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

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What is the rationale for GLP-1 based combination therapy in general, and amylin analogues specifically, for the management of obesity with OR without T2D

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What is the rationale for GLP-1–based combination strategies for obesity with or without type 2 diabetes?

Current therapies for obesity with OR without T2D

	Semaglutide[1,2]	Liraglutide[1,2]	Tirzepatide[1,2]
Mechanism of action	GLP-1RA	GLP-1RA	GIP RA and GLP-1RA
Indication	• **Glycaemic control** (T2D) • **Reduce excess body weight** and maintain weight reduction (obesity) • To **reduce risk of major CV events** in adults with known heart disease and **obesity or overweight** • To **reduce the risk of MACE** in adults with **T2D** and established CVD (US only) • To **reduce the risk of sustained eGFR decline**, end-stage kidney disease, and cardiovascular death in adults **with type 2 diabetes** and chronic kidney disease (US only)	• Improve glycaemic control (T2D) • Chronic weight management (obesity)	• Improve glycaemic control (T2D) • Reduce excess body weight and maintain weight reduction (obesity) • Treat moderate to severe OSA (obesity)
Age	• Adults (T2D) • Adults and paediatrics ≥12 (obesity)	• Adults and paediatrics ≥10 years (T2D) • Adults and paediatrics ≥12 years (obesity)	Adults
Frequency of dose	Once weekly SC	Once daily SC	Once weekly SC

CV, cardiovascular; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; OSA, obstructive sleep apnoea; RA, receptor agonist; SC, subcutaneous; T2D, type 2 diabetes.

1. FDA. PI. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed 15 January 2025); 2. EMA. SmPC. Available at: www.medicines.org.uk/emc (accessed 15 January 2025).

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Functions of gut hormones in GLP-1 based treatments

Glucagon[1]	GLP-1[2]		GIP[2,3]	Amylin[1]
↓ Appetite ↓ Food intake ↑ Nausea	↑ Satiety	Brain	↓ Food intake?	↓ Appetite ↓ Food intake
↑ Insulin ↑ Blood glucose	↑ Insulin ↓ Glucagon ↓ Blood glucose ↑ β-cell proliferation ↓ β-cell apoptosis	Pancreas	↑ Insulin ↑ Glucagon ↓ Blood glucose ↑ β-cell proliferation ↓ β-cell apoptosis	↓ Glucagon ↓ Blood glucose
↓ Gastric emptying	↑ Nausea ↓ Gastric emptying	GI tract	↓ Nausea	↓ Gastric emptying
↑ Hepatic glucose production ↑ Lipid oxidation ↓Hepatic lipid synthesis	↓ Hepatic glucose production	Liver		
↑ Energy expenditure	↑ Insulin sensitivity	Adipose tissue	↑Lipid buffering capacity ↓ Triglycerides ↑ Insulin sensitivity	

GLP-1, glucagon-like peptide-1; GI, gastrointestinal; GIP, gastric inhibitory polypeptide.

1. Melson E, et al. *Int J Obes (Lond)*. 2024; doi.org/10.1038/s41366-024-01473-y; 2. Andraos J, et al. *Rev Endocr Metab Disord*. 2023;24:1089–101; 3. Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31:410–21.

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How can GLP-1–based combination strategies improve outcomes?

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

Potential for increased therapeutic efficacy due to **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]

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

1. Coutinho W, Halpern B. *Diabetol Metab Syndr*. 2024;16:6; 2. Melson E, et al. *Int J Obes*. 2024; doi.org/10.1038/s41366-024-01473-y.

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What do we know about amylin analogues in obesity with or without T2D?

Pramlintide in type 2 diabetes

Pramlintide is used as an adjunctive to insulin in patients with type 1 or type 2 diabetes in the US[1]

Data from a pooled analysis of two long-term clinical trials in patients with overweight or obesity and type 2 diabetes treated with insulin[2]

BMI >25 kg/m^2 (n=498)

Insulin plus pramlintide 120 µg BID or insulin plus placebo

Average weight of patients receiving pramlintide 96.1 kg ± 19.2

HbA1c

- **Significant reduction in HbA1c from baseline to week 26** with pramlintide vs placebo (0.59% vs 0.18%; p<0.0001)
- Change in HbA1c **not significantly related to weight loss** at week 26

Mean reduction in body weight from baseline with pramlintide:

- Significant from week 2 onwards and increased over time
- **Average 1.5 kg at week 26**

BID, twice daily; BMI, body mass index; HbA1c, glycated haemoglobin.

1. FDA. Pramlintide PI. Available at: https://bit.ly/42a4pHf (accessed 10 January 2024); 2. Hollander P, et al. *Obes Res*. 2004;12:661–8.

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Cagrilintide in obesity

Cagrilintide is a long-acting amylin analogue

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

BMI ≥30 kg/m^2 or ≥27 kg/m^2 with hypertension or dislipdaemia (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)

Proportion of patients achieving weight loss of at least 5%, 10% and 15%

- Cagrilintide 4.5 mg: 88.7%,* 53.5%,* 18.7%†
- Placebo: 30.9%, 10.4%, 2.9%

Changes comparable with cagrilintide and liraglutide for

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

*p<0.001 vs placebo; †p<0.01 vs placebo; ‡cagrilintide 2.4 mg and 4.5 mg vs liraglutide.
AE, adverse event; BMI, body mass index; TFEQ-R18, Three-Factor Eating Questionnaire -R18; VLDL, very low-density lipoprotein.
Lau DCW. *Lancet*. 2021;398:2160–72.

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What do clinicians need to understand about the current and future management of obesity with or without type 2 diabetes?

What do we know about the efficacy of novel GLP-1–based combination therapies for obesity with or without type 2 diabetes, based on available clinical evidence?

Dr Donna Ryan

Pennington Biomedical Research Center,
Baton Rouge, LA, USA

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What do we know about the overall efficacy of GLP-1–based combination therapy for obesity with or without type 2 diabetes?

What evidence do we have so far regarding the efficacy of GLP-1–based combination therapies for obesity with or without type 2 diabetes?

Study designs for phase II trials

	Patients with type 2 diabetes **CagriSema (NCT04982575)***	Patients with type 2 diabetes **Eloralintide + tirzepatide (NCT06603571)†**
Estimated primary completion	**COMPLETED**	June 2026
Treatment arms	1. Cagrilintide + semaglutide 2. Cagrilintide + placebo 3. Placebo + semaglutide Doses gradually increased to 2.4 mg Dosed for 32 weeks	1. Eloralintide 2. Eloralintide + tirzepatide 3. Tirzepatide 4. Placebo
Inclusion criteria	• T2D for ≥180 days • ≥18 years of age • BMI ≥27.0 kg/m^2 • HbA1c 7.5–10.0% inclusive • *T2D treatment*: stable daily dose of metformin ± SGLT2i for ≥90 days	• T2D • 18–75 years of age • BMI ≥27.0 kg/m^2 • HbA1c 7.0–10.5% • Stable body weight (<5% gain/loss) for previous 3 months • *T2D treatment*: diet and exercise alone OR stable dose of metformin ± SGLT2i for ≥3 months
Primary endpoint	• Change in HbA1c	• % change in body weight from baseline

'CagriSema' refers to co-administered semaglutide with cagrilintide. *Actual enrolment N=92; †estimated enrolment N=350. **Information on clinical trials found at clinicaltrials.gov by searching the NCT number.** BMI, body mass index; HbA1c, glycated haemoglobin; SGLT2i, sodium–glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.

Clinicaltrials.gov. Available at https://clinicaltrials.gov/ (accessed 10 January 2025).

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Phase II clinical trial data for CagriSema (NCT04982575)

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)

Achieved target HbA1c:

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

Change in fasting plasma glucose from baseline:

CagriSema: –3.3 mmol/L

Semaglutide: –2.5 mmol/L

Cagrilintide: –1.7 mmol/L

Mean change in body weight:

CagriSema: –15.6% (–16.3 kg)

Semaglutide: –5.1% (–5.3 kg)

Cagrilintide: –8.1% (–8.4 kg)

Achieved ≥10%/≥15% reduction in body weight:

CagriSema: n=20/n=15 (71.4%/53.6%)

Semaglutide: n=4/n=0 (13.8%/0%)

Cagrilintide: n=7/n=2 (23.3%/6.7%)

Ratio of leptin to soluble leptin (baseline/week 32):

CagriSema: 0.8/0.5 (p<0.001)

Semaglutide: 0.7/0.7

Cagrilintide: 0.8/0.6 (p=0.023)

'CagriSema' refers to co-administered semaglutide with cagrilintide.
HbA1c, glycated haemoglobin.
Frias JP, et al. *Lancet*. 2023;402:720–30.

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Study designs for phase III REDEFINE trials

	Patients without diabetes	Patients with type 2 diabetes	
	REDEFINE 1 (NCT05567796)*	**REDEFINE 2 (NCT05394519)†**	**REDEFINE 3 (NCT05669755)§**
Treatment arms	1. Cagrilintide + semaglutide 2. Cagrilintide + placebo 3. Placebo + semaglutide 4. Placebo Doses gradually increased to 2.4 mg over 16 weeks. Dosed for 68 weeks.	1. Cagrilintide + semaglutide 2. Placebo	1. Cagrilintide + semaglutide 2. Placebo
Inclusion criteria	• ≥18 years of age • BMI ≥30.0 kg/m^2 • No history of T2D or T1D	• T2D for ≥180 days • ≥18 years of age • BMI ≥27.0 kg/m^2 • HbA1c 7–10.0% inclusive • *T2D treatment*: lifestyle intervention OR stable dose of 1–3 OADs‡ for ≥90 days	• ≥55 years of age • BMI ≥25.0 kg/m^2 • Established CVD‖ For participants with T2D • T2D for ≥180 days • HbA1c 6.5–10.0% inclusive • *T2D treatment*: lifestyle intervention OR stable dose of 1–3 OADs¶ OR baslin insulin ± ≤2 OADs
Primary endpoint	• Relative change in body weight (%) from baseline • Achievement of ≥5% weight reduction from baseline	• Relative change in body weight (%) from baseline • Achievement of ≥5% weight reduction from baseline	• Time to first MACE**

'CagriSema' refers to co-administered semaglutide with cagrilintide. *Estimated enrolment N=3,400; †actual enrolment N=1,200; ‡metformin, AGI, glinides, SGLT2i, thiazolidinediones or SU as a single agent or in combination; §estimated enrolment N=7,000; ‖as evidenced by ≥1 of prior MI, prior stroke, symptomatic peripheral arterial disease; ¶metformin, AGI, glinides, SGLT2i, DPP4i, thiazolidinediones or SU as a single agent or in combination; **consisting of CV death, non-fatal MI, non-fatal stroke. **Information on clinical trials found at clinicaltrials.gov by searching the NCT number.** AGI, α-glucosidase inhibitors; BMI, body mass index; CV, cardiovascular; CVD, CV disease; DPP4i, dipeptidyl peptidase 4 inhibitors; HbA1c, glycated haemoglobin; MACE, major adverse CV event; MI, myocardial infarction; OAD, oral anti-diabetes drugs; SGLT2i, sodium–glucose co-transporter-2 inhibitor; SU sulphonylureas; T1D, type 1 diabetes; T2D, type 2 diabetes. Clinicaltrials.gov. Available at https://clinicaltrials.gov/ (accessed 10 January 2025).

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Study designs for phase III REIMAGINE trials

Patients with type 2 diabetes

	REIMAGINE 1 (NCT06323174)*	REIMAGINE 2 (NCT06065540)†	REIMAGINE 3 (NCT06323161)‡
Treatment arms	1. Cagrilintide + semaglutide 2. Placebo Doses gradually increased over 8-weeks or 16-weeks Dosed for 40 weeks	1. Cagrilintide + semaglutide 2. Semaglutide 3. Cagrilintide 4. Placebo Maintenance dose of 1.0 mg or 2.4 mg Dosed for 68 weeks	1. Cagrilintide + semaglutide 2. Placebo Doses gradually increased over 8 weeks or 16 weeks Dosed for 40 weeks
Inclusion criteria	• T2D for ≥30 days • ≥18 years of age • BMI ≥23.0 kg/m^2 • HbA1c 7.0–9.5% inclusive • *T2D treatment*: diet and exercise	• T2D for ≥180 days • ≥18 years of age • BMI ≥25 kg/m^2 • HbA1c 7.0–10.5% inclusive • *T2D treatment*: stable dose of metformin ± SGLT2i for ≥90 days	• T2D for ≥180 days • ≥18 years of age • BMI ≥25 kg/m^2 • HbA1c 7.0–10.5% inclusive • *T2D treatment*: stable basal insulin QD ± metformin for ≥90 days
Primary endpoint	• Change in HbA1c	• Change in HbA1c • Relative change in body weight	• Change in HbA1c

'CagriSema' refers to co-administered semaglutide with cagrilintide. *Estimated enrolment N=180; †actual enrolment N=2,734; ‡estimated enrolment N=270.
Information on clinical trials found at clinicaltrials.gov by searching the NCT number.
BMI, body mass index; HbA1c, glycated haemoglobin; QD, once daily; SGLT2i, sodium–glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.
Clinicaltrials.gov. Available at https://clinicaltrials.gov/ (accessed 10 January 2025).

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Study designs for additional phase III CagriSema trials

	Patients without diabetes **REDEFINE 4 (NCT06131437)***	Patients with or without type 2 diabetes **NCT05813925†**
Treatment arms	1. Cagrilintide + semaglutide 2. Tirzepatide Doses gradually increased to 2.4 mg over 16 weeks (CagriSema) or 15 mg over 20 weeks (tirzepatide) Dosed for 72 weeks	1. Cagrilintide + semaglutide 2. Semaglutide + placebo Doses gradually increased to 2.4 mg over 16 weeks Dosed for 68 weeks
Inclusion criteria	• ≥18 years of age • BMI ≥30.0 kg/m^2 • No history of T2D or T1D	• Study in patients in East Asia • ≥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‡ For participants with T2D • T2D for ≥180 days • HbA1c 7.0–10.0% inclusive • *T2D treatment*: lifestyle intervention OR stable dose of 1–3 OADs§
Primary endpoint	• Relative change in body weight	• Relative change in body weight

'CagriSema' refers to co-administered semaglutide with cagrilintide. *Estimated enrolment N=800; †estimated enrolment N=330; ‡≥1 complication should be hypertension, dyslipidaemia or T2D; §metformin, AGI, glinides, SGLT2i, thiazolidinediones or SU as a single agent or in combination. **Information on clinical trials found at clinicaltrials.gov by searching the NCT number.** AGI, α-glucosidase inhibitors; BMI, body mass index; HbA1c, glycated haemoglobin; OAD, oral anti-diabetes drugs; SGLT2i, sodium–glucose co-transporter-2 inhibitor; SU sulphonylureas; T1D, type 1 diabetes; T2D, type 2 diabetes.

Clinicaltrials.gov. Available at https://clinicaltrials.gov/ (accessed 10 January 2025).

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What are the implications for future management of obesity with or without type 2 diabetes?

What do we know about the safety of novel GLP-1–based combination therapies for obesity with or without type 2 diabetes, based on available clinical evidence?

Prof. Carel le Roux

University College Dublin,
Dublin, Ireland

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What do we know about the overall safety of GLP-1–based combination therapy for obesity with or without type 2 diabetes?

Why are additional therapies needed?

A systematic review of clinical trials examining the use of GLP-1RAs and co-agonists in obesity without T2D [1]

GI AEs are commonly reported with GLP-1 RA based treatments, with the most frequent being nausea, diarrhoea, constipation and vomiting

Across studies in the systematic review, the majority of **GI AEs were mild to moderate in severity**, transient **and related to dose escalation**

Most treatment discontinuations occurred during the dose-escalation phase before maintenance dose was reached

A real-world study in the US examining persistence,* adherence and switch rates of GLP-1–based therapies† in patients with obesity and no diagnosis of diabetes between 1 January and 31 December 2021 (N=4,066)[2]

Adherence

27.2% of patients had therapy on **≥80% of days**

Persistence

32.3% of patients were **persistent** with therapy*

Greater persistence observed with less frequent injections

Median time to discontinuation

120–279 days depending on the treatment

*Considered persistent if they did not have a 60-day gap in therapy; †semaglutide, dulaglutide and liraglutide (>1 formulation of each treatment was evaluated).
AE, adverse event; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1RA, GLP-1 receptor agonist; T2D, type 2 diabetes

1. Moiz A, et al. *Ann Intern Med*. doi:10.7326/ANNALS-24-01590 [Online ahead of print]; 2. Gleason PP, et al. *J Manag Care Spec Pharm*. 2024;30:860–7.

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What evidence do we have so far regarding the safety of GLP-1–based combination therapies for obesity with or without type 2 diabetes?

Study designs for phase II trials

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Inclusion criteria	• T2D for ≥180 days • ≥18 years of age • BMI ≥27.0 kg/m^2 • HbA1c 7.5–10.0 % inclusive • *T2D treatment*: stable daily dose of metformin ± SGLT2i for ≥90 days	• T2D • 18–75 years of age • BMI ≥27.0 kg/m^2 • HbA1c 7.0–10.5% • Stable body weight (<5% gain/loss) for previous 3 months • *T2D treatment*: diet and exercise alone OR stable dose of metformin ± SGLT2i for ≥3 months
Key safety endpoints	• Number of TEAEs • Number of clinically significant or severe hypoglycaemic episodes	• No safety endpoints listed

'CagriSema' refers to co-administered semaglutide with cagrilintide. *Actual enrolment N=92; †estimated enrolment N=350. **Information on clinical trials found at clinicaltrials.gov by searching the NCT number.** BMI, body mass index; HbA1c, glycated haemoglobin; SGLT2i, sodium–glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; TEAE, treatment emergent adverse event. Clinicaltrials.gov. Available at https://clinicaltrials.gov/ (accessed 10 January 2025).

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Phase II clinical trial safety data for CagriSema (NCT04982575)

2 August–18 October 2021

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

Clinically significant or severe hypoglycaemic episodes:

n=0

Adverse events:

CagriSema: 68%

Semaglutide: 71%

Cagrilintide: 80%

Discontinued treatment:

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

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

Cagrilintide: n=0

Serious adverse events:

CagriSema: n=0

Semaglutide: n=2

Cagrilintide: n=4

GI adverse events:*

CagriSema: 58%

Semaglutide: 32%

Cagrilintide: 33%

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

Injection site reactions:

n=3

Acute gall bladder disease or acute pancreatitis:

n=0

'CagriSema' refers to co-administered semaglutide with cagrilintide.
*Including nausea, constipation, diarrhoea, vomiting and GORD
AE, adverse event; GORD, gastro-oesophageal reflux disease; GI, gastrointestinal.
Frias JP, et al. *Lancet*. 2023;402:720–30.

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Key safety endpoints	• Number of TEAEs and TESAEs	• Number of TEAEs and TESAEs • Number of clinically significant or severe hypoglycaemic episodes	• Number of TESAEs • Number of severe hypoglycaemic episodes • Number of EAC-confirmed neoplasms

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Key safety endpoints	• 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. *Estimated enrolment N=180; †actual enrolment N=2,734; ‡estimated enrolment N=270.
Information on clinical trials found at clinicaltrials.gov by searching the NCT number. BMI, body mass index; HbA1c, glycated haemoglobin; QD, once daily; SGLT2i, sodium–glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; TEAE, treatment emergent adverse event.
Clinicaltrials.gov. Available at https://clinicaltrials.gov/ (accessed 10 January 2025).

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Study designs for additional phase III CagriSema trials

	Patients without diabetes **REDEFINE 4 (NCT06131437)***	Patients with or without type 2 diabetes **NCT05813925†**
Treatment arms	1. Cagrilintide + semaglutide 2. Tirzepatide Doses gradually increased to 2.4 mg over 16 weeks (CagriSema) or 15 mg over 20 weeks (tirzepatide) Dosed for 72 weeks	1. Cagrilintide + semaglutide 2. Semaglutide + placebo Doses gradually increased to 2.4 mg over 16 weeks Dosed for 68 weeks
Inclusion criteria	• ≥18 years of age • BMI ≥30.0 kg/m^2 • No history of T2D or T1D	• Study in patients in East Asia • ≥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‡ For participants with T2D • T2D for ≥180 days • HbA1c 7.0–10.0% inclusive • *T2D treatment*: lifestyle intervention OR stable dose of 1–3 OADs§ for ≥90 days
Key safety endpoints	• Number of TEAEs and SAEs	• Number of TEAEs and TESAEs

'CagriSema' refers to co-administered semaglutide with cagrilintide. *Estimated enrolment N=800; †estimated enrolment N=330; ‡≥1 complication should be hypertension, dyslipidaemia or T2D; §metformin, AGI, glinides, SGLT2i, thiazolidinediones or SU as a single agent or in combination. **Information on clinical trials found at clinicaltrials.gov by searching the NCT number.** AGI, α-glucosidase inhibitors; BMI, body mass index; HbA1c, glycated haemoglobin; OAD, oral anti-diabetes drugs; SAE, serious adverse event; SGLT2i, sodium–glucose co-transporter-2 inhibitor; SU sulphonylureas; T1D, type 1 diabetes; T2D, type 2 diabetes; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse events. Clinicaltrials.gov. Available at https://clinicaltrials.gov/ (accessed 10 January 2025).

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What are the implications for future management of obesity with or without type 2 diabetes?