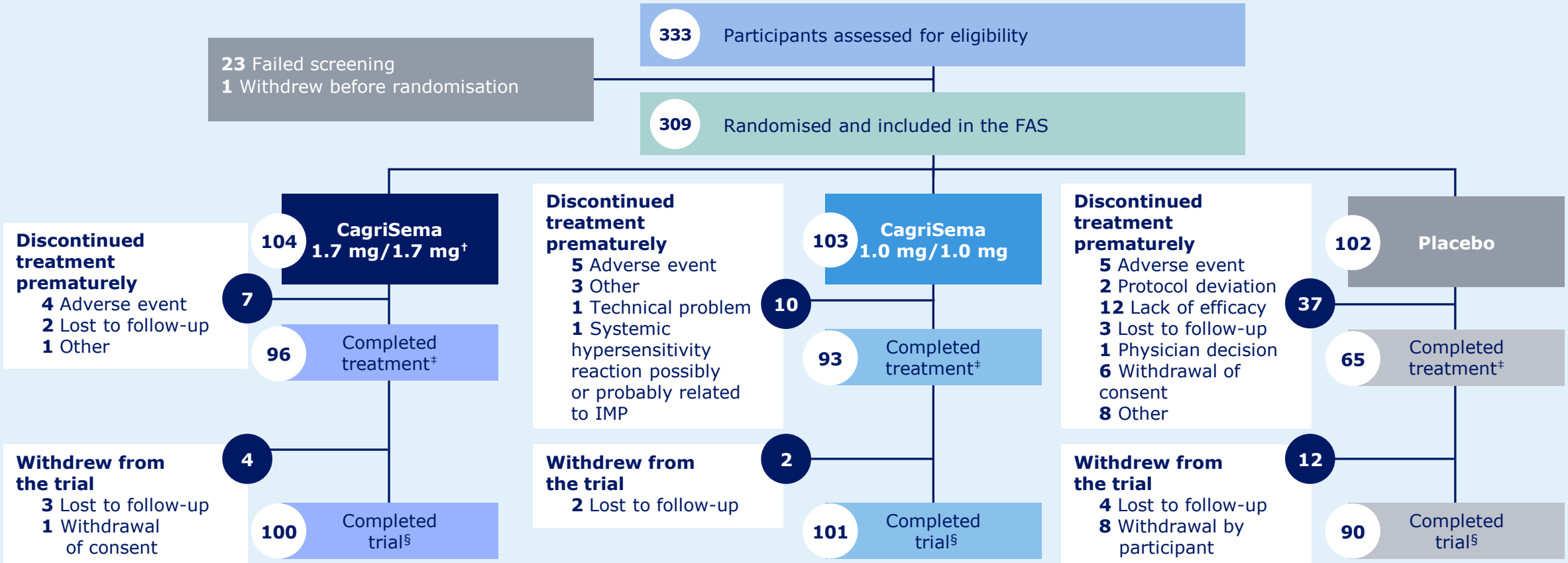
Safety endpoints



AEs and serious AEs[†]

[†]Assessed from baseline to end of treatment + 6 weeks.
AE, adverse event; DBP, diastolic blood pressure; HbA_{1c}, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure.
Wharton S et al. *Lancet Diabetes Endocrinol* 2026; doi.org//10.1016/S2213-8587(26)00275-5 [Epub ahead of print].

Participant distribution



†One participant withdrew following randomisation and before receiving their first dose of trial product; ‡Participants were considered to have completed treatment if they were on treatment at week 68; §Participants were considered to have completed the trial if they attended the end-of-trial visit at week 68, regardless of whether they completed treatment.
FAS, full analysis set.
Wharton S et al. *Lancet Diabetes Endocrinol* 2026; doi.org//10.1016/S2213-8587(26)00275-5 [Epub ahead of print].

Demographics and baseline characteristics

	CagriSema 1.7 mg/1.7 mg	CagriSema 1.0 mg/1.0 mg	Pooled placebo
Female	83%	82%	70%
Age, years	47.6 (14.3)	48.3 (13.0)	48.1 (13.5)
Body weight, kg	108.1 (20.3)	108.9 (21.7)	111.5 (23.6)
BMI, kg/m^2	38.9 (6.3)	39.1 (6.3)	39.2 (7.8)
Waist circumference, cm	115.8 (13.6)	115.4 (15.0)	116.8 (16.4)

Data are mean (SD) or %, unless otherwise stated.
*n=102. †n=101.
BMI, body mass index; SD, standard deviation.
Wharton S et al. *Lancet Diabetes Endocrinol* 2026; doi.org//10.1016/S2213-8587(26)00275-5 [Epub ahead of print].

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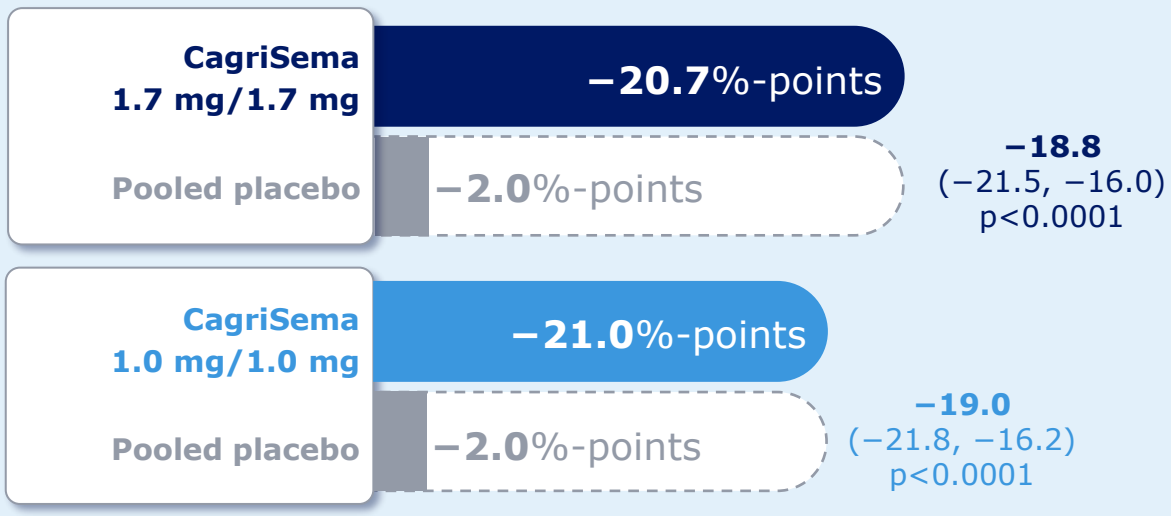
Both doses of CagriSema led to superior reductions in body weight versus placebo

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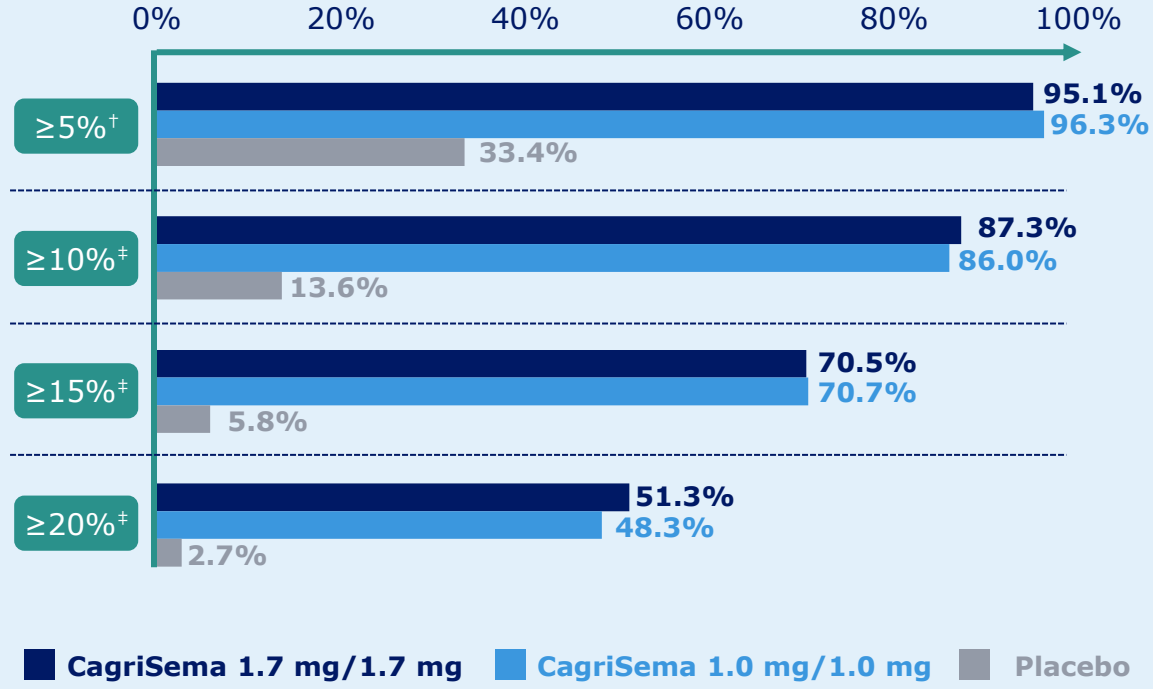
Mean relative change from baseline in body weight at week 68†

Please note that the study was not designed or powered to detect differences between the two active doses

Mean baseline body weight: 109.5 kg



Proportion of participants achieving body weight reduction thresholds at week 68



Data show the efficacy estimand. Comparison values are estimated treatment differences (95% CI) versus placebo.
†Coprimary endpoint. ‡Confirmatory secondary endpoint
CI, confidence interval.
Wharton S et al. *Lancet Diabetes Endocrinol* 2026; doi.org//10.1016/S2213-8587(26)00275-5 [Epub ahead of print].

02

Reductions in body weight were accompanied by improvements in cardiometabolic risk factors

Reductions in body weight were accompanied by improvements in cardiometabolic risk factors

	CagriSema 1.7 mg/1.7 mg	CagriSema 1.0 mg/1.0 mg	Pooled placebo
Change in waist circumference, cm†	−17.2 (1.0)	−17.5 (1.0)	−3.6 (1.1)
Change in SBP, mmHg‡	−8.8 (1.4)	−7.5 (1.3)	0.5 (1.5)
Ratio to baseline in lipids, mmol/L‡			
Total cholesterol	0.98 (1.01)	0.96 (1.01)	1.00 (1.02)
HDL cholesterol	1.13 (1.02)	1.16 (1.02)	1.07 (1.02)
LDL cholesterol	0.96 (1.02)	0.94 (1.02)	0.99 (1.03)
VLDL cholesterol	0.75 (1.04)	0.69 (1.04)	0.93 (1.04)
Triglycerides	0.75 (1.04)	0.69 (1.04)	0.94 (1.04)
Free fatty acids	0.94 (1.06)	0.90 (1.07)	0.94 (1.07)
Change in HbA_{1c}, mmol/mol§	−6.0 (0.4)	−6.3 (0.4)	−0.9 (0.4)
Ratio to baseline in hsCRP, mg/L§	0.27 (1.13)	0.33 (1.13)	0.94 (1.15)

Data are for the efficacy estimand and presented as mean (SD). †Confirmatory secondary endpoint. ‡Supportive secondary endpoint. §Key exploratory endpoint.
HbA_{1c}, glycaemic index; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; VLDL, very low-density lipoprotein.
Wharton S et al. *Lancet Diabetes Endocrinol* 2026; doi.org//10.1016/S2213-8587(26)00275-5 [Epub ahead of print].

Both doses of CagriSema were well tolerated, with safety profiles consistent with those in previous studies investigating CagriSema for weight management

Both CagriSema doses were well tolerated, with a safety profile consistent with previous studies investigating CagriSema for weight management

Most AEs were mild to moderate in severity	CagriSema 1.7 mg/1.7 mg	CagriSema 1.0 mg/1.0 mg	Pooled placebo
Any AE	**99%**	**95%**	**91%**
SAE	**15%**	**13%**	**12%**
The most frequent AEs with CagriSema were **gastrointestinal events**			
Nausea	**66%**	**62%**	**26%**
Constipation	**48%**	**37%**	**21%**
Diarrhoea	**38%**	**34%**	**25%**
Vomiting	**32%**	**27%**	**7%**
AEs leading to permanent treatment discontinuation†	**3%**	**5%**	**5%**

Data are proportion of participants (%). Data are shown for the in-study period unless otherwise stated.
†On-treatment period
AE, adverse event; SAE, serious adverse event.
Wharton S et al. *Lancet Diabetes Endocrinol* 2026; doi.org//10.1016/S2213-8587(26)00275-5 [Epub ahead of print].

Conclusions

- CagriSema 1.7 mg/1.7 mg and 1.0 mg/1.0 mg provided superior reductions in body weight versus placebo and resulted in improvements in cardiometabolic risk factors
- The substantial body weight reduction seen with CagriSema 1.7 mg/1.7 mg and 1.0 mg/1.0 mg indicates that lower doses are highly effective for some people
- The safety and tolerability profile of CagriSema was consistent with previous safety data for CagriSema
- These findings provide important evidence of the potential benefits of CagriSema at different doses and expand the understanding of how efficacy, tolerability and dose flexibility may support individualised care