The Role of Amylin in Obesity Care

From Biology to Clinical Potential

Welcome

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Speaker disclosures

- **Speaker engagement/honoraria:**
  - Novo Nordisk Canada
- **Consultant:**
  - Novo Nordisk, Sysmex
- **Advisory Board:**
  - Johnson & Johnson Canada

Objectives

1. Describe the physiology of amylin and its role in appetite regulation, satiety, energy balance, and metabolic health in people living with obesity

2. Evaluate emerging evidence for amylin-based therapeutics and their clinical potential in obesity management, including benefits beyond weight reduction

3. Discuss the potential integration of emerging therapies, (i.e. amylin-based, oral formulations, etc.) into comprehensive obesity care, including their role across the metabolic and bariatric surgery pathway and in long-term obesity management

Speakers

Dr. Mehran Anvari

Professor, McMaster University
Clinical Lead, Ontario Bariatric Network

Moderator

Dr. Ahmed Jad

Assistant Professor & Surgeon
Dalhousie University
Nova Scotia Health

Speaker

Dr. Tayyab Khan

Associate Professor & Endocrinologist
Western University

Speaker

Agenda

12:50 – 1:10 pm	**Understanding Amylin: Biology and Mechanisms in Obesity** Dr. Ahmed Jad
1:10 – 1:30 pm	**The Clinical Potential of Amylin in Obesity Care: Emerging Evidence and Future Directions** Dr. Tayyab Khan
1:30 – 1:45 pm	**Expert Discussion and Q&A: Integrating Future Therapies into Comprehensive Obesity Management** All

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Understanding Amylin: Biology and Mechanisms in Obesity

Dr. Ahmed Jad, MD, FRCSC, FACS, FASMBS, Dip ABOM

Speaker disclosures

- **Speaker engagement/honoraria:**
  - Novo Nordisk Canada

Learning objectives and talk map

1. Physiology

Describe amylin as a nutrient-stimulated pancreatic hormone and explain its role in satiation, satiety, energy intake and metabolic health.

2. Mechanisms

Connect amylin biology to appetite-regulating circuits: area postrema, NTS, ARC, reward pathways and gastric emptying.

3. Translation

Place amylin-based therapies in comprehensive obesity care and the metabolic/bariatric surgery pathway.

Disease context | **NuSH physiology** | **Brain mechanisms** | **Therapeutic logic** | **Obesity-care pathway**

ARC, arcuate nucleus; NTS, nucleus tractus solitarius; NuSH, nutrient-stimulated hormone

Obesity is a chronic, relapsing, adiposity-based disease with defended physiology

Energy homeostasis

Peripheral signals from pancreas, gut and adipose tissue are continuously integrated in hypothalamus and brainstem to regulate hunger, satiation, gastric emptying and energy expenditure.

Reward and cue reactivity

Palatable food, stress, sleep disruption and environmental cues engage mesolimbic circuits that amplify wanting and eating beyond metabolic need.

Long-term defence

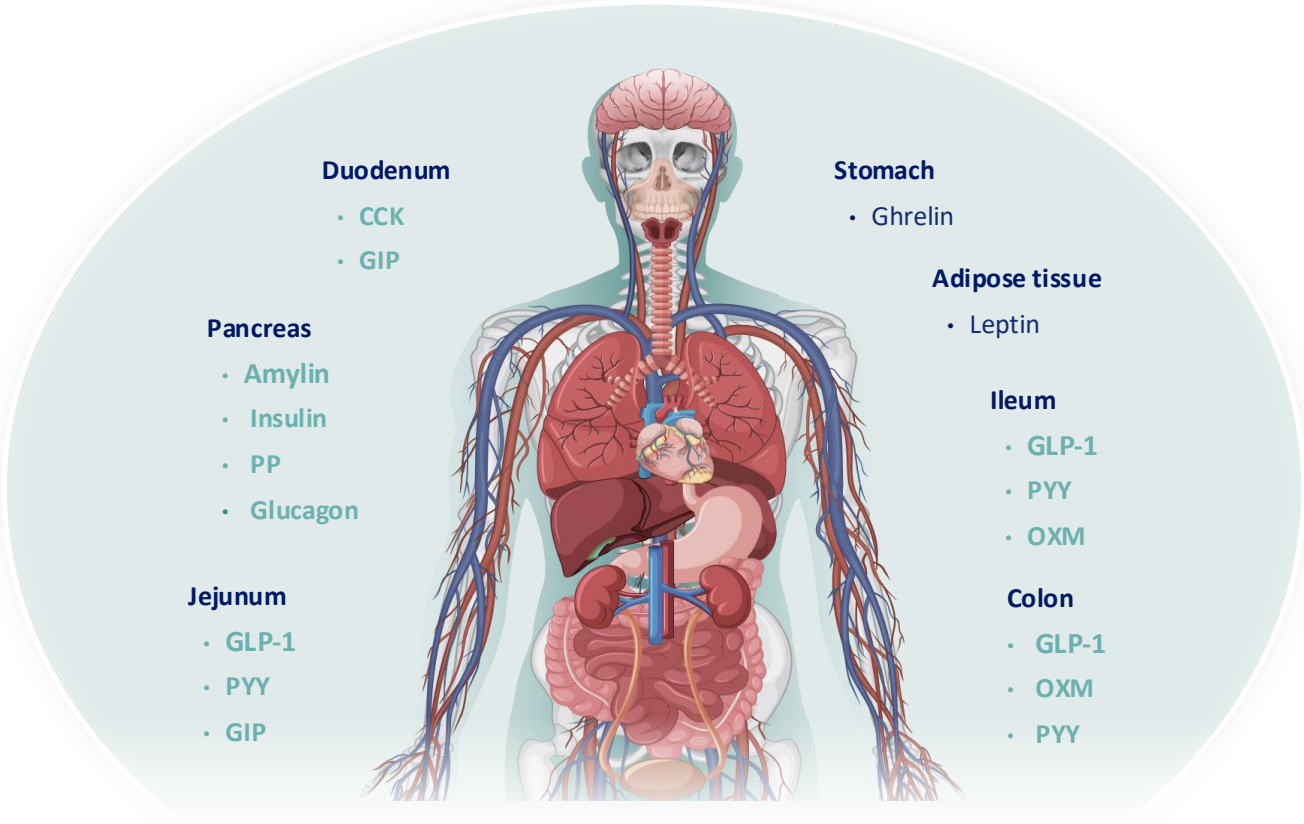
Weight loss triggers adaptive biology: lower energy expenditure, increased hunger signals, and increased drive to regain weight.

Modern obesity pharmacology targets the biology that drives intake, satiety, metabolic health and long-term weight maintenance.

Peripheral hormones are key regulators of appetite and energy balance

Nutrient-stimulated hormones (NuSH)[1–3]

A group of entero-endocrine and endo-pancreatic peptides secreted in response to intake of nutrients

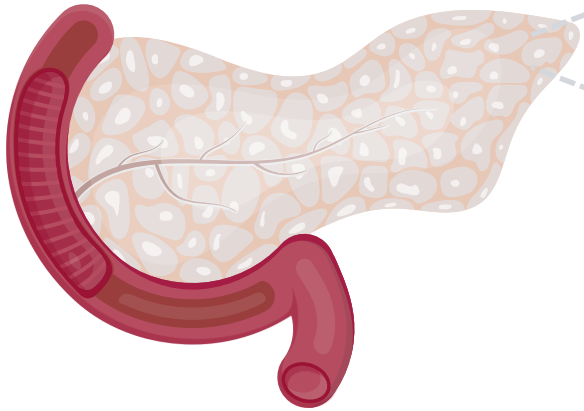


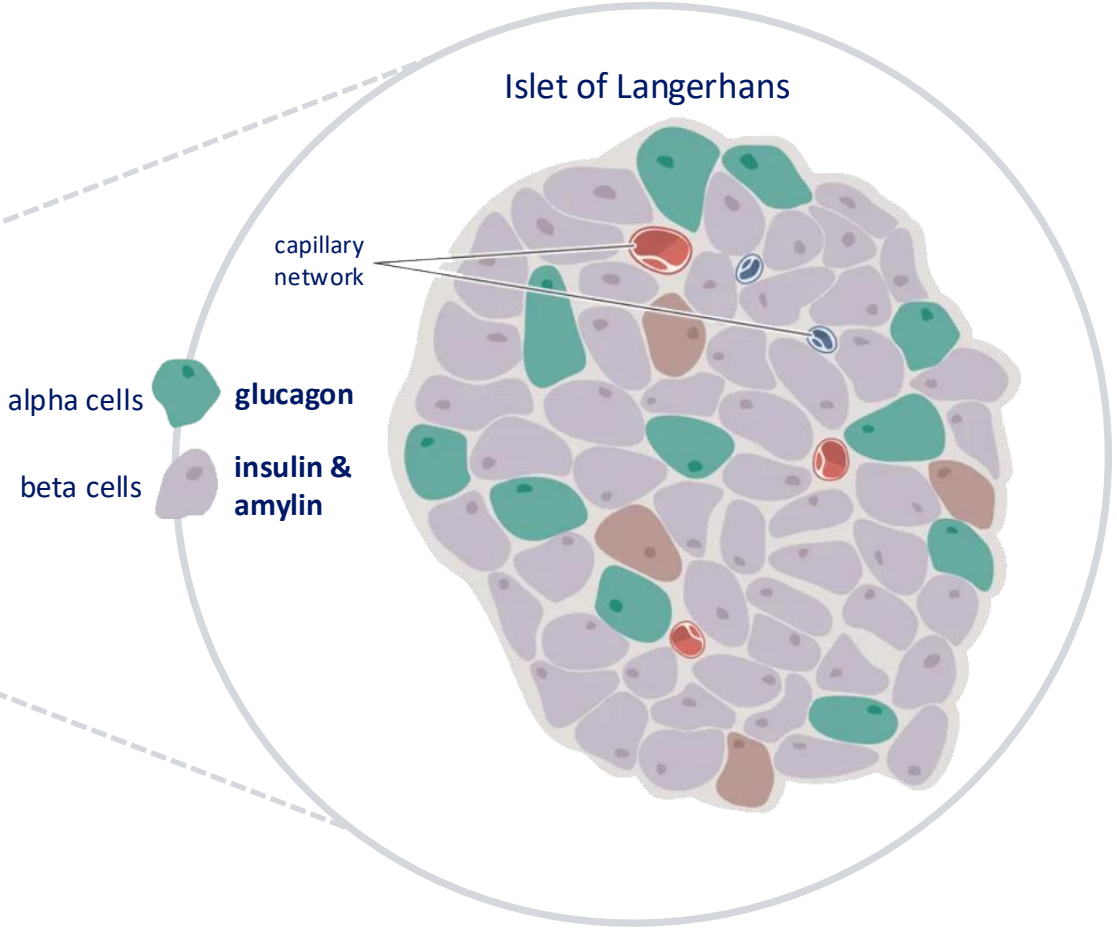
CCK, cholecystokinin; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; NuSH, nutrient-stimulated hormones; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide YY.

1. Jastreboff M and Kushner RF. Annu Rev Med. 2023;74:125–39; 2. Koliaki C et al. Curr Obes Rep. 2020;9:255–71; 3. Remmers F et al. Endocr Rev. 2011;32:272–311.

Amylin is a nutrient-stimulated hormone (NuSH)[1–6]

Native amylin is co-located and co-secreted with insulin from **pancreatic beta cells*** in rapid response to food intake[1,2]



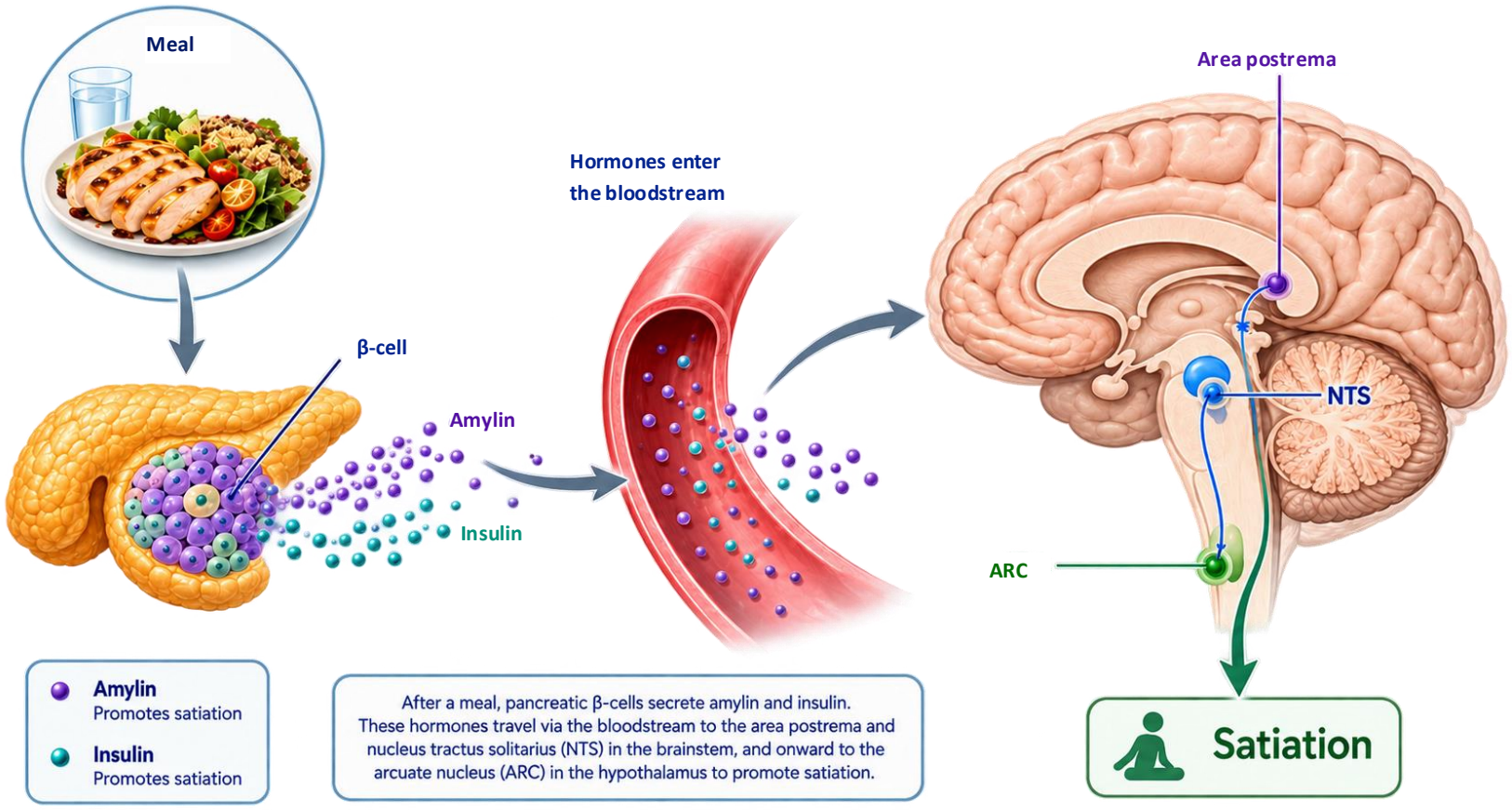


*Lesser degree of amylin expression in the brain, spinal ganglia, stomach and developing kidney.

1. Jastreboff AM et al. Annu Rev Med. 2023;74:125–39; 2. Bower RL and Hay DL. Br J Pharmacol. 2016;173(12):1883–98; 3. Hay DL et al. Pharmacol Rev. 2015;67:564–600; 4. Lutz T. Endocrine Abstracts. 2022;86:S2.1; 5. Lundh S et al. Poster presented at 40th Annual Meeting of the Obesity Society at ObesityWeek®. 2022. Poster #174. November 1-4, 2022. San Diego, CA; 6. Boccia L et al. Peptides. 2020;132:170366.

Image adapted from Encyclopaedia Britannica, Inc. https://www.britannica.com/science/islets-of-Langerhans. Accessed November 2024.

Amylin is co-secreted with insulin after a meal



What is it?

A 37–amino acid neuroendocrine peptide, rapidly released by pancreatic β-cells after nutrient intake.

What does it signal?

Meal termination: reduced meal size, delayed gastric emptying and lower post-prandial glucagon.

Where does it act?

Primarily AP/NTS in the brainstem, with additional hypothalamic ARC engagement.

Clinical implication

Amylin analogues try to pharmacologically restore and amplify this native satiation signal.

AP, area postrema; ARC, arcuate nucleus; NTS, nucleus tractus solitarius

1. Hay DL et al. Pharmacol Rev. 2015;67:564–600. **2**. Bower RL, Hay DL. Br J Pharmacol. 2016;173:1883–1898. **3**. Boccia L et al. Peptides. 2020;132:170366.

Challenges in amylin pharmacological development

Native human amylin

37 amino acids

short endogenous half-life ≈12 minutes

aggregation / fibrillation limits therapeutic use

Drug-design challenge

To create amylin mimetics that preserve appetite/metabolic signalling while reducing aggregation and extending exposure.

Pramlintide proof of concept

Short-acting amylin analogue approved for insulin-treated type 1 and type 2 diabetes; demonstrates that amylin pharmacology can be translated clinically.

Next generation: long-acting analogues

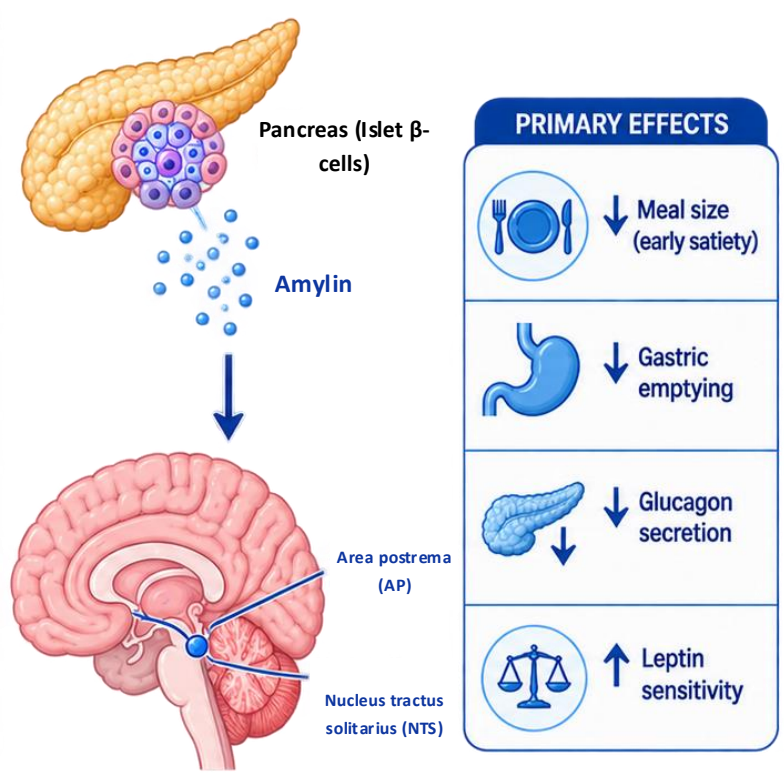
Cagrilintide was engineered for weekly dosing and is being studied for obesity as monotherapy and in combination with GLP-1 receptor agonism.

GLP-1, glucagon-like peptide

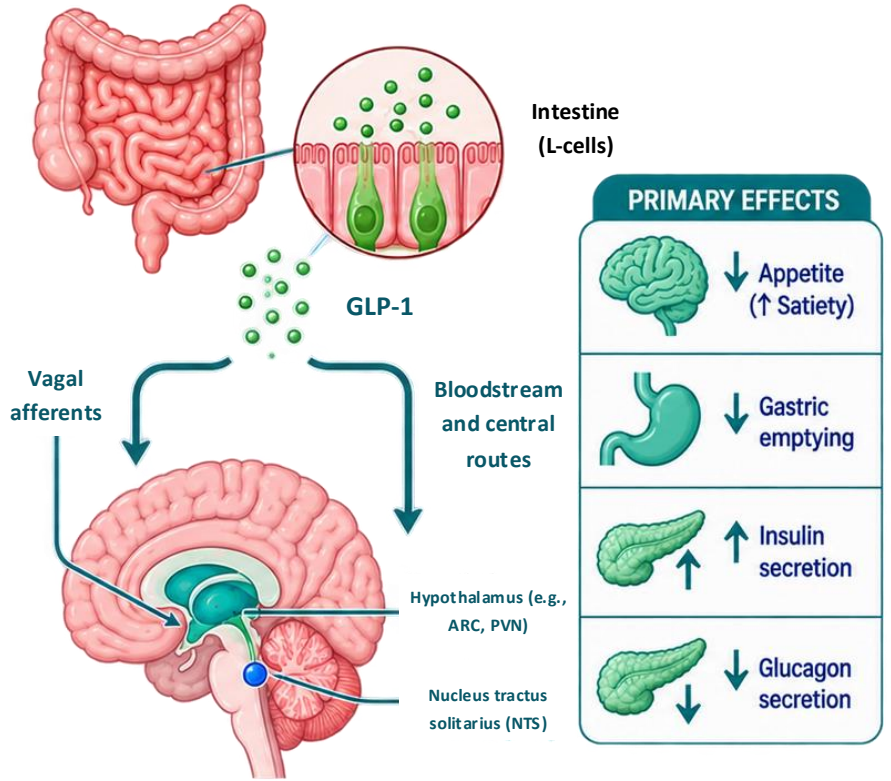
1. Hay DL et al. Pharmacol Rev. 2015;67:564–600. 2. Bower RL, Hay DL. Br J Pharmacol. 2016;173:1883–1898. 3. Clodi M et al. American Journal of Physiology. 1998;274(5):E903–8 4.. Lorenzo A et al. Nature. 1994;368:756-760. 5. Enebo LB et al. Lancet. 2021;397:1736–48.

Amylin vs GLP-1: converging signalling pathways

Amylin



GLP-1



AP, area postrema; ARC, arcuate nucleus; GLP-1, glucagon-like peptide; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus

1. *Jastreboff AM, Kushner RF. Annu Rev Med. 2023;74:125–139.* **2.** *Hay DL et al. Pharmacol Rev. 2015;67:564–600.* **3.** *Bower RL, Hay DL. Br J Pharmacol. 2016;173:1883–1898.* **4.** *Secher A et al. J Clin Invest. 2014;124:4473–4488.*

Amylin vs GLP-1: converging signalling pathways

Useful clinical distinction

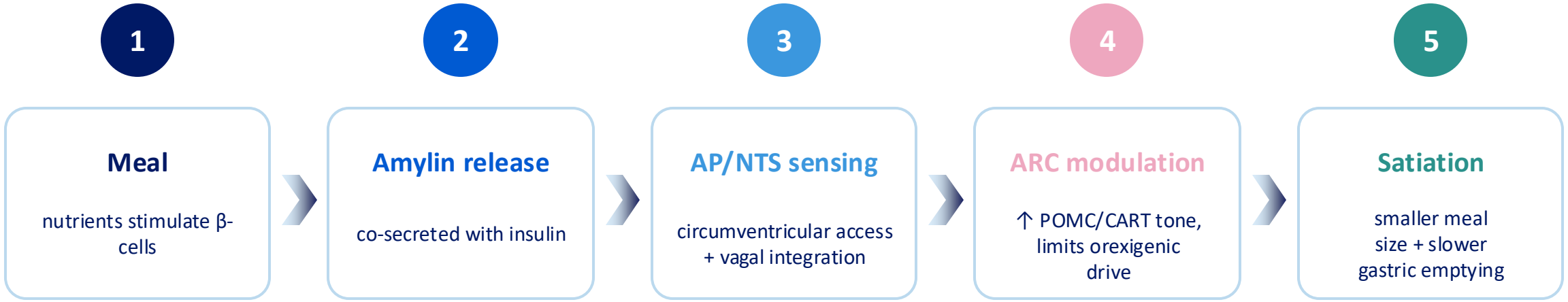
Source	Pancreatic β-cell	Intestinal L-cell
Meal effect	Satiation: smaller meal size	Satiety/appetite reduction + insulinotropic effect
Brain routes	AP/NTS; ARC engagement	Vagal afferents, NTS, hypothalamus and central routes
Metabolic action	↓ glucagon; ↑ leptin responsiveness	↑ insulin; ↓ glucagon
Why combine?	β-cell meal signal	gut-brain incretin signal

- **Amylin is especially a meal-size/satiation signal**
- **GLP-1 is a broader incretin/appetite signal.**
- **Their convergence in brainstem-hypothalamic networks is biologically attractive.**

AP, area postrema; ARC, arcuate nucleus; GLP-1, glucagon-like peptide; NTS, nucleus tractus solitarius

1. Jastreboff AM, Kushner RF. Annu Rev Med. 2023;74:125–139. 2. Hay DL et al. Pharmacol Rev. 2015;67:564–600. 3. Bower RL, Hay DL. Br J Pharmacol. 2016;173:1883–1898. 4. Secher A et al. J Clin Invest. 2014;124:4473–4488.

Amylin reduces meal size through brainstem–hypothalamic signalling

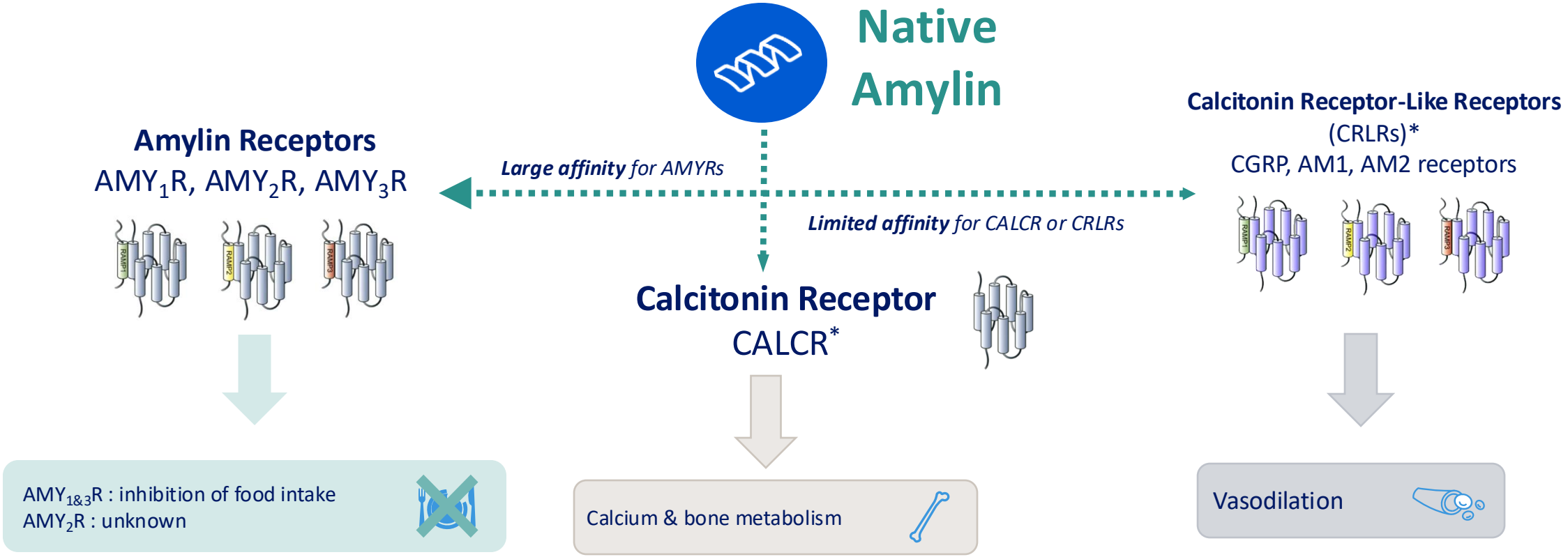


Mechanistic consequences **↓ meal size • ↑ fullness/satiation • ↓ gastric emptying • ↓ glucagon • potential leptin interaction**

AP, area postrema; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; NTS, nucleus tractus solitarius; POMC, pro-opiomelanocortin

1. Lutz TA et al. Physiol Behav. 1995;58:1197–1202. 2. Reidelberger RD et al. Am J Physiol Regul Integr Comp Physiol. 2004;287:R568–R574. 3. Boccia L et al. Peptides. 2020;132:170366. 4. Zakariassen HL et al. Basic Clin Pharmacol Toxicol. 2020;127:163-177.

Amylin-binding receptors have diverse biological effects[1–5]



**Native amylin has limited affinity for the calcitonin receptor and calcitonin receptor-like receptors*

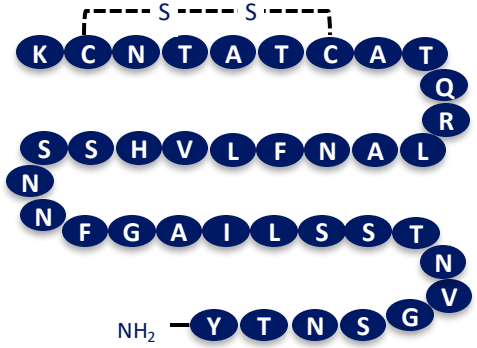
"Amylin-binding receptor" refers here to different members of the calcitonin receptor family capable of binding amylin.

AM1, adrenomedullin 1; AM2, adrenomedullin 2 (intermedin); AMY_1R, amylin receptor 1; AMY_2R, amylin receptor 2; AMY_3R, amylin receptor 3; CALCR, symbol for gene encoding for calcitonin receptor; CGRP, calcitonin gene-related peptide; RAMPs, receptor activity-modifying proteins.

1. Hay DL et al. Pharmacol Rev. 2015;67(3):564–600; **2.** Brower RL, Hay, DL. Br J Pharmacol. 2016;173(12):1883–98; **3.** Mathiesen DS et al. Front Endocrinol (Lausanne). 2021;11:617400; **4.** Fletcher MM et al. J Pharmacol Exp Ther. 2021;377:417–40; **5.** Dahl K et al. J Med Chem. 2024;67(14):11688–700.

Endogenous amylin has a brief half-life and strong fibrillating properties

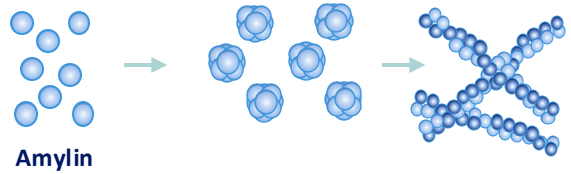
Endogenous human amylin can **self-aggregate,** eventually forming insoluble **amyloid deposits**[2,3]



$t_{½}$ approx. 12 mins in humans

Amylin[1,2]

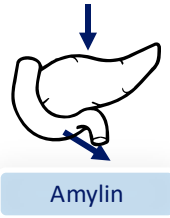
Fibrillation Process



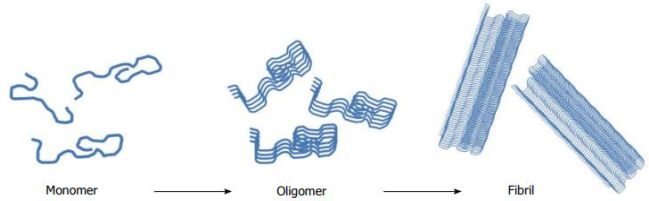
*Only in **humans**, **primates** and **cats** (not rodents)*[7]

Clinical Relevance

Amylin and insulin synthesis is markedly increased in early phase of T2D due to insulin resistance



In a hyperamylinemic state, endogenous amylin can develop **fibrils** that may generate amyloid deposits with **tissue-disruptive properties**[2-6]



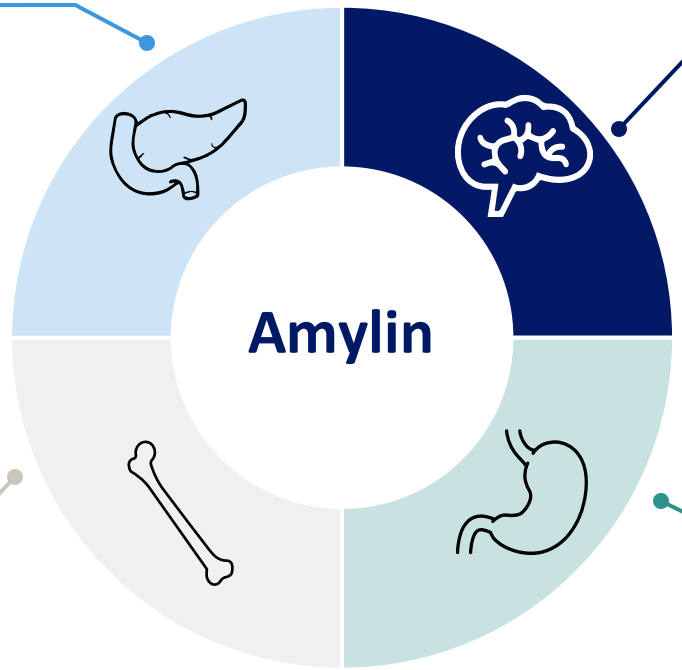
$t_{1/2}$, half-life; T2D, type 2 diabetes.

1. Clodi M et al. American Journal of Physiology. 1998;274(5):E903–8; 2. Lutz TA, Meyer U. Front Neurosci. 2015;9:216; 3. Henson MS, O'Brien TD. ILAR Journal. 2006;47(3): 234–42; 4. Albariqi MM et al. J Clin Invest. 2023;133(8):e156993; 5. Despa S et al. Circ Res. 2012;110(4):598–608; 6. Srodulski S et al. Circulation. 2014;130:A13963; 7. Bretherton-Watt D et al. Diabetologia.1990;33:115–7.

Amylin's effects are multifactorial

Glucose regulation

- ⬆ Responsiveness to leptin[1]
- ⬇ Glucagon secretion[1,4,12]
- Improves insulin sensitivity[13]



Appetite regulation
(both homeostatic and hedonic feedback systems)

- ⬇ Appetite[1,2]
- ⬇ Energy intake[1-4]
- ⬆ Satiety[1-5]
- ⬆ Partially restores leptin responsiveness[14]

Bone regulation

- Inhibition of resorption[7–9]
- Bone formation[9–11]

GI tract

- ⬇ Gastric acid secretion[1,4,6]
- Gastric emptying[1,4,6,15] ⬇

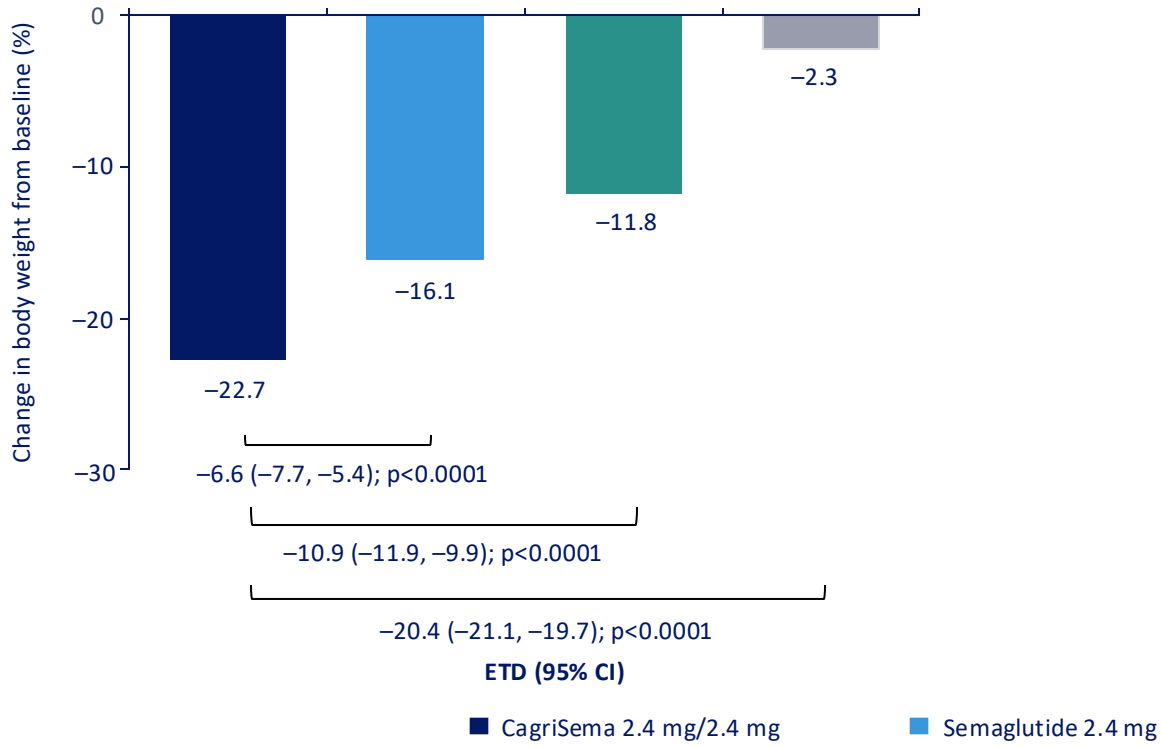
Emerging amylin-based therapies may matter because they target meal biology, metabolic signals and long-term regulation—not because they are simply "another appetite suppressant."

GI, gastrointestinal.

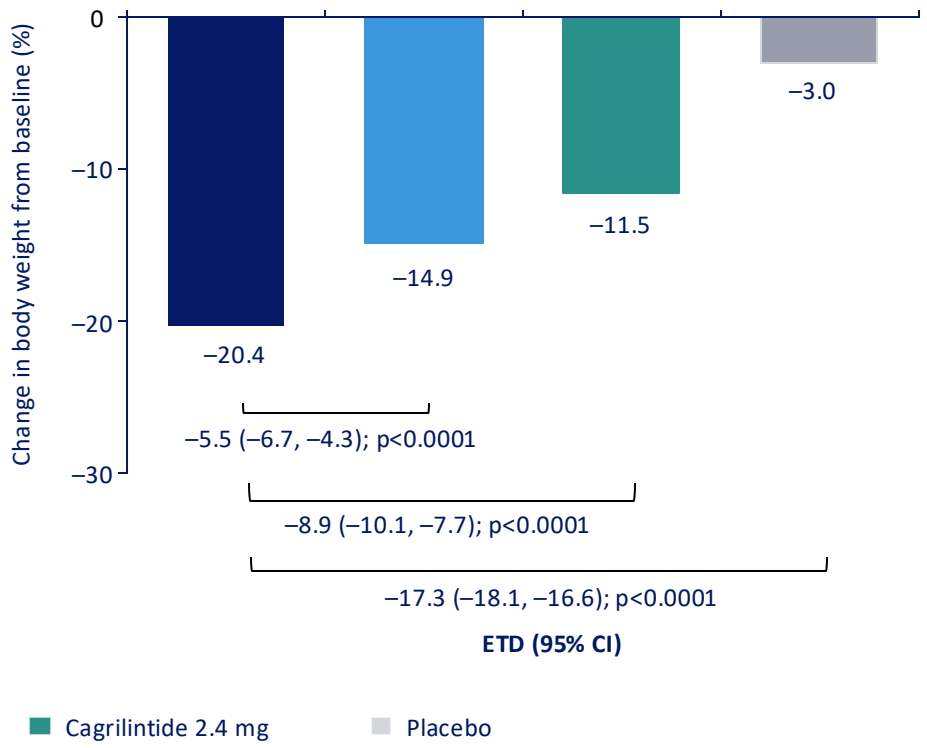
1. Hay DL et al. Pharmacol Rev. 2015;67:564–600; 2. Lutz TA et al. Physiol Behav. 1994;55:891–95; 3. Morley JE et al. Am J Physiol. 1994;267:R178–84; 4. Lutz TA et al. Curr Drug Targets. 2005;6:181–89; 5. Boyle CN et al. Mol Metab. 2018;8:203–10; 6. Young AA et al. Diabetologia. 1995;38:642–48; 7. Cornish J et al. Bone. 2001;29(2):162–8; 8. Horcajada-Molteni MN et al. J Endocrinol. 2000;165(3):663–8; 9. Horcajada-Molteni MN et al. J Bone Miner Res. 2001;16(5):958–65; 10. Cornish J et al. Biochem Biophys Res Commun. 1995;207(1):133–9; 11. Romero DF et al. Calcif Tissue Int. 1995;56(1):54–61; 12. Gedulin BR et al. Metab Clin Exp. 1997;46:67–70; 13. Kusakabe T et al. Am J Physiol Endocrinol Metab. 2012;302(8):E924–31;
14. Trevaskis JL et al. Endocrinology. 2008;149:5679–87; 15. Bak N et al. Presented at the American Diabetes Association (ADA) 85th Scientific Sessions, June 20–23, 2025, Chicago, IL, USA. Abstract #2025-LB-6564-Diabetes.

Amylin and incretin combination therapy may target multiple regulatory nodes

Percentage change in body weight at week 68
Trial product estimand†



Percentage change in body weight at week 68
Treatment policy estimand‡

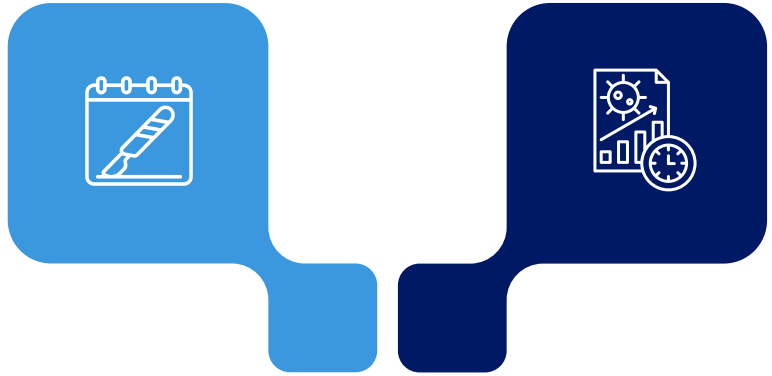


† Observed data are from the on-treatment period. Estimated means, ETDs are for the trial productestimand.
‡ Observed data are from the in-trial period. Estimated means, ETDs are for the treatment policy estimand.
CI, confidence interval; ETD, estimated treatment difference.
Garvey WT et al. New Engl J Med 2025; 14;393(7):635-647

Where could amylin-based therapy fit in comprehensive obesity care?

Before surgery

Pre-operative optimization, improved glycemia/metabolic risk, potential bridge while awaiting bariatric surgery.



Long-term disease management

Obesity is chronic; pharmacotherapy may need to be episodic, long-term or combined with procedural strategies depending on phenotype and response.

After surgery

Adjunctive therapy for inadequate response or weight recurrence, while preserving nutrition-first and behavior-first care.

Future direction

Better matching of therapy to biology: meal-size phenotype, glycemic profile, appetite pattern, side-effect tolerance and patient preference.

1. Wharton S et al. CMAJ. 2020;192:E875–E891. 2. Busetto L et al. Nat Med. 2024;30:2395–2399. 3. Jastreboff AM, Kushner RF. Annu Rev Med. 2023;74:125-139.

Summary

- Amylin is co-secreted with insulin and targets the AP/NTS and downstream ARC/reward circuitry in the brainstem, where it modulates homeostatic and hedonic eating.
- Amylin also reduces meal size, delays gastric emptying and modulates glucagon/leptin pathways.
- It offers a potentially complementary biological pathway to GLP-1, which could support combination therapy.
- The future of obesity care is integrated, and amylin-based therapies may become a tool used across medical, surgical, and long-term obesity management.

AP, area postrema; ARC, arcuate nucleus; GLP-1, glucagon-like peptide-1; NTS, nucleus tractus solitarius

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The Clinical Potential of Amylin in Obesity Care:

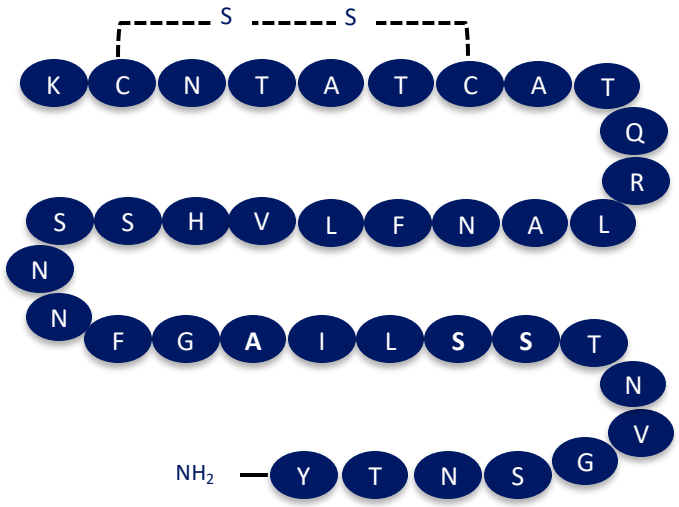
Emerging Evidence and Future Directions

Dr. Tayyab Khan, MD, FRCP(C), Dip ABOM

Speaker disclosures

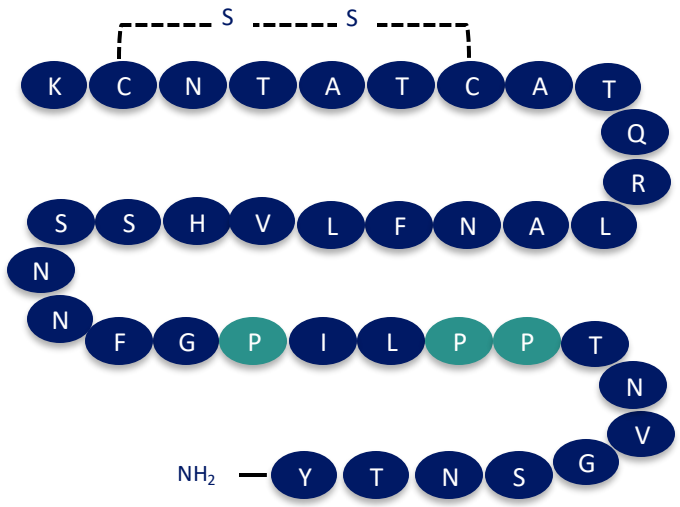
- **Speaker engagement/honoraria**:
  - Bausch, Sutherland Global Services Canada ULC, Novo Nordisk Canada, Abbott, AstraZeneca, Canadian Medical and Surgical Knowledge Translation Research Group, Amgen, Boehringer Ingelheim, Eli Lily Canada, Janssen, Pedopharm, Ascendis, Kyowa Kirin
- **Advisory Board**: Novo Nordisk Canada, Eli Lily Canada.
- **Employment**: Western University.

The evolution of amylin therapy



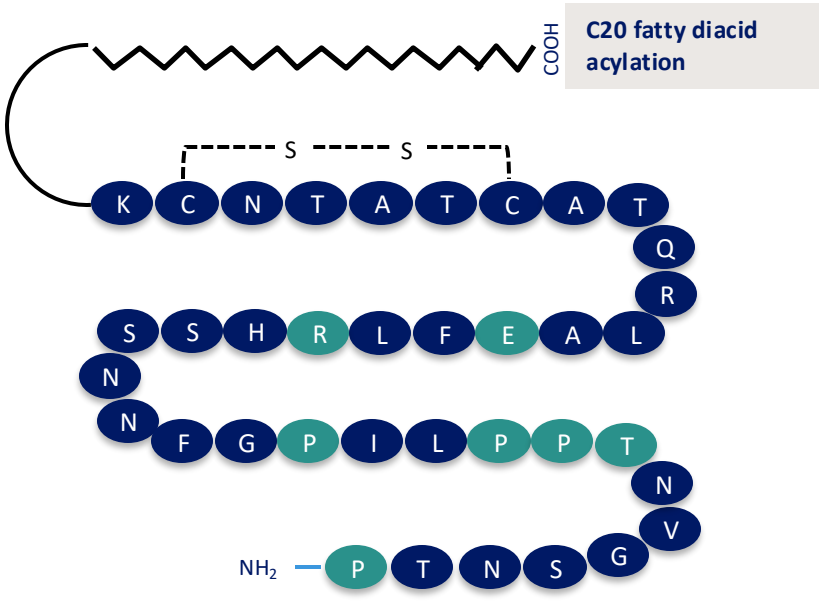
$t_{½}$ ~12 mins in humans

Human Amylin[1,2]



$t_{½}$ ~50 mins in humans

Pramlintide[3]



$t_{½}$ = 159-195 hours in humans

Cagrilintide[4,5]

Pramlintide is the only approved amylin analogue, for treatment of type 1 and type 2 diabetes.
$t_{1/2}$, half-life.

1. *Bower RL and Hay DL. Br J Pharmacol. 2016;173(12):1883–98.* ***2.*** *Clodi M et al. Am J Physiol-Endo & Metab. 1998;274(5):E903–8.* ***3.*** *Pramlintide, FDA patient information label. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021332lbl.pdf. Accessed Sept 2020.* ***4.*** *Kruse T et al. Journal of Medicinal Chemistry. 2021;64(15):11183–94.* ***5.*** *Enebo LB et al. Lancet. 2021;397:1736–48.*

What is CagriSema?

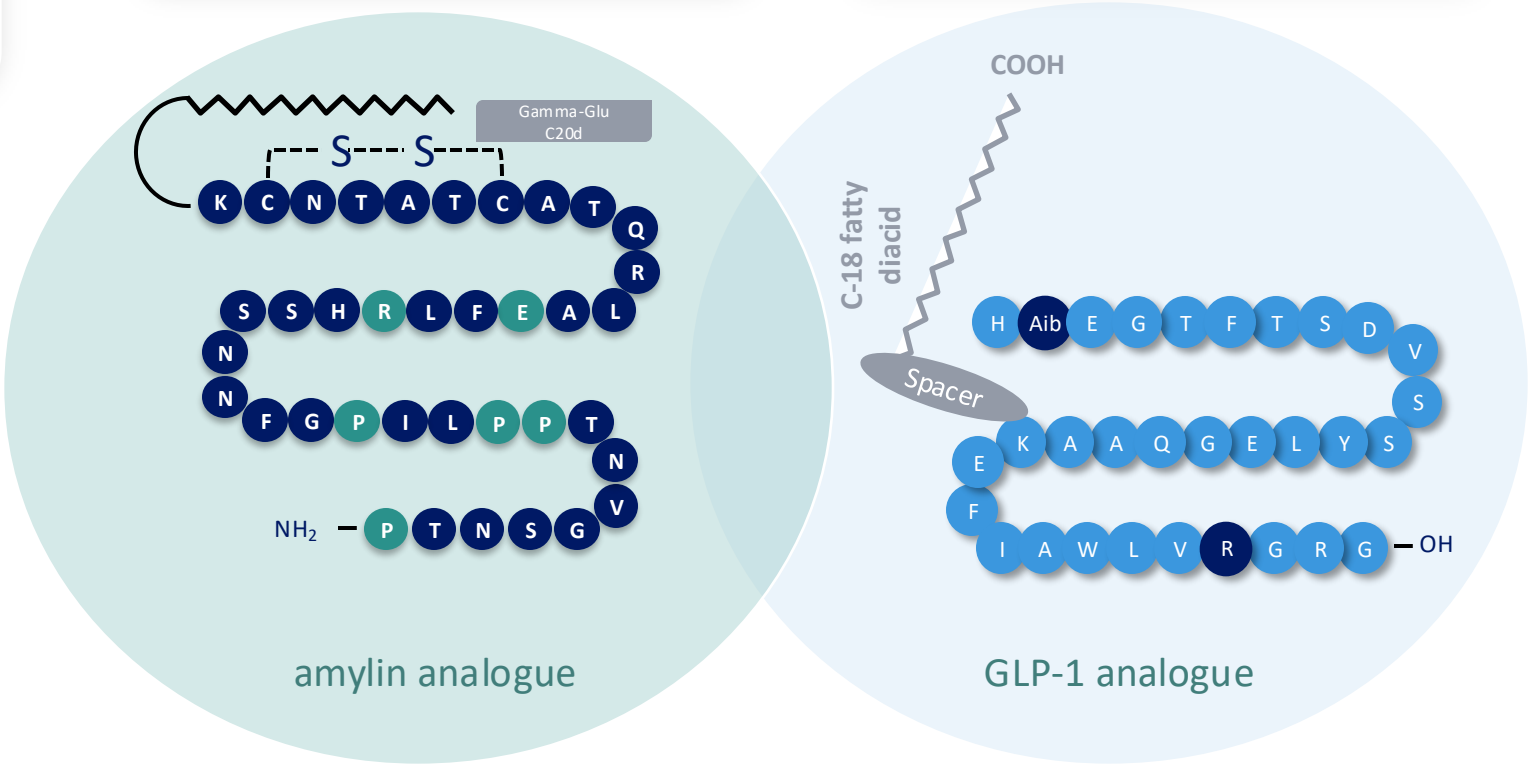
CagriSema

s.c. 2.4 mg/2.4 mg
is a once weekly fixed-dose combination product[1,2]

=

Two molecules:

Cagrilintide[3-5] + **Semaglutide**[6,7]

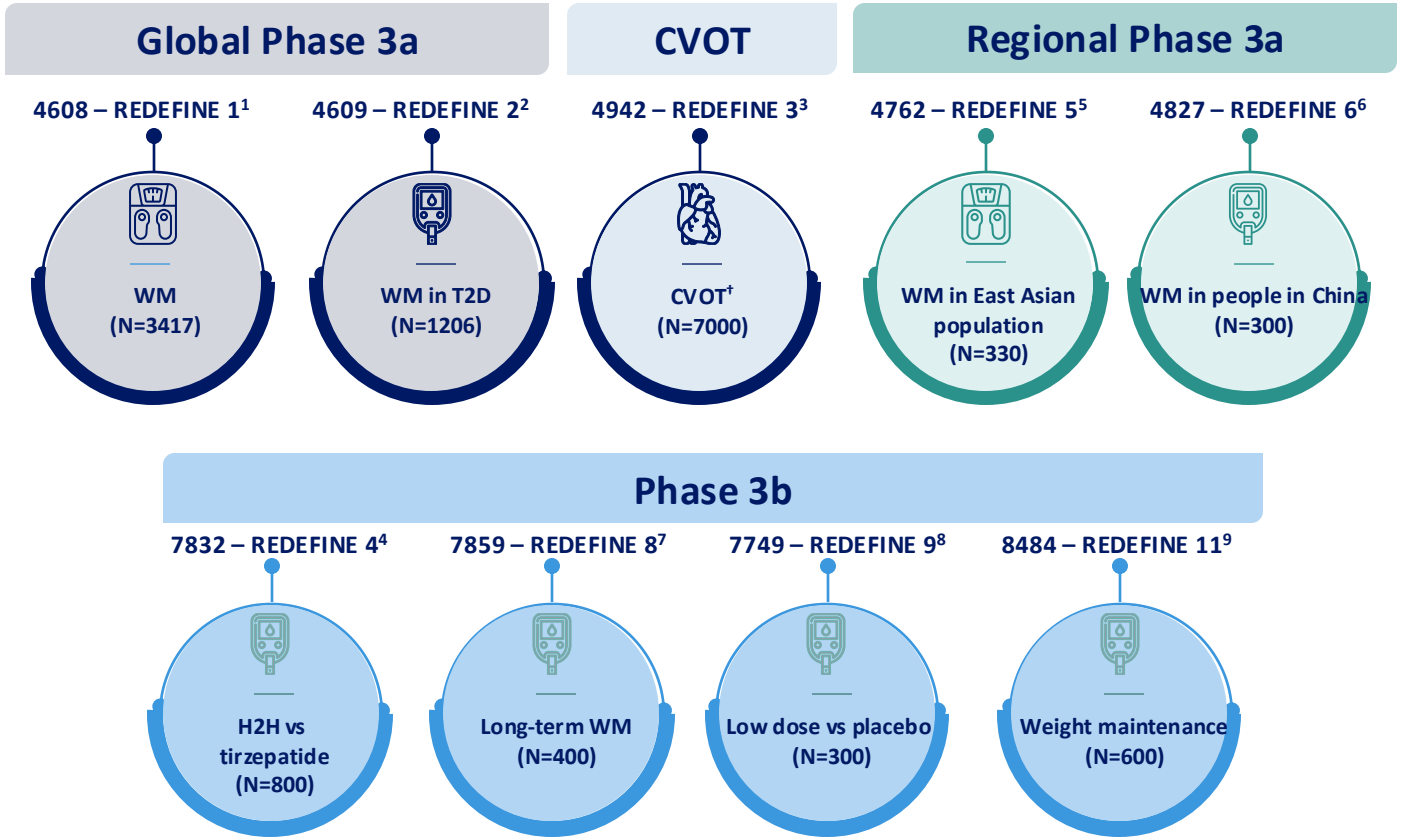


Glu, glutamic acid; GLP-1, glucagon-like peptide 1; s.c., subcutaneous injection.

1. Enebo LB et al. Lancet (Lond.). 2021;397(10286):1736–48. 2. Frias JP et al. Lancet. 2023;402:720–30. 3. Dahl KD et al. Poster presented at 38th Annual Meeting of the Obesity Society at ObesityWeek®. 2020. Poster #330. 4. Kruse T et al. J Med Chem. 2021;64:11183–94. 5. Lau DCW et al. Lancet. 2021;398:2160–72. 6. Friedrichsen M et al. Diabetes Obes Metab. 2021;23:754–62. 7. Blundell J et al. Diabetes Obes Metab. 2017;19:1242–51.

REDEFINE programme at a glance

Ongoing trials*



*currently registered on clinicaltrials.gov, accessed June 2025

**to assess the CV safety and CV benefits of CagriSema 2.4 mg/2.4 mg in individuals with established CVD and obesity or overweight, with or without comorbidities such as T2D and CKD.

CKD, chronic kidney disease; CV; cardiovascular, CVD; cardiovascular disease, CVOT; cardiovascular outcomes trial, H2H, head to head; REDEFINE, REDEfining treatment oF obesity with cagriINtide and semaglutidE combination; T2D, type 2 diabetes; WM, weight management.

1. NCT05567796. Available from: https://clinicaltrials.gov/ct2/show/NCT05567796. Accessed February 2025. **2.** NCT05394519. Available from: https://clinicaltrials.gov/ct2/show/NCT05394519. Accessed February 2025. **3.** NCT05669755. Available from: https://clinicaltrials.gov/ct2/show/NCT05669755. Accessed February 2025. **4.** NCT06131437. Available from: https://clinicaltrials.gov/study/NCT06131437. Accessed February 2025. **5.** NCT05813925. Available from: https://clinicaltrials.gov/study/NCT05813925. Accessed February 2025. **6.** NCT05996848. Available from: https://clinicaltrials.gov/study/NCT05996848. Accessed February 2025. **7.** NCT05394519. Available from: https://clinicaltrials.gov/study/NCT06780449. Accessed February 2025. **8.** NCT06388187. Available from: https://clinicaltrials.gov/study/NCT06388187. Accessed February 2025. **9.** NCT07011667. Available from: https://clinicaltrials.gov/study/NCT07011667. Accessed June 2025.

REDEFINE 1: weight management in participants with overweight or obesity

NN9838-4608

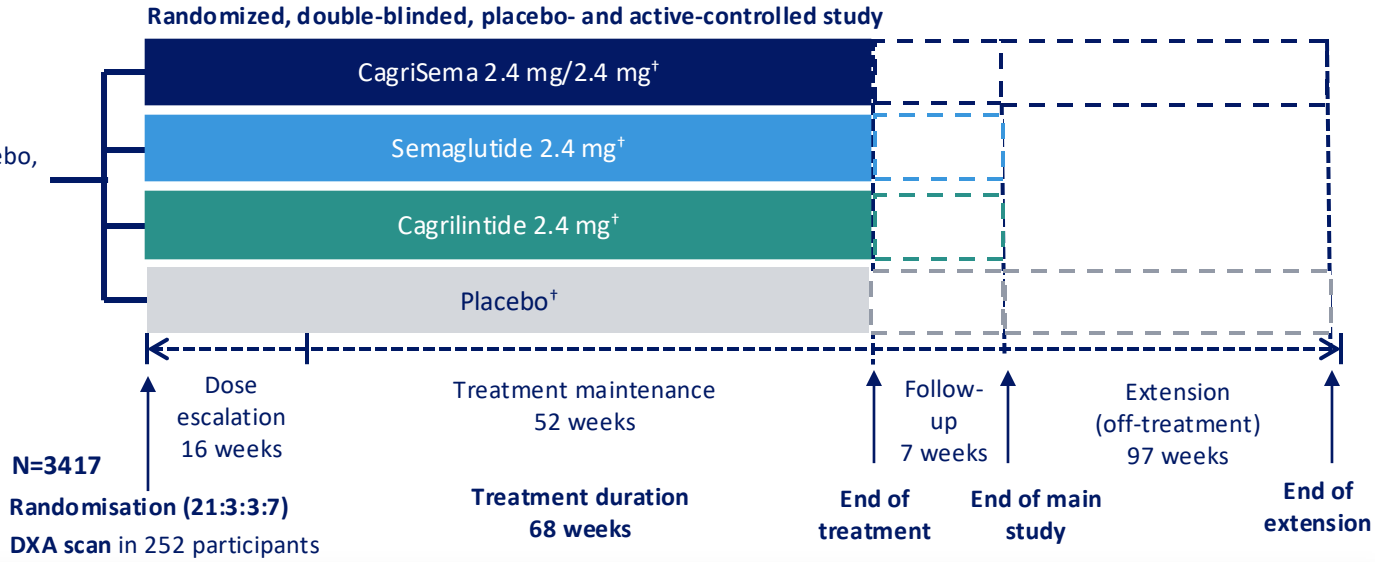
Study objective: To confirm superiority of CagriSema 2.4 mg/2.4 mg versus placebo, semaglutide 2.4 mg, and cagrilintide 2.4 mg on body weight reduction

Key inclusion criteria

- Male or female
- ≥18 years
- BMI ≥30 kg/m^2,
- Or ≥27 kg/m^2 with ≥1 comorbidity

Key exclusion criteria

- History of type 1 or type 2 diabetes or HbA_{1c} ≥6.5%



Key endpoints

Co-primary: (vs placebo)

- Relative change (%) in body weight from baseline to week 68
- Proportion of participants who achieve ≥5% body weight loss from baseline to week 68

Confirmatory secondary:

- Proportion of participants who achieve ≥20%, ≥25%, ≥30% body weight loss from baseline to week 68, vs placebo
- Relative change in body weight from baseline to week 8 and week 20, vs placebo
- Relative change in body weight vs monotherapies from baseline to week 68
- Change from baseline to week 68 in waist circumference, SBP and physical function,‡ vs placebo

Safety:

- Number of TEAEs to week 75
- Number of TESAEs to week 75

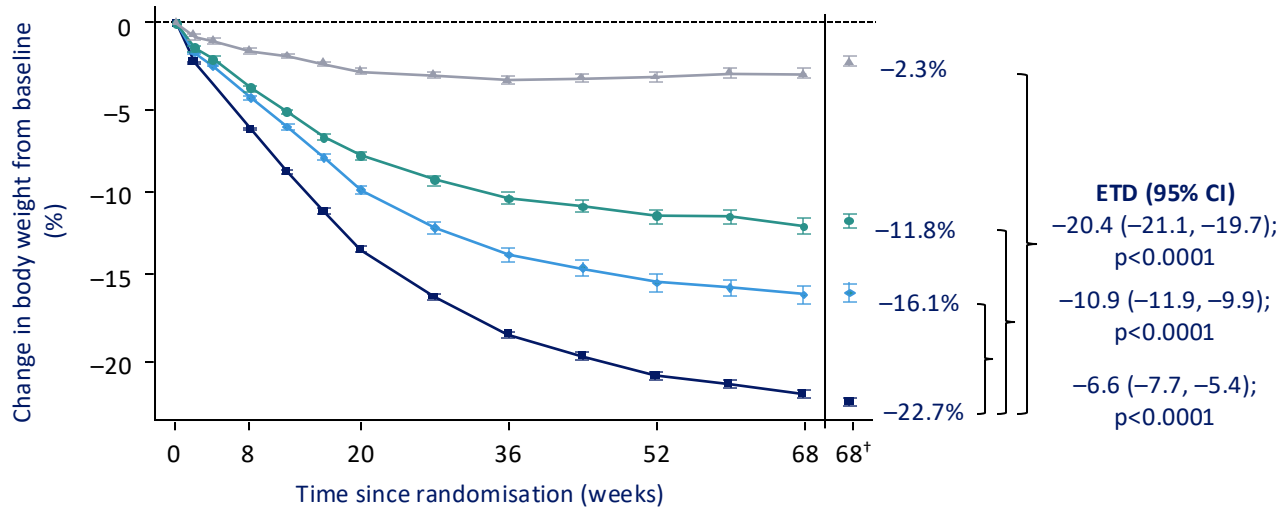
†As an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity or overweight during main phase only; ‡IWQOL-Lite-CT Physical Function and SF-36v2 Physical Functioning.
BMI, body mass index; DXA, dual energy-Xray absorption; HbA1c, glycated haemoglobin; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials version; SF-36v2, Short Form 36-item Health Survey version 2; SBP, systolic blood pressure; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse event.
NCT05567796. Available from: https://clinicaltrials.gov/study/NCT05567796. Accessed June 2025. Garvey WT et al. New Engl J Med 2025; 14;393(7):635-647

Change in body weight

REDEFINE 1

Trial product estimand

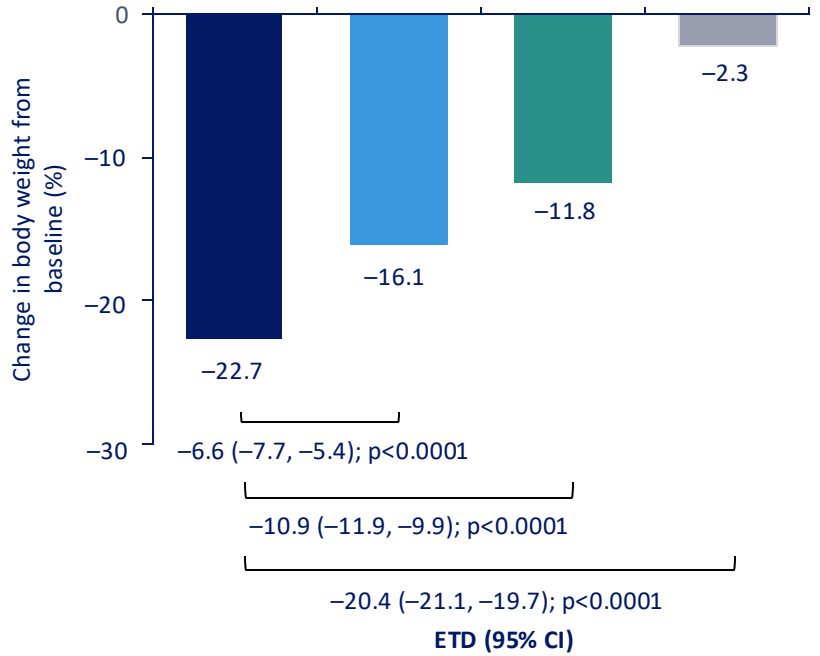
Change in body weight over time



CagriSema 2.4 mg/2.4 mg	2108	2016	1837	1691	1586	1455	2108
Semaglutide 2.4 mg	302	290	269	253	238	220	302
Cagrilintide 2.4 mg	302	290	275	262	250	223	302
Placebo	705	672	619	551	487	452	705

Percentage change in body weight at week 68

Overall mean body weight at baseline: 106.9 kg



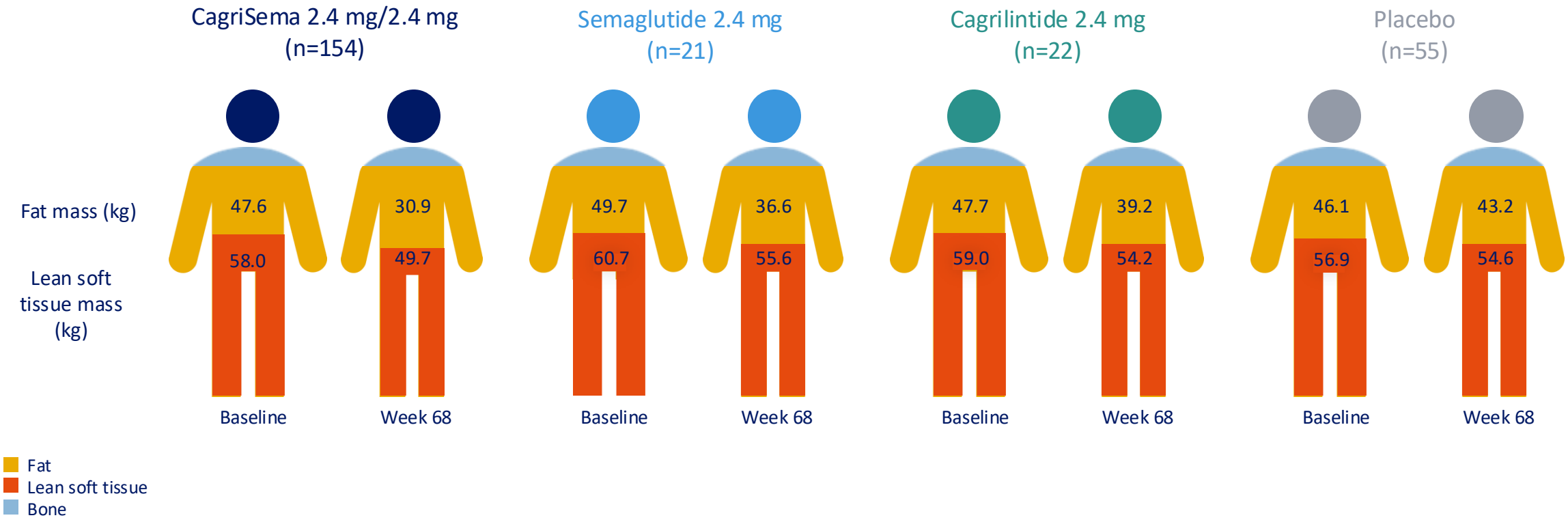
CagriSema 2.4 mg/2.4 mg Semaglutide 2.4 mg Cagrilintide 2.4 mg Placebo

Observed data are from the on-treatment period; error bars are +/- standard error of the mean. Estimated means, ETDs and corresponding CIs are for the trial product estimand. Lower panel shows numbers of participants contributing to the mean.
†Estimated means.
CI, confidence interval; ETD, estimated treatment difference.
Garvey WT et al. New Engl J Med. 2025; 14;393(7):635-647.

Change in body composition (DXA)

REDEFINE 1

Trial product estimand

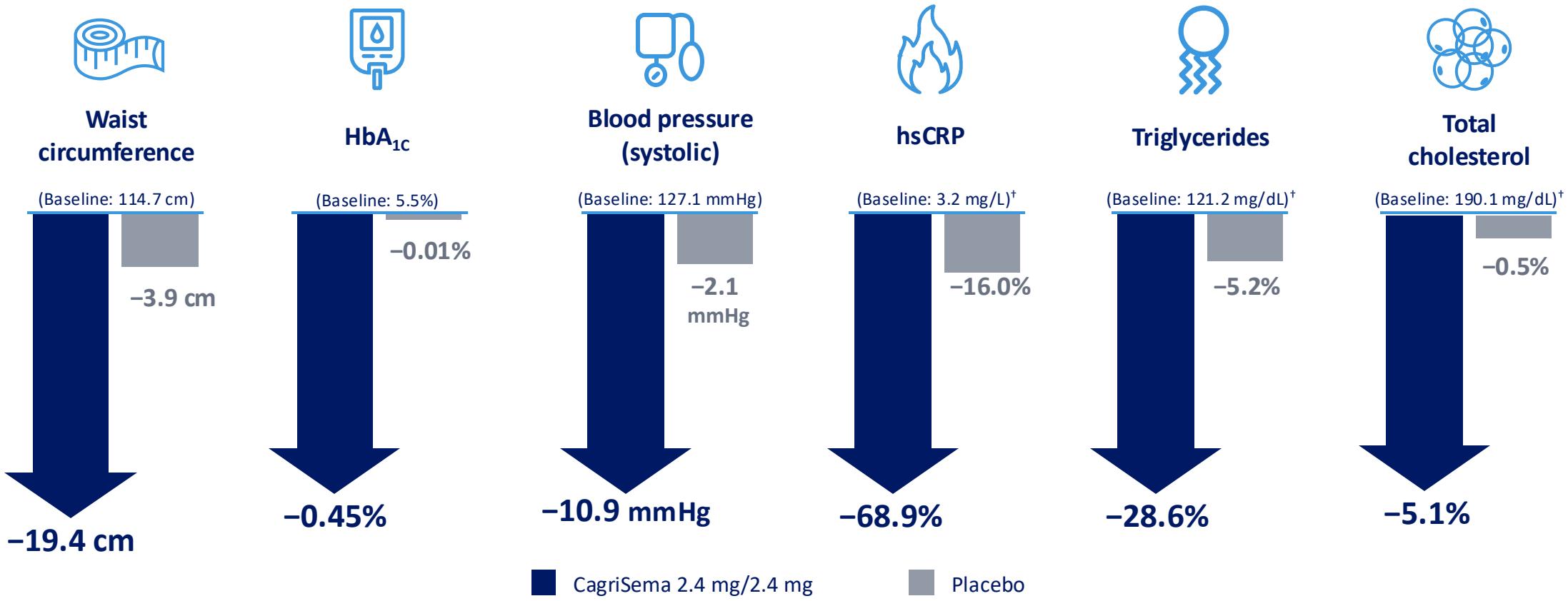


Percentage bone mass was not quantified.
DXA, dual energy X-ray absorptiometry.
Garvey WT et al. New Engl J Med. 2025; 14;393(7):635-647.

Overview of cardiometabolic endpoints

REDEFINE 1

Trial product estimand



†Geometric mean.
hsCRP, high-sensitivity C-reactive protein; HbA_{1c}, glycated haemoglobin.
Garvey WT et al. New Engl J Med. 2025; 14;393(7):635-647.

Common adverse events (≥10%†) (1/2)

REDEFINE 1

	CagriSema 2.4 mg/2.4 mg (N=2106)	Semaglutide 2.4 mg (N=302)	Cagrilintide 2.4 mg (N=302)	Placebo (N=705)
Gastrointestinal-related disorders	1676 (79.6)	223 (73.8)	163 (54.0)	281 (39.9)
Nausea	1159 (55.0)	132 (43.7)	72 (23.8)	89 (12.6)
Constipation	646 (30.7)	84 (27.8)	62 (20.5)	82 (11.6)
Vomiting	549 (26.1)	70 (23.2)	21 (7.0)	29 (4.1)
Diarrhoea	517 (24.5)	79 (26.2)	46 (15.2)	85 (12.1)
Dyspepsia	234 (11.1)	48 (15.9)	18 (6.0)	21 (3.0)
Metabolism and nutrition disorders	585 (27.8)	73 (24.2)	69 (22.8)	125 (17.7)
Decreased appetite	343 (16.3)	33 (10.9)	32 (10.6)	46 (6.5)

Adverse events (n [%)] by MedDRA preferred term

Data are from the safety analysis set from the on-treatment period.
†AEs occurring in ≥10% of participants in the CagriSema group.
MedDRA, Medical Dictionary for Regulatory Activities.
Garvey WT et al. New Engl J Med. 2025; 14;393(7):635-647.

Common adverse events (≥10%†) (2/2)

REDEFINE 1

	CagriSema 2.4 mg/2.4 mg (N=2106)	Semaglutide 2.4 mg (N=302)	Cagrilintide 2.4 mg (N=302)	Placebo (N=705)
General disorders and administration site conditions	838 (39.8)	88 (29.1)	103 (34.1)	132 (18.7)
Fatigue	437 (20.8)	41 (13.6)	43 (14.2)	45 (6.4)
Nervous system disorders	629 (29.9)	85 (28.1)	75 (24.8)	140 (19.9)
Headache	267 (12.7)	42 (13.9)	35 (11.6)	72 (10.2)
Infections and infestations	950 (45.1)	161 (53.3)	142 (47.0)	339 (48.1)
COVID-19	230 (10.9)	36 (11.9)	34 (11.3)	79 (11.2)
Nasopharyngitis	228 (10.8)	42 (13.9)	41 (13.6)	83 (11.8)
Skin and subcutaneous tissue disorders	399 (18.9)	53 (17.5)	43 (14.2)	67 (9.5)
Musculoskeletal and connective tissue disorders	433 (20.6)	76 (25.2)	80 (26.5)	169 (24.0)

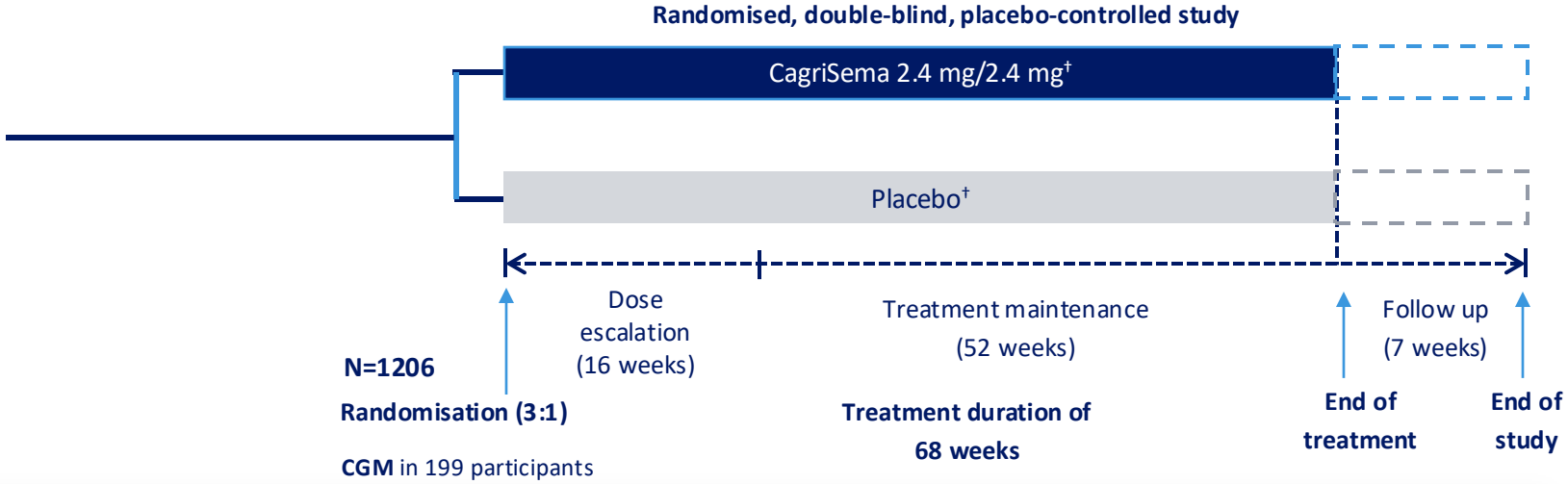
Adverse events (n [%)] by MedDRA preferred term

Data are from the safety analysis set from the on-treatment period.
†AEs occurring in ≥10% of participants in the CagriSema group.
MedDRA, Medical Dictionary for Regulatory Activities.
Garvey WT et al. New Engl J Med. 2025; 14;393(7):635-647.

REDEFINE 2: WM in participants with overweight or obesity and T2D

NN9838-4609

Study objective: To confirm superiority of CagriSema 2.4 mg/2.4 mg vs placebo on body weight reduction



Key endpoints

Co-primary:

- Relative change (%) in body weight from baseline to week 68
- Proportion of participants who achieve ≥5% weight reduction from baseline to week 68

Confirmatory secondary:

- Achievement of ≥20% body weight reduction
- Relative change in body weight at week 20
- Change in waist circumference
- Change in HbA_{1c}
- Change in systolic blood pressure
- Change in IWQOL-Lite-CT and SF-36v2 physical functioning scores

Safety:

- Number of clinically significant/severe hypoglycaemic episodes at 75 weeks
- Number of TEAEs at 75 weeks
- Number of TESAEs at 75 weeks

†As an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity or overweight during main phase only.

BMI, body mass index; BW, body weight; CGM, continuous glucose monitoring; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite clinical trial; OAD, oral antidiabetes drug; RA, receptor agonist; SF-36v2, SF-36v2 Health Survey acute version 2; SBP, systolic blood pressure; T2D, type 2 diabetes; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse event; WM, weight management.

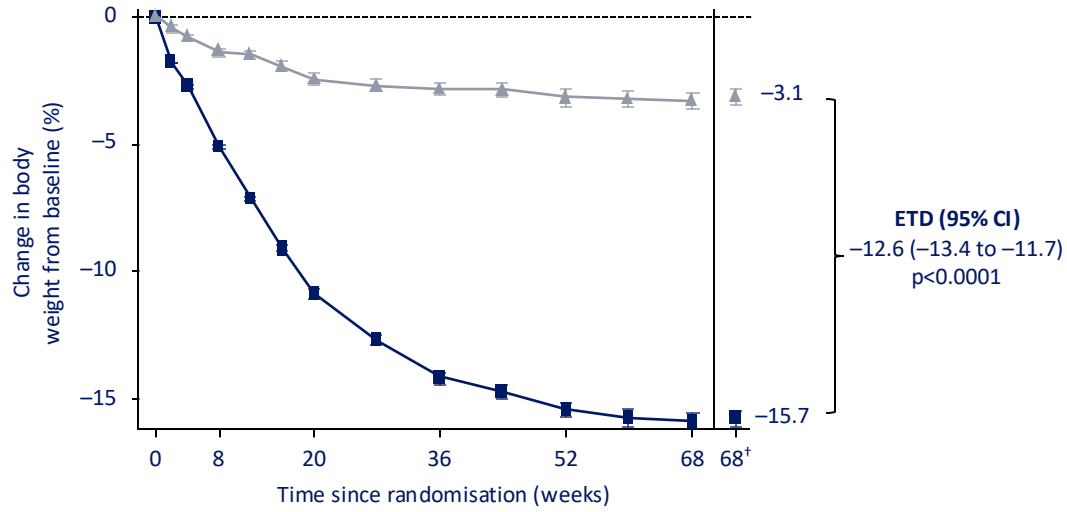
ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05394519 (accessed June 2025); Davies MJ et al. New Engl J Med. 2025; 14;393(7):648-659.

Change in body weight

REDEFINE 2

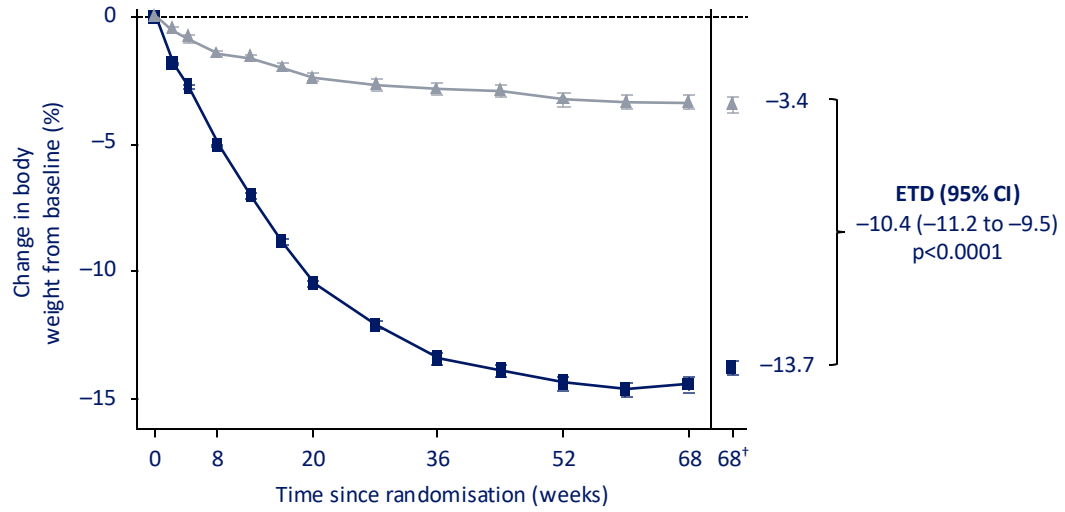
Trial product estimand

Overall mean at baseline: 102.2 kg



CagriSema 2.4 mg/2.4 mg	904	849	762	699	668	624	904
Placebo	302	284	262	244	225	214	302

Treatment policy estimand



CagriSema 2.4 mg/2.4 mg	904	888	872	855	845	837	904
Placebo	302	296	291	283	276	274	302

■ CagriSema 2.4 mg/2.4 mg ■ Placebo

Observed data are from the on-treatment period for the left panel, and from the in-trial period for the right panel; error bars are +/- standard error of the mean. Estimated means, ETDs and corresponding CIs are for the stated estimand. Lower panel shows numbers of participants contributing to the mean.

†Estimated means.

CI, confidence interval; ETD, estimated treatment difference; SE, standard error.

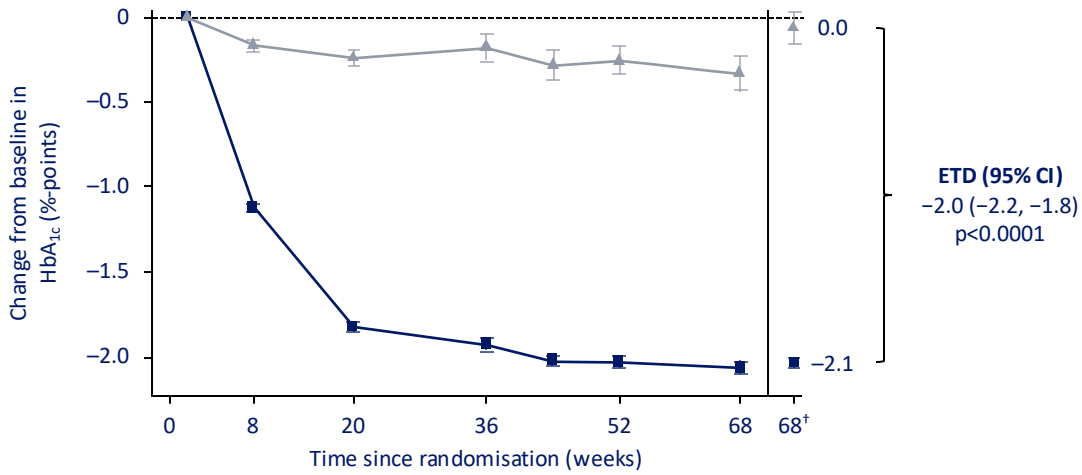
Davies MJ et al. New Engl J Med. 2025; 14;393(7):648-659.

Change in HbA_{1c}

REDEFINE 2

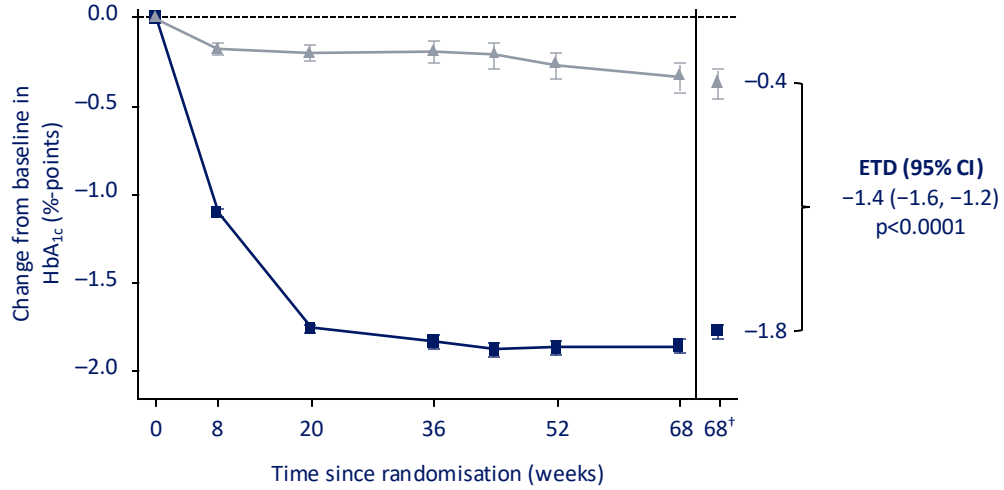
Trial product estimand

Overall mean at baseline 8.0%/64.2 mmol/mol



CagriSema 2.4 mg/2.4 mg	904	820	724	662	633	580	904
Placebo	302	270	215	175	142	127	302

Treatment policy estimand



CagriSema 2.4 mg/2.4 mg	904	880	860	843	842	822	904
Placebo	302	293	287	280	270	271	302

■ CagriSema 2.4 mg/2.4 mg ■ Placebo

Observed data are from the on-treatment period for the left panel, and from the in-trial period for the right panel; error bars are +/- standard error of the mean. Estimated means, ETDs and corresponding CIs are for the stated estimand. Lower panel shows numbers of participants contributing to the mean.

†Estimated means.

CI, confidence interval; ETD, estimated treatment difference; HbA1c, glycated haemoglobin; SE, standard error.

Davies MJ et al. New Engl J Med. 2025; 14;393(7):648-659.

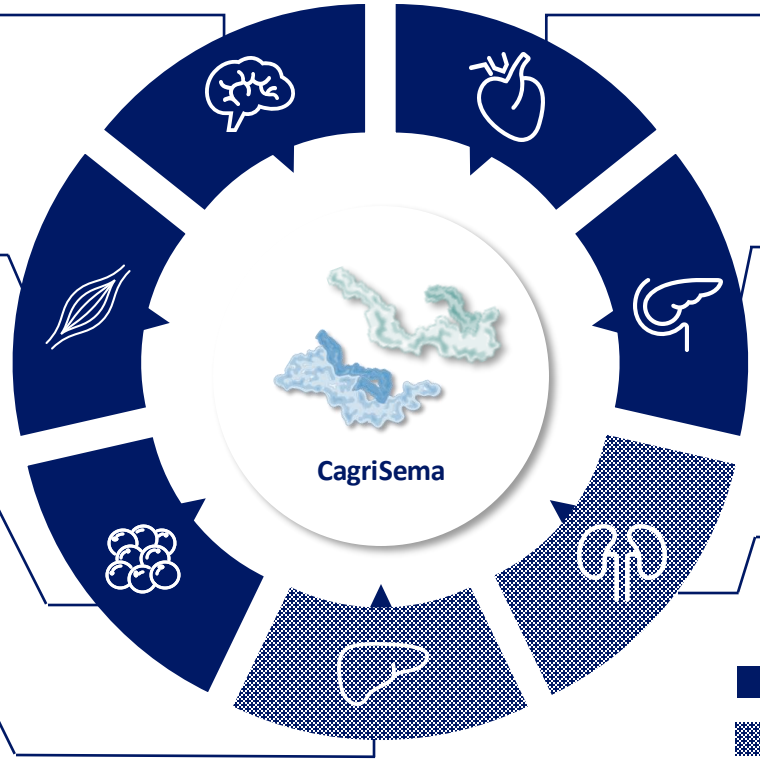
Combined mechanistic effects of CagriSema

Appetite regulation[1–8]
(Reduced food intake, emotional eating, hunger and cravings, with improved satiety and control of eating; decreased craving for savoury and sweet foods)

Metabolic adaptation[9,10]
(Reduces energy intake and appetite without affecting positive mood; maintained energy expenditure during weight loss in preclinical studies)

Improvement of body composition[2,6,11–15]
(Greater reduction of fat mass relative to lean mass with no decline in muscle strength)

Liver benefits [26–30]
(Reduced hepatic lipotoxicity, steatosis and fibrosis)



Cardiometabolic benefits[4,6,16–18]
(MACE risk reduction, improved CV risk factors including BP, hsCRP, lipid profile)*

Glucose regulation[7,18–21]
(Improved TIR, decreased fasting serum insulin, improved HbA_{1c} and C-peptide, increased insulin sensitivity and β-cell function)*

Kidney benefits [22–25]
(Reduced progression of CKD and improved kidney outcomes)

Effect shown with CagriSema or semaglutide and cagrilintide

Effect shown with semaglutide only, effect with CagriSema not yet established

Effects described refer to observation with semaglutide only.

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; HbA1c, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular events; TIR, time in range.

1. Lundh S et al. Poster presented at 40th Annual Meeting of the Obesity Society at ObesityWeek®. 2022. Poster #174. November 1-4, 2022. San Diego, CA. 2. Dahl K et al. Poster presented at 38th Annual Meeting of the Obesity Society at ObesityWeek®. 2020. Poster #329/330. November 2-6, 2020. Virtual meeting. 3. Pietiläinen KH et al. Poster/oral presented at ECO 2021. Poster/oral 015. May 10–13, 2021. Virtual meeting. 4. Enebo LB et al. Lancet. 2021;397:1736–48. 5. Blundell J et al. Diabetes Obes Metab. 2017;19:1242–51. 6. REDEFINE 1. Data on file. 7. REDEFINE 2. Data on file. 8. Poster 6508: Once-weekly CagriSema significantly reduces ad libitum energy intake compared with placebo (to be presented at the 2025 American Diabetes Association 85th Scientific Sessions). 9. Bak N et al. Poster presented at American Diabetes Association, 85th Scientific Sessions; 1969-LB; 20–23 June, 2025; Chicago, IL, US. 10. Kuhre R et al. Presented at the European Association for the Study of Diabetes (EASD). 2024. Abstract #73. September 9-13, 2024, Madrid, Spain. 11. REDEFINE 5. Data on file. 12. John LM et al. J Endocr Soc. 2021;5(Suppl 1):A54. 13. Uchiyama S et al. J Clin Med Res. 2023;15:377–83. 14. Volpe S et al. Nutrients. 2022;14:2414. 15. Wilding JP et al. J Endocr Soc. 2021;5(Suppl 1):A16–7. 16. Rakipovski G et al. JACC Basic Transl Sci. 2018;3:844–57. 17. Lincoff AM et al. N Engl J Med. 2023;389:2221–32. 18. Frias JP et al. Lancet. 2023;402:720–30. 19. Lingvay I et al. Lancet Diabetes Endocrinol. 2019;7:834–44. 20. Kapitza C et al. Diabetologia. 2017;60:1390–9. 21. Korsatko S et al. Diabetes Obes Metab. 2018;20:2565–73. 22. Marso SP et al. N Engl J Med. 2016;375:1834–44. 23. Heerspink HJL et al. Diabetes Care. 2023;46:801–10. 24. Colhoun HM et al. Nat Med. 2024;30:2058–66. 25. Perkovic V et al. N Engl J Med. 2024;391:109–21. 26. Soto-Catalán M et al. Int J Mol Sci. 2024;25:2961. 27. Newsome PN et al. N Engl J Med. 2021;384:1113–24. 28. Volpe S et al. Nutrients 2022;14:4673. 29. Shah P et al. JGH Open. 2024;8:e13037. 30. Newsome PN et al. Presented at The Liver Meeting®, American Association for the Study of Liver Diseases (AASLD). 2024. Abstract #5018. Nov 19, 2024. San Diego, CA.

Summary

- Amylin analogues, alone or in combination with other incretins analogues, offer exciting opportunities for treatment of obesity.
- Their effects may extend beyond weight loss to improvements in other cardiometabolic parameters.
- Given that they target a different pathway than GLP-1 RA, they could play a role in comprehensive obesity management, before or after bariatric surgery.

GLP-1 RA, glucagon-like peptide-1 receptor agonists

Expert discussion and Q&A:

Integrating Future Therapies into Comprehensive Obesity Management

Proceed to the microphone stand to ask your question

Thank You