Nuovi peptidi (e non-peptidi) in arrivo.
Amilina e Glucagone

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Riccardo C. Bonadonna dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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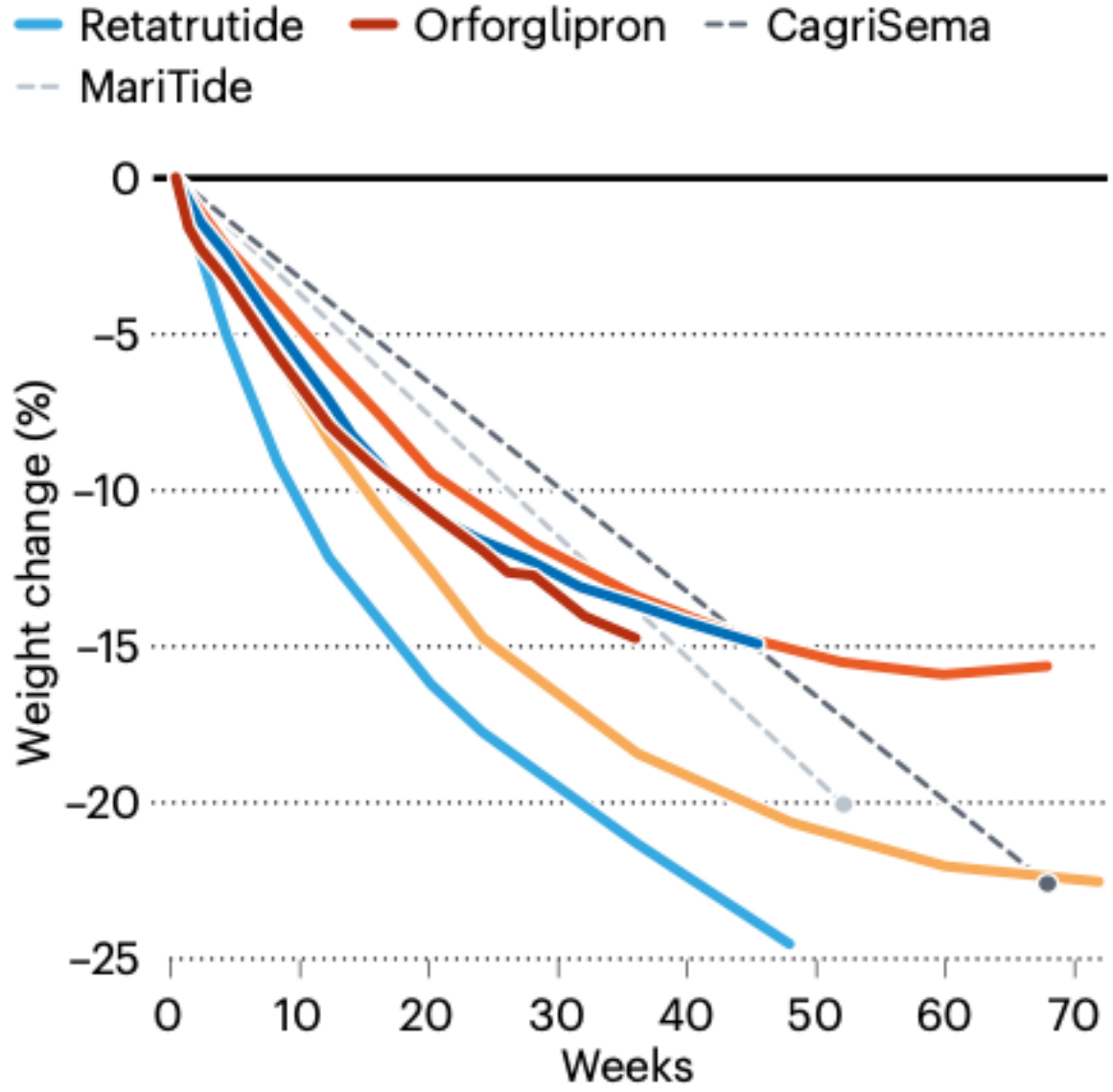
Altro: Nessuno

NEXT-GENERATION OBESITY DRUGS ARE ARRIVING SOON

More than 100 treatments are in development to deliver greater and healthier weight loss. Some should be available in the next few years. **By Elie Dolgin**



*Data are from company reports of the most recent trials, with no intermediate data available for CagriSema (cagrilintide and semaglutide) or MariTide (maridebart cafraglutide). Data are not placebo-adjusted.

Nature 2025

Perché ingaggiare il recettore del glucagone?

Physiological actions of glucagon

Actions identified in preclinical studies

- Brain
  - ↓ Appetite
- Heart
  - ↑ Cardiomyocyte survival
- Muscle
  - ↓ Glucose uptake
- Visceral adipose tissue
  - ↑ Lipolysis
- Brown adipose tissue
  - ↑ Thermogenesis
- Liver
  - ↑ Hepatocyte survival

Actions identified in clinical studies

- Brain
  - ↓ Food intake
- Heart
  - ↑ Heart rate
- Gastrointestinal tract
  - ↓ Gastric emptying
  - ↓ Peristaltic motility
- Brown adipose tissue
  - ↑ Resting energy expenditure
- Kidney
  - ↑ Glomerular filtration
- Liver
  - ↑ Hepatic glucose output
  - ↑ Ureagenesis
  - ↑ Lipid oxidation
  - ↓ Lipid synthesis

Clinical actions of glucagon agonism and antagonism

Glucagon agonism

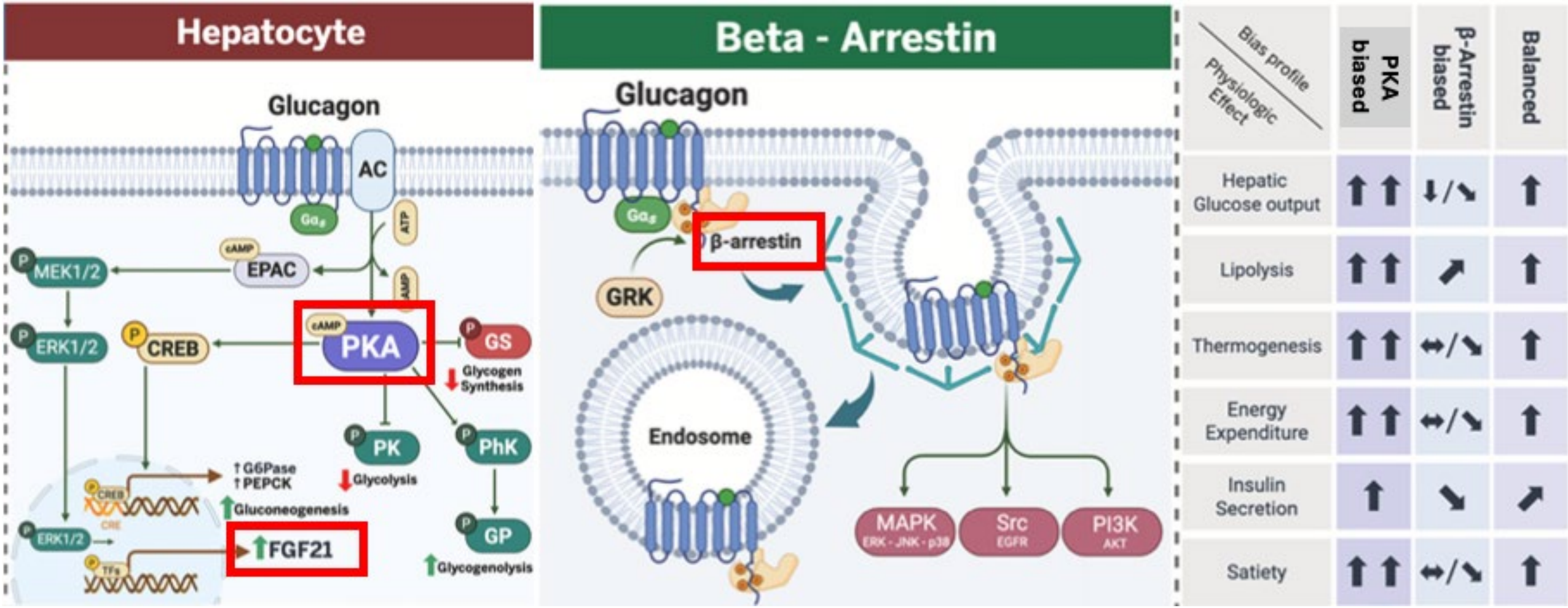
- Glucose metabolism
  - ↑ Hepatic glucose output
- Amino acid metabolism
  - ↑ Amino acid catabolism
- Lipid metabolism
  - ↓ Liver fat content
  - ↑ Hepatic lipid oxidation
  - ↓ Hepatic lipogenesis
- Haemodynamics
  - ↑ Blood pressure
  - ↑ Cardiac inotropy and chronotropy
- Pancreas
  - ↑ Insulin secretion
- Energy homeostasis
  - ↓ Food intake
  - ↑ Energy expenditure
- Other effects
  - ↓ Gastric emptying

Glucagon antagonism

- Glucose metabolism
  - ↓ Hepatic glucose output
  - ↓ HbA1c
- Amino acid metabolism
  - ↓ Amino acid catabolism
- Lipid metabolism
  - ↑ Liver fat accumulation
  - ↑ Circulating LDL cholesterol
  - ↑ Cholesterol absorption
- Haemodynamics
  - ↑ Blood pressure
- Pancreas
  - α-Cell hyperplasia
  - β-Cell proliferation?
- Energy homeostasis
  - ↑ Body weight
- Other effects
  - ↑ Liver transaminases

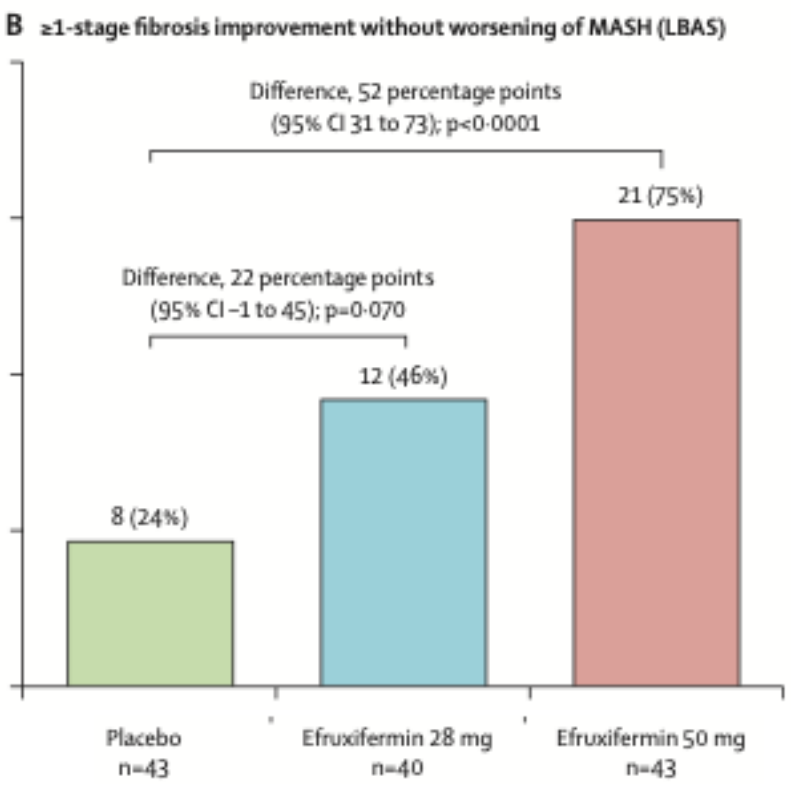
Hædersdal S et al.; Nature Rev Endocrinol 2023

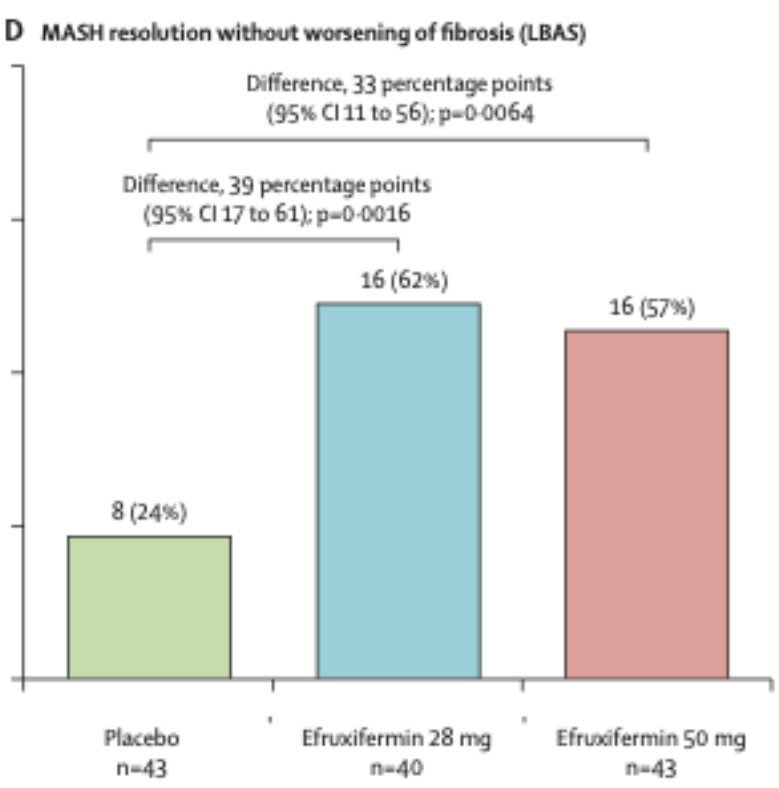
Intracellular glucagon signaling through PKA-dependent and β-arrestin dependent pathways

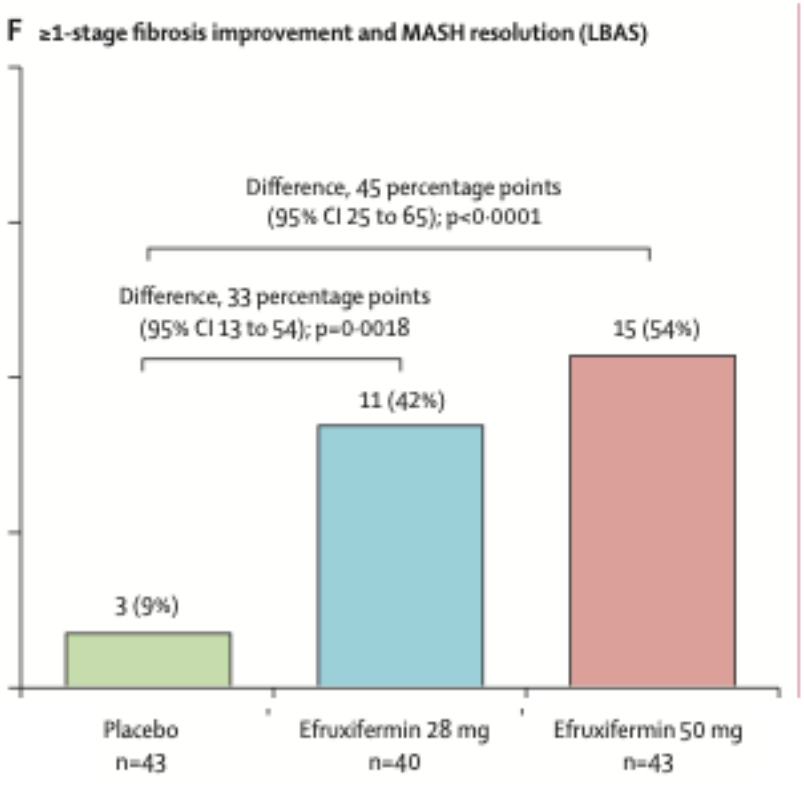


Elmendorf AJ et al; Pharmacol Res 2026

Effects of efruxifermin, an Fc-FGF21 analog, at week 96 in MASH: a pilot phase 2b RCT



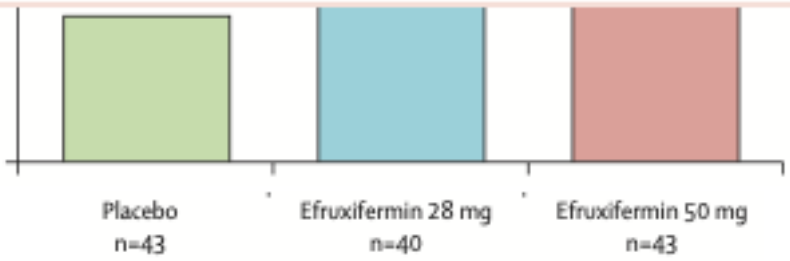


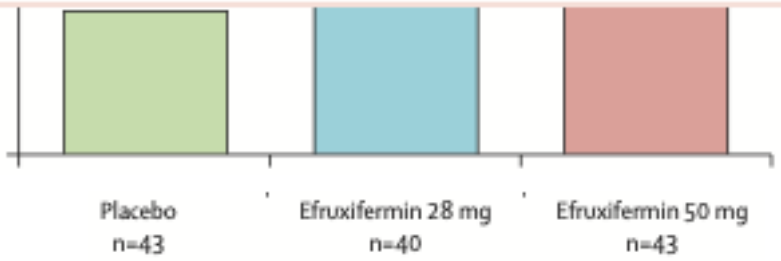


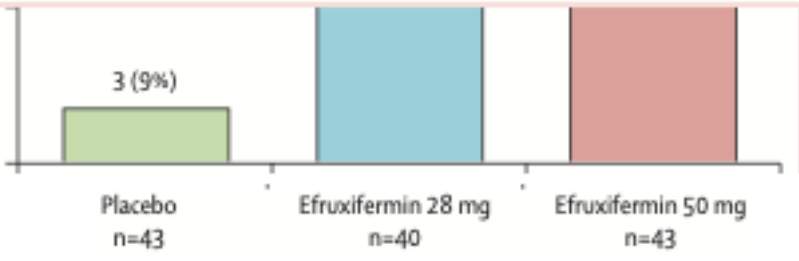
Noureddin M et al.; Lancet 2025

Effects of efruxifermin, an Fc-FGF21 analog, at week 96 in MASH: a pilot phase 2b RCT

	Placebo (n=43)	Efruxifermin 28 mg (n=40)	p value	Efruxifermin 50 mg (n=43)	p value
Liver fat content, %*†					
Percentage change from baseline	−9·9% (6·2)	−33·7% (7·1)	..	−40·8% (6·9)	..
LSM difference versus placebo (95% CI), percentage points	..	−23·8 (−42·2 to −5·5)	0·011	−30·9 (−48·9 to −12·9)	0·0009
Bodyweight, kg					
Absolute change from baseline	−1·5 (1·4)	−0·3 (1·5)	..	−3·5 (1·5)	..
LSM difference versus placebo (95% CI)	..	1·2 (−2·9 to 5·3)	0·56	−1·9 (−6·0 to −2·1)	0·35

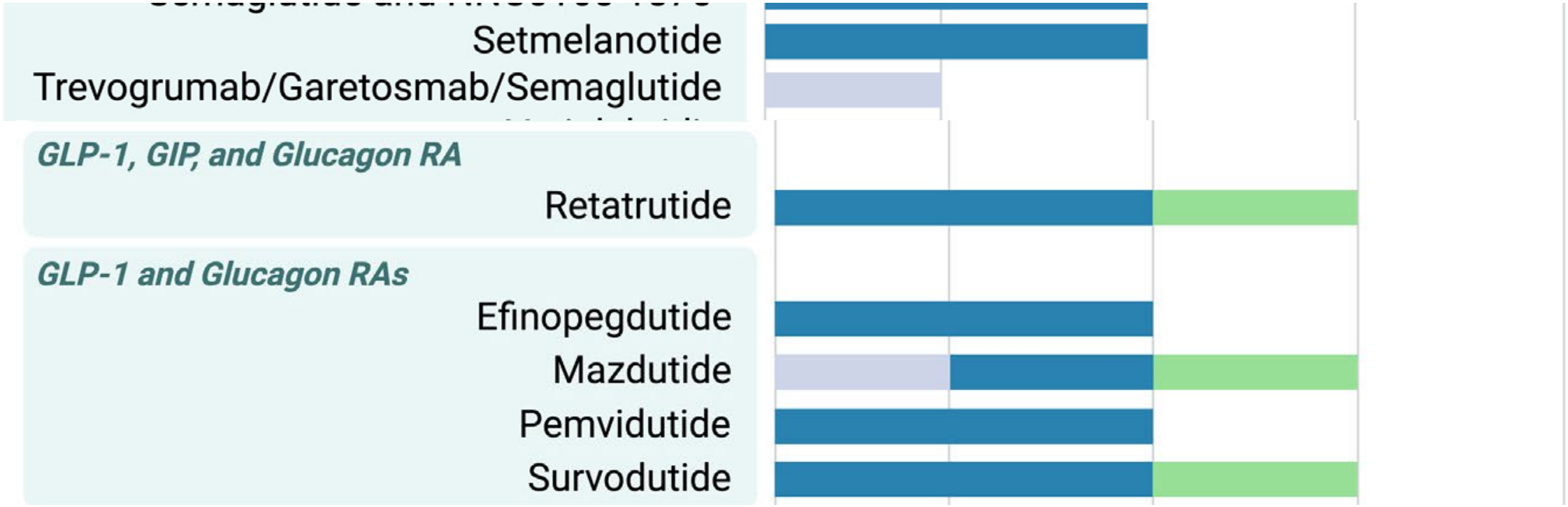






Noureddin M et al.; Lancet 2025

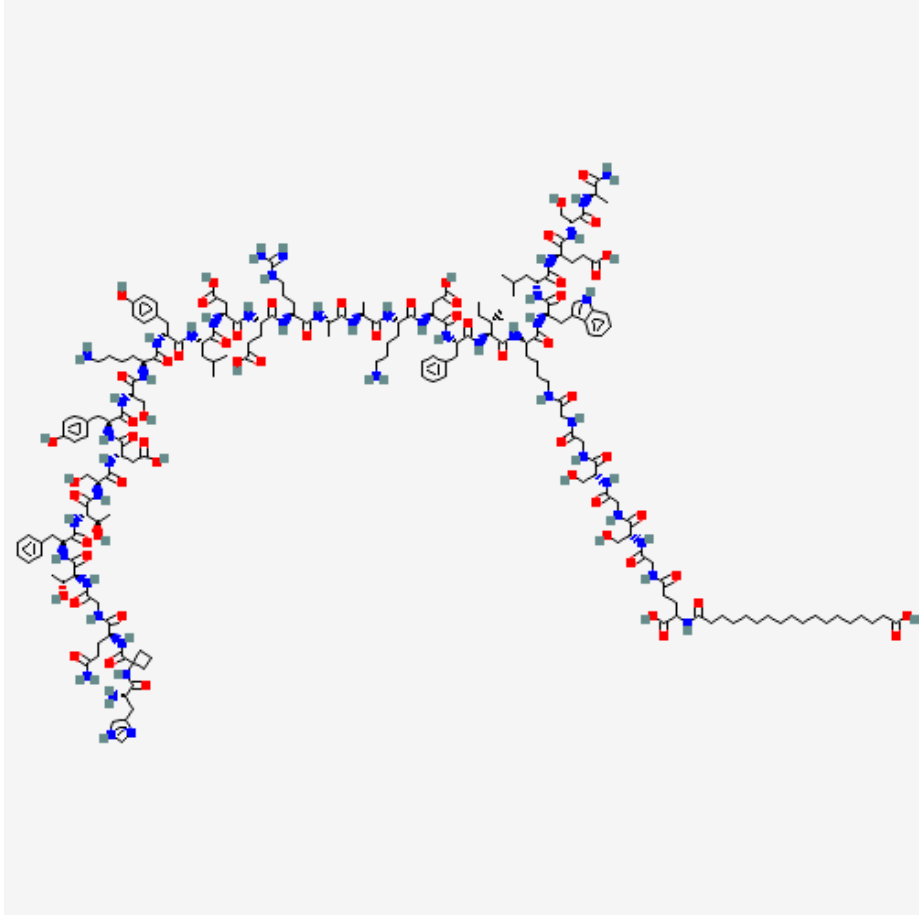
Overview of GLCRa agents under development for chronic weight loss



Kokkorakis M et al.; Pharmacol Rev 2025

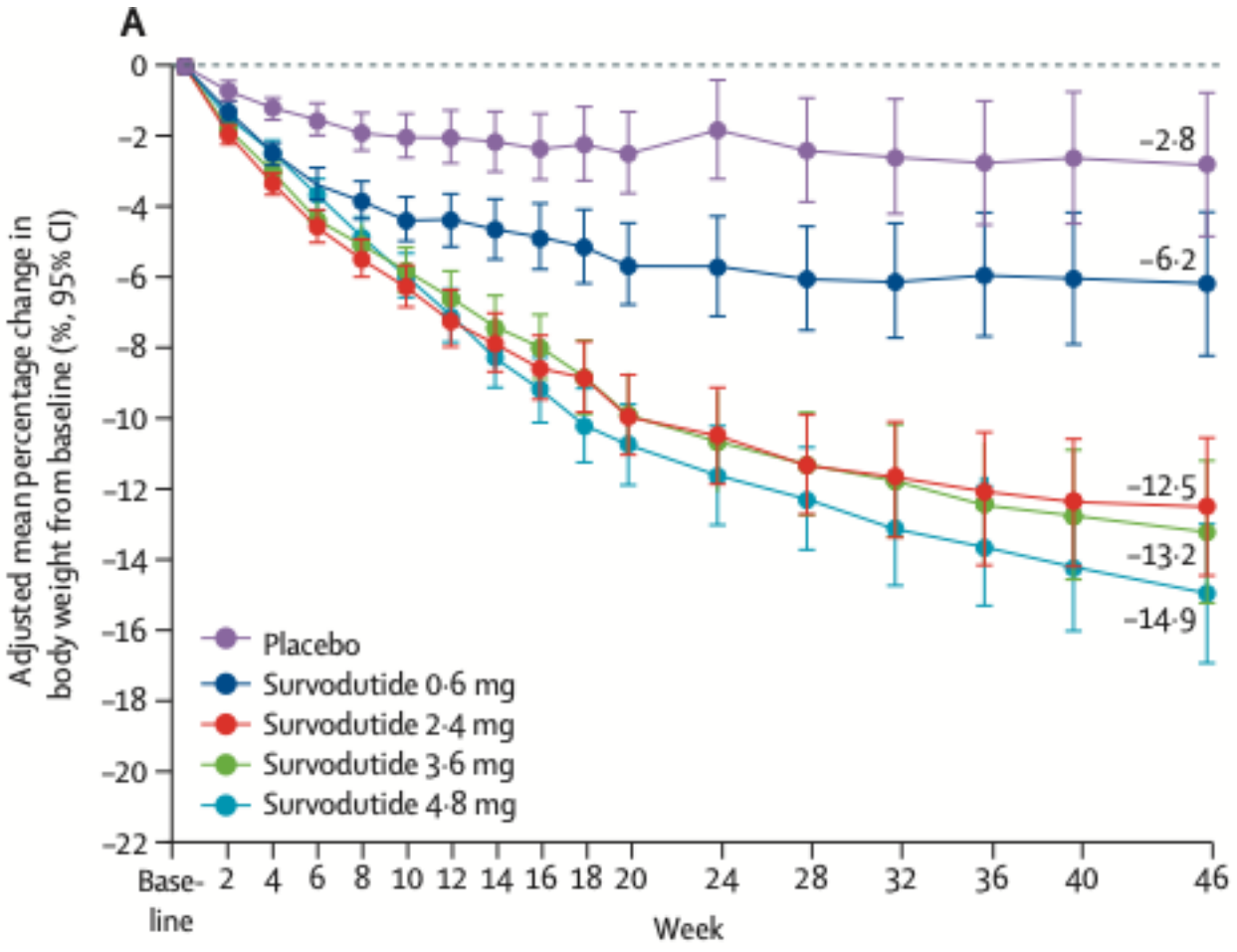
Survodutide: a dual GLP1-/GCG receptor agonist

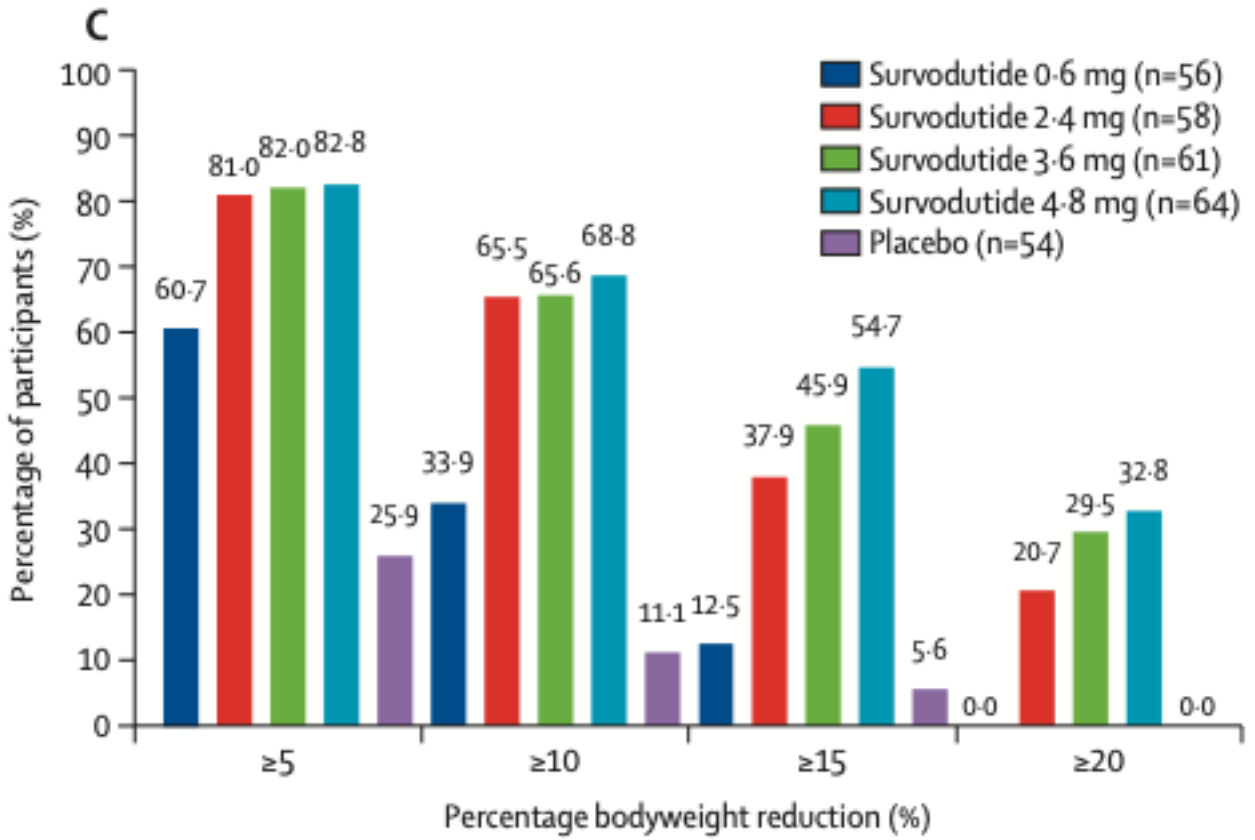
- Survodutide is a multi-functional peptide based on the native glucagon peptide sequence, modified to bind to both glucagon and GLP-1 receptors
- Survodutide is a 29 amino acid linear peptide and includes a C18 fatty diacid moiety[1]
- *In vitro*, it more potently activates GLP1-R than GLCR, with a ratio of about 8:1
- Survodutide is reported to have longer half-life than semaglutide (in mice), enabling once-weekly dosing



Klein T et al.; Diab Res Clin Pract 2023

Dose-dependent weight lowering effect of survodutide in nondiabetic obese people (baseline BMI ≈ 38.0 kg/m²)





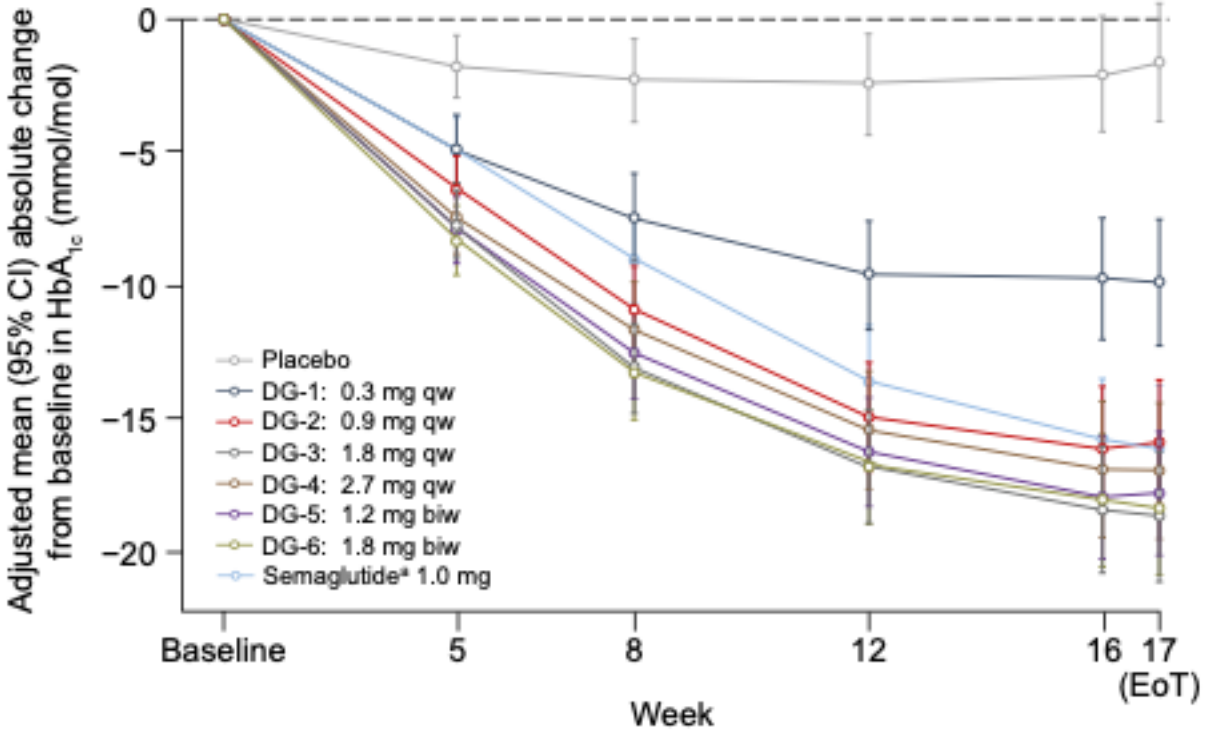
Le Roux CW et al.; Lancet Diabetes Endocrinol 2024

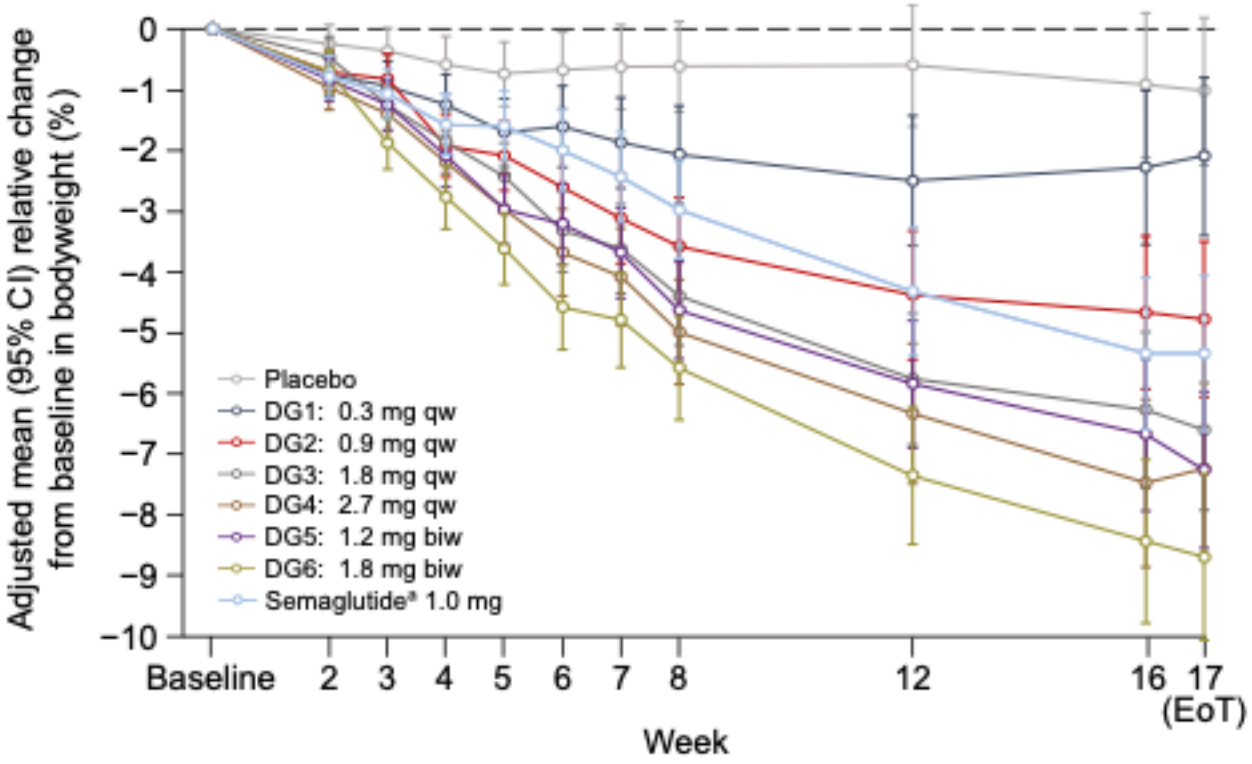
Treatment-emergent adverse events with survodutide in non diabetic obese people (baseline BMI ≈ 38.0 kg/m^2)

	Placebo (n=77)	Survodutide dose group				Survodutide total (n=309)
		0·6 mg (n=77)	2·4 mg (n=78)	3·6 mg (n=77)	4·8 mg (n=77)	
Any treatment-emergent adverse event	58 (75%)	70 (91%)	70 (90%)	71 (92%)	70 (91%)	281 (91%)
Gastrointestinal disorders	32 (42%)	44 (57%)	67 (86%)	58 (75%)	63 (82%)	232 (75%)
Nausea*	15 (20%)	26 (34%)	51 (65%)	48 (62%)	49 (64%)	174 (56%)
Vomiting*	4 (5%)	7 (9%)	23 (30%)	26 (34%)	27 (35%)	83 (27%)
Diarrhoea*	8 (10%)	14 (18%)	22 (28%)	18 (23%)	15 (20%)	69 (22%)
Constipation*	4 (5%)	9 (12%)	17 (22%)	19 (25%)	20 (26%)	65 (21%)
Infections and infestations	33 (43%)	34 (44%)	29 (37%)	35 (46%)	33 (43%)	131 (42%)
Coronavirus disease (COVID-19)*	17 (22%)	16 (21%)	11 (14%)	16 (21%)	10 (13%)	53 (17.2%)
Leading to treatment discontinuation	3 (4%)	15 (20%)	20 (26%)	19 (25%)	22 (29%)	76 (25%)
Gastrointestinal disorders	1 (1%)	5 (7%)	13 (17%)	13 (17%)	20 (26%)	51 (17%)
Nausea†	0	3 (4%)	12 (15%)	8 (10%)	9 (12%)	11 (4%)
Vomiting†	0	1 (1%)	4 (5%)	9 (12%)	10 (13%)	24 (8%)
Infections and infestations	0	4 (5%)	3 (4%)	3 (4%)	1 (1%)	11 (4%)
Coronavirus disease (COVID-19)†	0	4 (5%)	2 (3%)	2 (3%)	1 (1%)	9 (3%)
Serious‡	5 (7%)	1 (1%)	2 (3%)	6 (8%)	4 (5%)	13 (4%)

Le Roux CW et al.; Lancet Diabetes Endocrinol 2024

Effects of survodutide vs placebo, semaglutide on HbA1c and % body weight reduction in obese people with type 2 diabetes (baseline BMI ≈ 34.0 kg/m^2)





Bluher M et al.; Diabetologia 2024

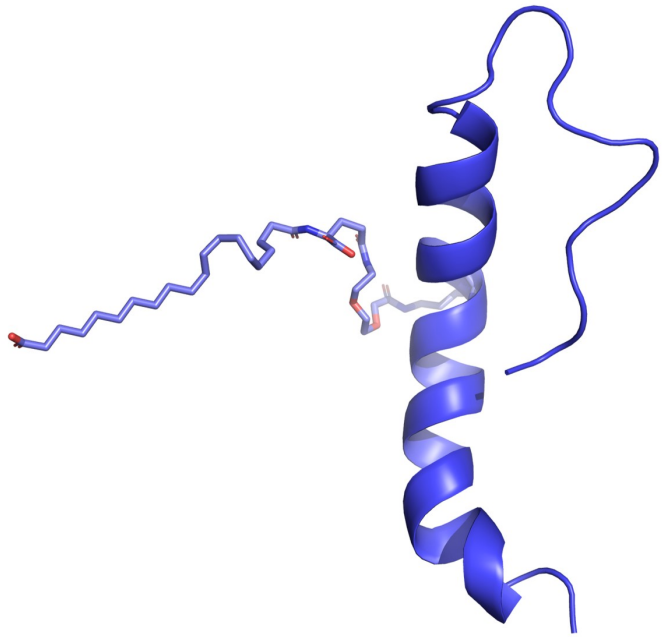
Adverse events in survodutide treated people with type 2 diabetes

AE	DG1: Survodutide 0.3 mg qw (*n*=50)	DG2: Survodutide 0.9 mg qw (*n*=50)	DG3: Survodutide 1.8 mg qw (*n*=52)	DG4: Survodutide 2.7 mg qw (*n*=50)	DG5: Survodutide 1.2 mg biw (*n*=51)	DG6: Survodutide 1.8 mg biw (*n*=49)	Semaglutide 1.0 mg qw (*n*=50)	Placebo (*n*=59)	Total survodutide (*n*=302)
Any TEAE	33 (66.0)	38 (76.0)	42 (80.8)	41 (82.0)	39 (76.5)	42 (85.7)	26 (52.0)	31 (52.5)	235 (77.8)
Investigator-defined, drug-related AEs[a]	25 (50.0)	26 (52.0)	33 (63.5)	29 (58.0)	28 (54.9)	36 (73.5)	19 (38.0)	13 (22.0)	177 (58.6)
Nausea	10 (20.0)	13 (26.0)	24 (46.2)	20 (40.0)	14 (27.5)	22 (44.9)	6 (12.0)	5 (8.5)	103 (34.1)
Vomiting	6 (12.0)	7 (14.0)	12 (23.1)	13 (26.0)	6 (11.8)	10 (20.4)	2 (4.0)	1 (1.7)	54 (17.9)
Diarrhoea	11 (22.0)	5 (10.0)	8 (15.4)	7 (14.0)	8 (15.7)	9 (18.4)	4 (8.0)	5 (8.5)	48 (15.9)
Dyspepsia	4 (8.0)	3 (6.0)	3 (5.8)	4 (8.0)	3 (5.9)	6 (12.2)	1 (2.0)	0	23 (7.6)
Decreased appetite	6 (12.0)	7 (14.0)	5 (9.6)	9 (18.0)	8 (15.7)	15 (30.6)	3 (6.0)	2 (3.4)	50 (16.6)
Headache	2 (4.0)	5 (10.0)	3 (5.8)	0	3 (5.9)	2 (4.1)	0	1 (1.7)	15 (5.0)
Severe AEs[b]	3 (6.0)	1 (2.0)	4 (7.7)	3 (6.0)	2 (3.9)	3 (6.1)	0	4 (6.8)	16 (5.3)
Nausea	1 (2.0)	0	1 (1.9)	0	0	1 (2.0)	0	0	3 (1.0)
Vomiting	2 (4.0)	0	0	0	2 (3.9)	0	0	0	4 (1.3)
Dizziness	0	0	0	0	0	2 (4.1)	0	0	2 (0.7)
Serious AEs	1 (2.0)	4 (8.0)	3 (5.8)	2 (4.0)	1 (2.0)	0	0	3 (5.1)	11 (3.6)
Drug-related serious AEs	1 (2.0)	1 (2.0)	1 (1.9)	1 (2.0)	0	0	0	0	4 (1.3)
AEs leading to treatment discontinu-ation	5 (10.0)	5 (10.0)	11 (21.2)	15 (30.0)	4 (7.8)	8 (16.3)	2 (4.0)	3 (5.1)	48 (15.9)

Bluher M et al.; Diabetologia 2024

Retatrutide

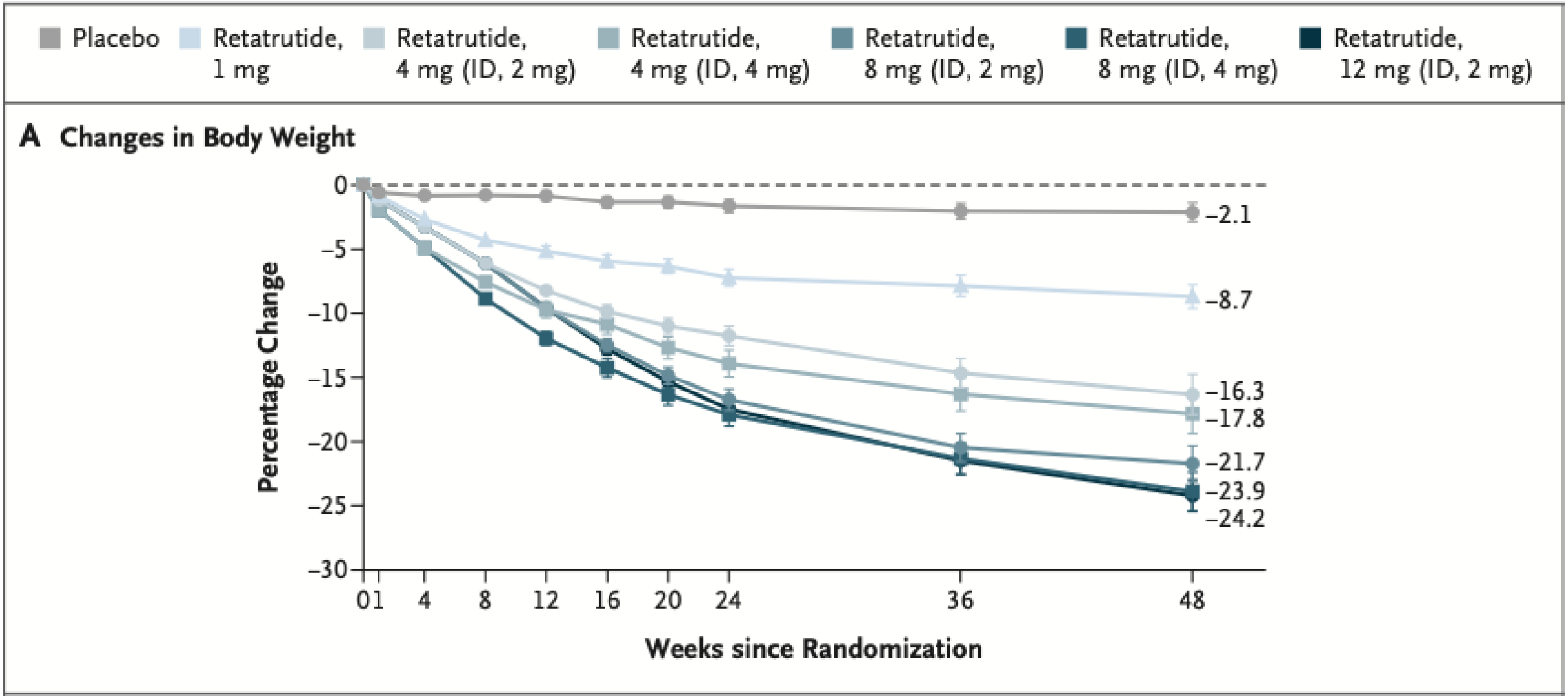
- Retatrutide is a novel single molecule engineered from a glucose-dependent insulinotropic polypeptide (GIP) backbone with triple agonist activity on GIP, glucagon-like peptide-1 (GLP-1), and glucagon receptors[1]
- C20 fatty acid is attached to the peptide for albumin binding to enable once-weekly subcutaneous dosing
- GIP receptor activity is 9 times more potent compared with the native GIP ligand
- GLP-1 and glucagon receptor activities are balanced and are less potent compared with their native ligands



Retatrutide

1. Coskun T, et al. *Cell Metab*. 2022;34:1234-1247.

Dose-response of retatrutide effect on body weight in people with obesity (baseline BMI ≈ 37.0 kg/m^2)



Jastreboff AM et al.; NEJM 2023

Dose-response of retatrutide effects on lipids and hormones in obese people

	Placebo (N=68)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=33)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)
Percent Change from baseline							
Fasting triglycerides (%)	-3.1 (-10.8, 4.6)	-15.3 (-21.3, -9.3)	-31.1 (-39.8, -22.4)	-28.8 (-37.8, -19.7)	-39.3 (-47.5, -31.0)	-29.2 (-36.3, -22.1)	-34.0 (-39.1, -29.0)
Fasting total cholesterol (%)	-2.2 (-4.8, 0.4)	-4.6 (-8.3, -0.9)	-11.8 (-16.1, -7.5)	-9.2 (-13.8, -4.6)	-17.7 (-21.3, -14.0)	-15.3 (-19.1, -11.4)	-17.3 (-20.5, -14.1)
Fasting LDL cholesterol (%)	-3.6 (-7.5, 0.4)	-4.1 (-9.2, 1.0)	-11.6 (-17.8, -5.4)	-6.3 (-13.1, 0.6)	-16.9 (-22.4, -11.3)	-15.6 (-21.3, -9.9)	-16.4 (-21.0, -11.8)
Fasting VLDL cholesterol (%)	-2.8 (-10.6, 4.9)	-14.7 (-20.7, -8.8)	-30.6 (-39.3, -21.8)	-28.1 (-37.1, -19.0)	-39.1 (-47.4, -30.9)	-28.5 (-35.7, -21.4)	-33.4 (-38.7, -28.2)
Fasting HDL cholesterol (%)	0.4 (-3.6, 4.4)	1.8 (-1.7, 5.3)	-1.2 (-6.0, 3.5)	1.1 (-5.5, 7.7)	-6.2 (-10.6, -1.9)	-7.4 (-11.0, -3.8)	-8.4 (-11.6, -5.1)
Change from baseline							
Fasting glucose (mg/dL)	3.4 (0.5, 6.2)	-3.4 (-5.7, -1.1)	-6.5 (-9.3, -3.6)	-.9.0 (-11.7, -6.2)	-9.8 (-12.6, -7.1)	-9.9 (-12.8, -6.9)	-10.2 (-12.7, -7.8)
Fasting insulin (mU/L)	-0.8 (-2.8, 1.2)	-3.6 (-4.9, -2.4)	-6.3 (-7.8, -4.7)	-5.1 (-7.3, -3.0)	-6.6 (-8.4, -4.8)	-5.3 (-7.1, -3.6)	-6.5 (-8.1, -5.0)
Fasting HbA1c (%)	0.1 (0.0, 0.1)	-0.1 (-0.2, 0.0)	-0.2 (-0.3, -0.1)	-0.3 (-0.4, -0.2)	-0.4 (-0.5, -0.3)	-0.4 (-0.5, -0.3)	-0.3 (-0.4, -0.3)

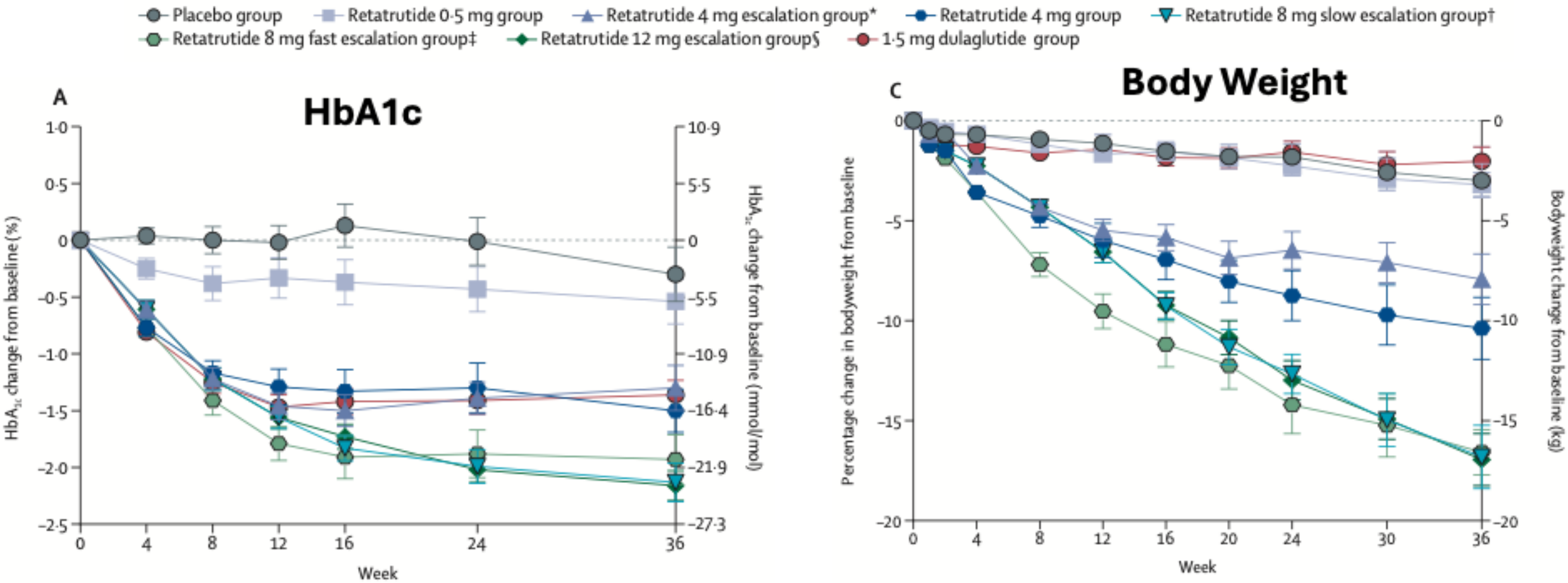
Jastreboff AM et al.; NEJM 2023

Safety of retatrutide in people with obesity (baseline BMI ≈ 37.0 kg/m^2)

Adverse Event	Placebo Group (N=70)	Retatrutide Groups						Overall (N=337)
		1 mg (N=69)	4 mg (ID, 2 mg) (N=33)	4 mg (ID, 4 mg) (N=33)	8 mg (ID, 2 mg) (N=35)	8 mg (ID, 4 mg) (N=35)	12 mg (ID, 2 mg) (N=62)	
	number of participants (percent)							
Any adverse event during treatment	49 (70)	58 (84)	24 (73)	28 (85)	28 (80)	33 (94)	57 (92)	277 (82)
Serious adverse event	3 (4)	3 (4)	0	2 (6)	1 (3)	2 (6)	2 (3)	13 (4)
Death†	0	0	0	1 (3)	0	0	0	1 (<1)
Adverse events leading to discontinuation of retatrutide or placebo‡								
Any event	0	5 (7)	2 (6)	3 (9)	5 (14)	2 (6)	10 (16)	27 (8)
Nausea	0	0	0	0	1 (3)	0	3 (5)	4 (1)
Vomiting	0	1 (1)	0	1 (3)	0	0	1 (2)	3 (1)
Diarrhea	0	0	0	0	1 (3)	0	1 (2)	2 (1)
Dyspepsia	0	0	1 (3)	0	0	0	1 (2)	2 (1)
Increase in lipase level	0	1 (1)	1 (3)	0	0	0	0	2 (1)

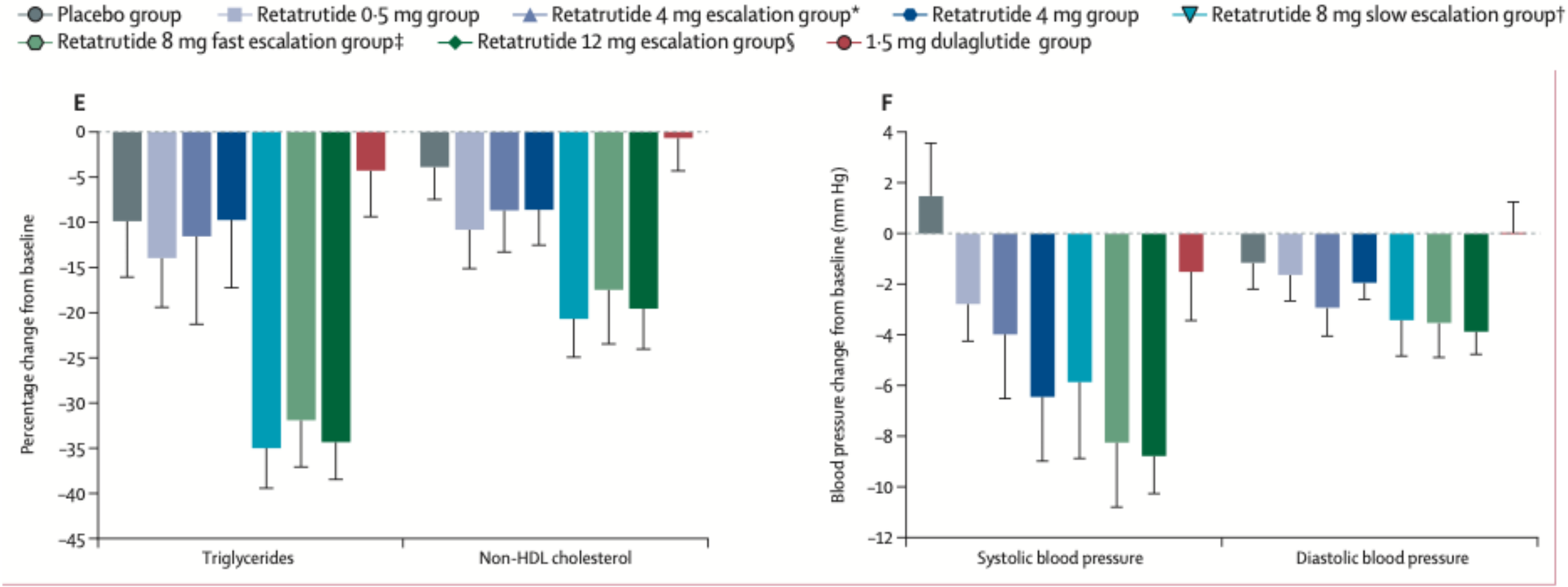
Jastreboff AM et al.; NEJM 2023

Effects of retatrutide, a triple (GLP1R-GCR-GIPR) co-agonist, on HbA_{1c} and body weight (BMI ≈ 34 - 36 kg/m²) in people with type 2 diabetes (baseline HbA1c ≈ 8.2%)



Rosenstock J et al.; The Lancet 2023

Effects of retatrutide, a triple (GLP1R-GCR-GIPR) co-agonist, on blood lipids, blood pressure in people with obesity (BMI ≈ 34 - 36 kg/m^2) and type 2 diabetes (baseline HbA1c ≈ 8.2%)



Rosenstock J et al.; The Lancet 2023

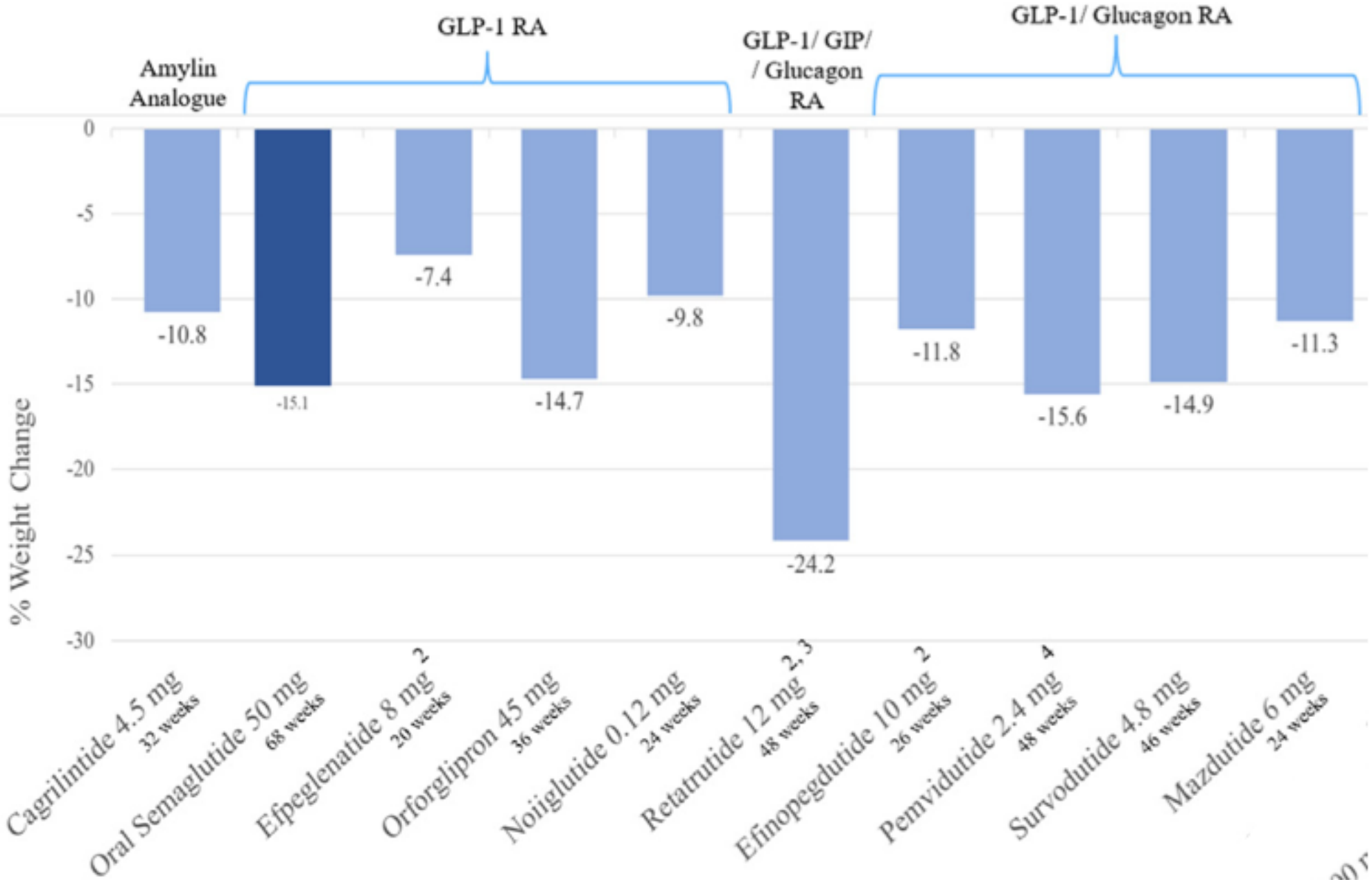
Safety of retatrutide in subjects with obesity and type 2 diabetes

	Placebo group (n=45)	Retatrutide 0·5 mg group (n=47)	Retatrutide 4 mg escalation group* (n=23)	Retatrutide 4 mg group (n=24)	Retatrutide 8 mg slow escalation group† (n=26)	Retatrutide 8 mg fast escalation group‡ (n=24)	Retatrutide 12 mg escalation group§ (n=46)	1·5 mg dulaglutide group (n=46)	Total (n=281)
Participants with ≥1 treatment-emergent adverse event	28 (62%)	26 (55%)	13 (57%)	19 (79%)	19 (73%)	17 (71%)	35 (76%)	31 (67%)	188 (67%)
Serious adverse events	3 (7%)	3 (6%)	1 (4%)	2 (8%)	2 (8%)	1 (4%)	2 (4%)	1 (2%)	15 (5%)
Death	0	0	0	0	0	0	0	0	0
Adverse events leading to discontinuation of study drug	2 (4%)	1 (2%)	0	1 (4%)	3 (12%)	4 (17%)	7 (15%)	1 (2%)	19 (7%)
Vomiting¶	0	0	0	0	1 (4%)	1 (4%)	1 (2%)	0	3 (1%)
Diarrhoea¶	0	0	0	1 (4%)	0	1 (4%)	0	0	2 (1%)
Acute pancreatitis¶	0	0	0	0	1 (4%)	0	0	0	1 (<1%)
Treatment-emergent adverse events occurring in ≥5% of total participants									
Nausea	2 (4%)	2 (4%)	2 (9%)	6 (25%)	7 (27%)	10 (42%)	9 (20%)	8 (17%)	46 (16%)
Diarrhoea	2 (4%)	1 (2%)	2 (9%)	6 (25%)	5 (19%)	7 (29%)	7 (15%)	4 (9%)	34 (12%)
Decreased appetite	0	2 (4%)	1 (4%)	5 (21%)	5 (19%)	4 (17%)	9 (20%)	6 (13%)	32 (11%)
Constipation	1 (2%)	3 (6%)	2 (9%)	4 (17%)	3 (12%)	2 (8%)	5 (11%)	3 (7%)	23 (8%)
COVID-19	3 (7%)	5 (11%)	3 (13%)	1 (4%)	1 (4%)	1 (4%)	2 (4%)	4 (9%)	20 (7%)
Vomiting	1 (2%)	1 (2%)	1 (4%)	0	2 (8%)	4 (17%)	5 (11%)	4 (9%)	18 (6%)
Headache	2 (4%)	2 (4%)	1 (4%)	1 (4%)	3 (12%)	1 (4%)	1 (2%)	3 (7%)	14 (5%)
Lipase increased	2 (4%)	1 (2%)	1 (4%)	2 (8%)	3 (12%)	1 (4%)	2 (4%)	1 (2%)	13 (5%)
Urinary tract infection	2 (4%)	0	0	1 (4%)	1 (4%)	3 (13%)	5 (11%)	1 (2%)	13 (5%)

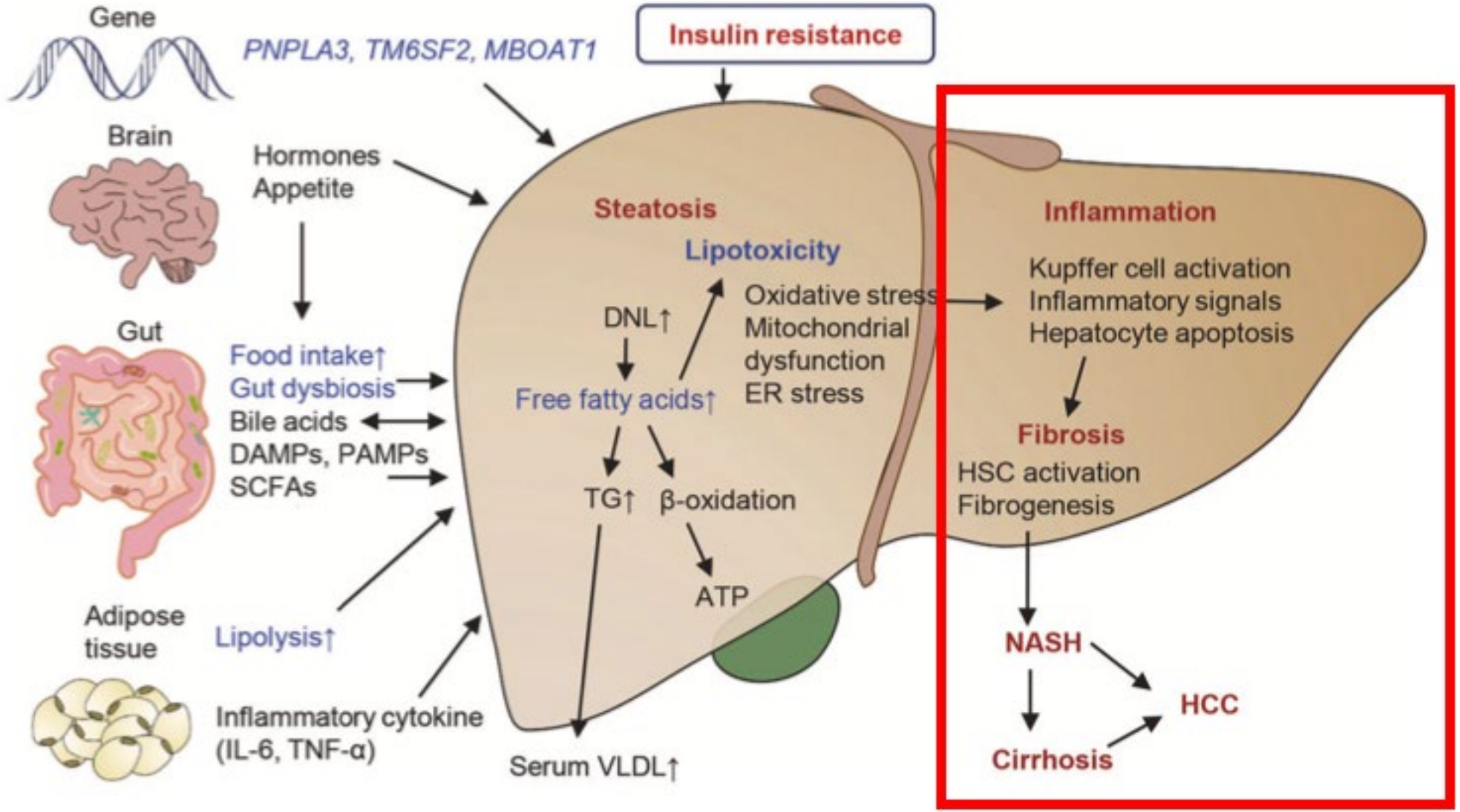
Rosenstock J et al.; The Lancet 2023

Summary of the highest percent weight change in completed phase 2 and phase 3 trials of GLP1 agonists, of GLP1/GCG agonists, and of the GLP1/GIP/GCG agonist retatrutide

(Kokkorakis M et al.; Pharmacol Rev 2025)

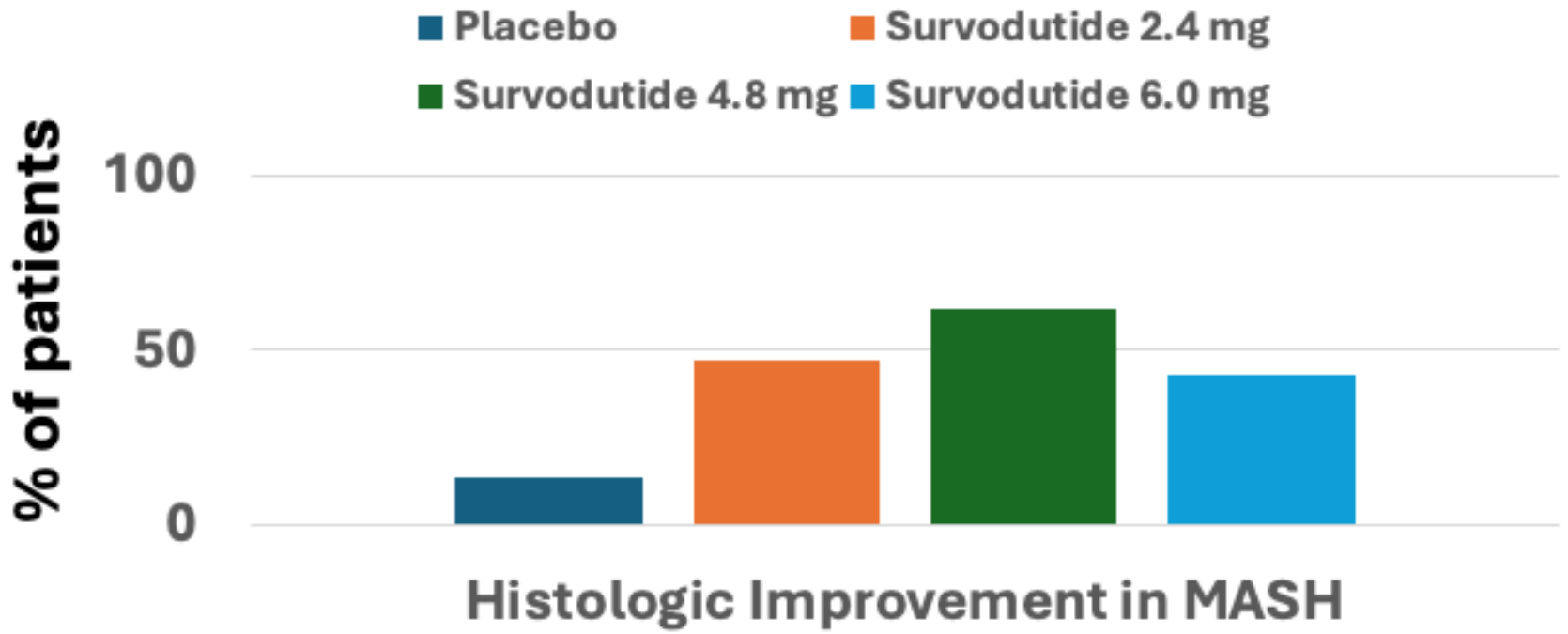


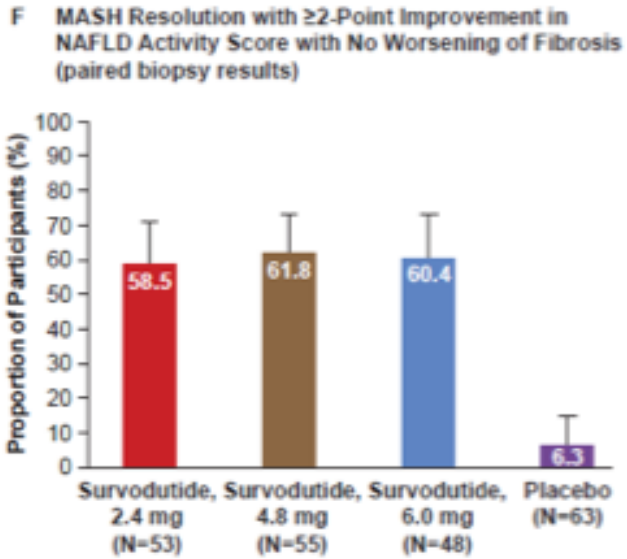
What about NASH/MASH/MASLD?

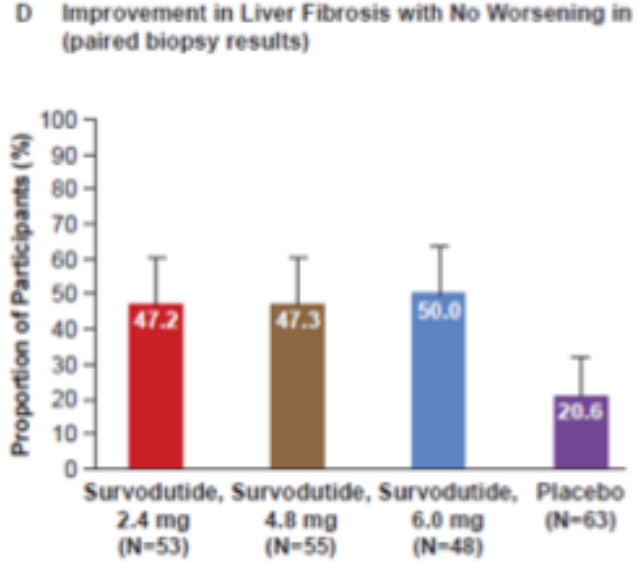


Huang YY et al.; Acta Pharmacol Sin 202

Survodutide in people with metabolic-dysfunction associated steatohepatitis (MASH)



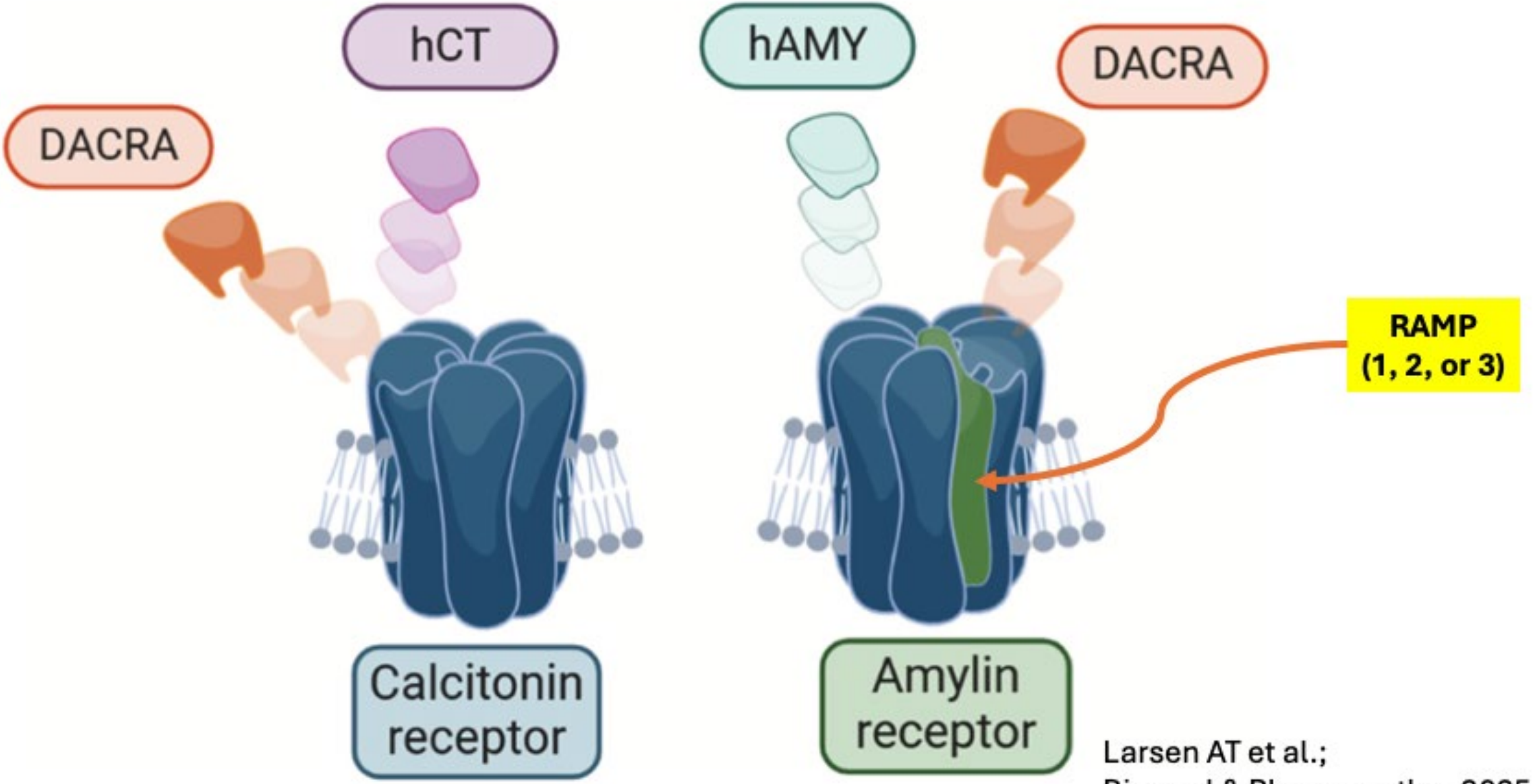




Sanyal AJ et al.; N Eng J Med 2024

Amilina

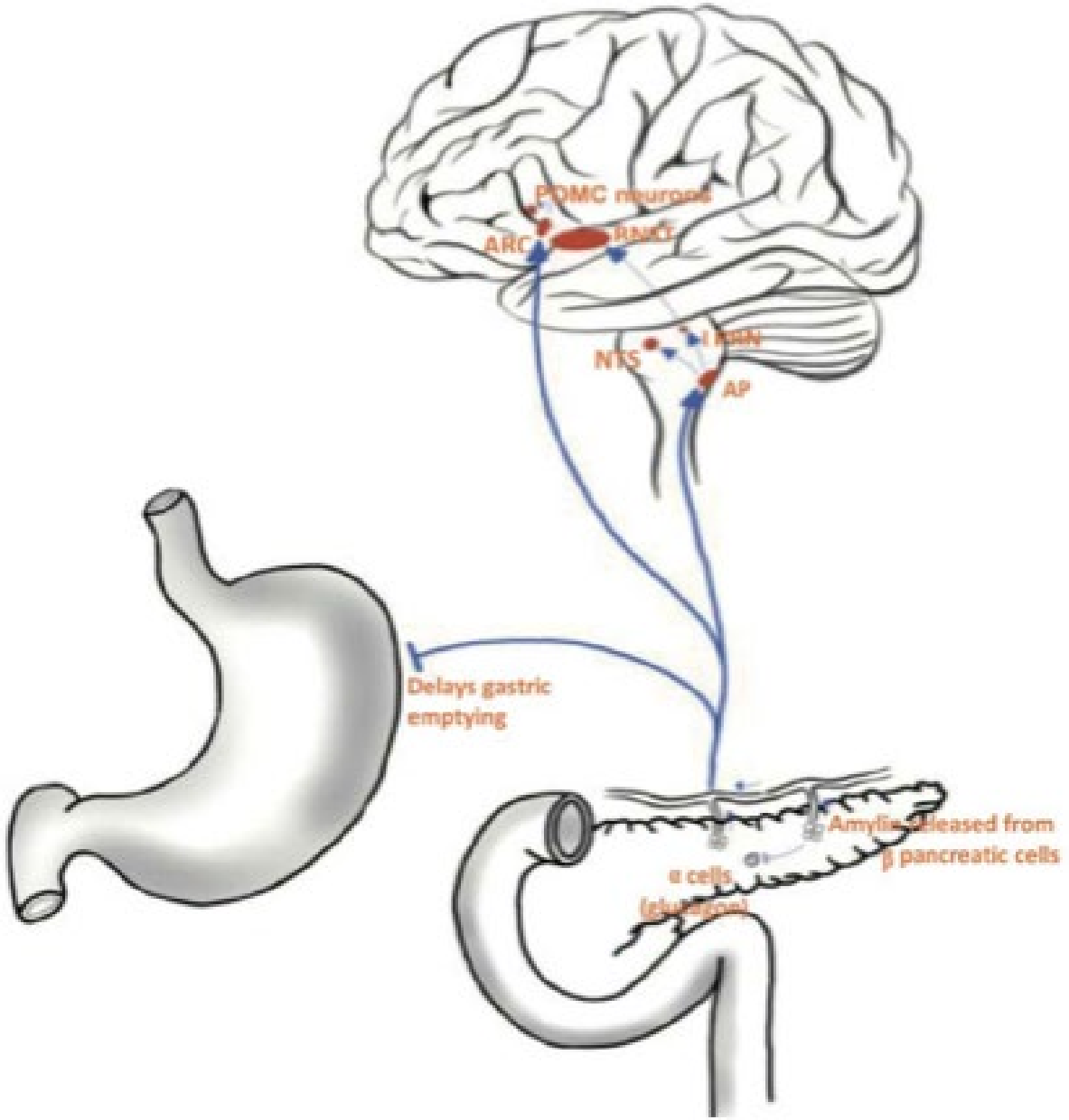
Schematic illustration of the calcitonin and amylin receptor



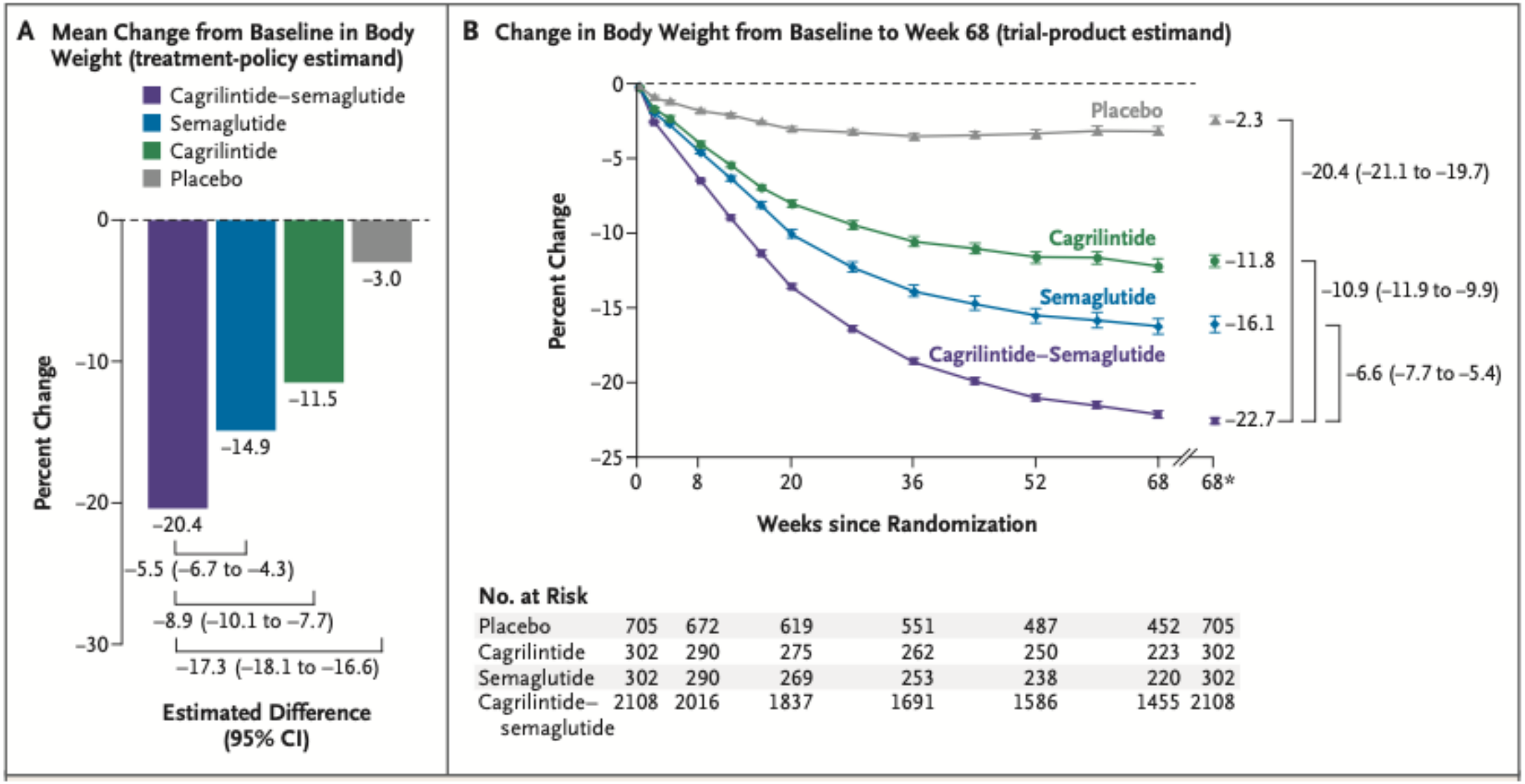
Larsen AT et al.;
Biomed & Pharmacother 2025

Expected effects of a DACRA (e.g. cagrilintide, salmon calcitonin) in humans

(D'Ascanio AM et al.; Cardiol Rev 2024)



CagriSema effectively lowers body weight in obese people (BMI ≈ 38 kg/m^2) without diabetes



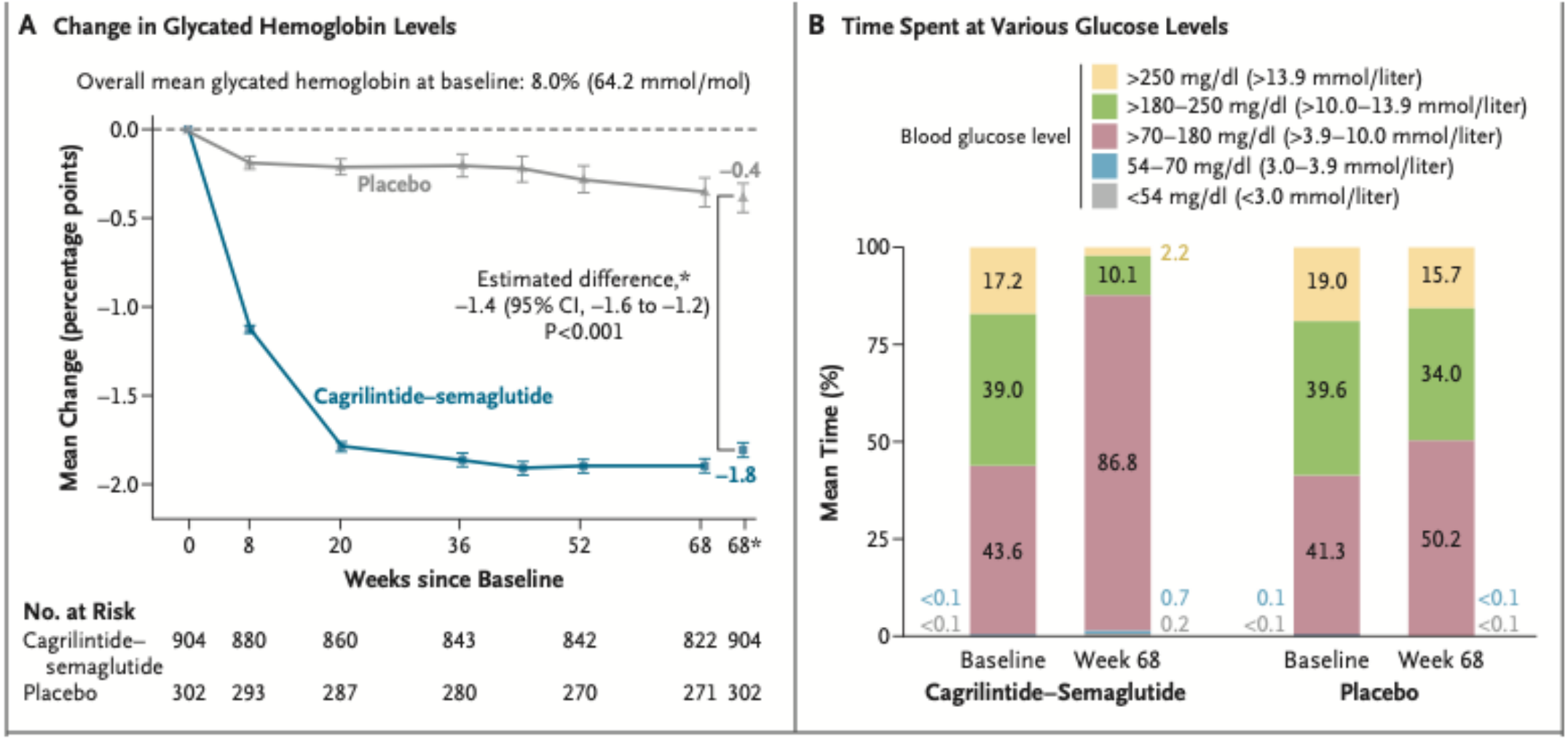
Garvey WT et al.; N Eng J Med 2025

Adverse events in the CagriSema trial in people with obesity (BMI ≈ 38 kg/m^2) without diabetes

Event	Cagrilintide–Semaglutide (N = 2106)	Semaglutide (N = 302)	Cagrilintide (N = 302)	Placebo (N = 705)
	number of participants (percent)			
Any adverse event	1943 (92.3)	271 (89.7)	254 (84.1)	580 (82.3)
Serious adverse event	206 (9.8)	15 (5.0)	27 (8.9)	43 (6.1)
Adverse event leading to permanent trial-product discontinuation†	125 (5.9)	11 (3.6)	8 (2.6)	25 (3.5)
Gastrointestinal adverse events leading to permanent trial-product discontinuation†	76 (3.6)	4 (1.3)	4 (1.3)	4 (0.6)
Fatal event‡	2 (0.1)	0	0	0
Selected safety event				
Gastrointestinal adverse events†	1676 (79.6)	223 (73.8)	163 (54.0)	281 (39.9)
Injection-site reactions†	256 (12.2)	8 (2.6)	51 (16.9)	21 (3.0)
Allergic reactions†	110 (5.2)	17 (5.6)	23 (7.6)	39 (5.5)
Neoplasms	134 (6.4)	20 (6.6)	5 (1.7)	31 (4.4)
Gallbladder-related disorders†	87 (4.1)	9 (3.0)	7 (2.3)	7 (1.0)
Malignant neoplasms§	14 (0.7)	2 (0.7)	2 (0.7)	4 (0.6)
Pancreatitis†	4 (0.2)	1 (0.3)	0	0

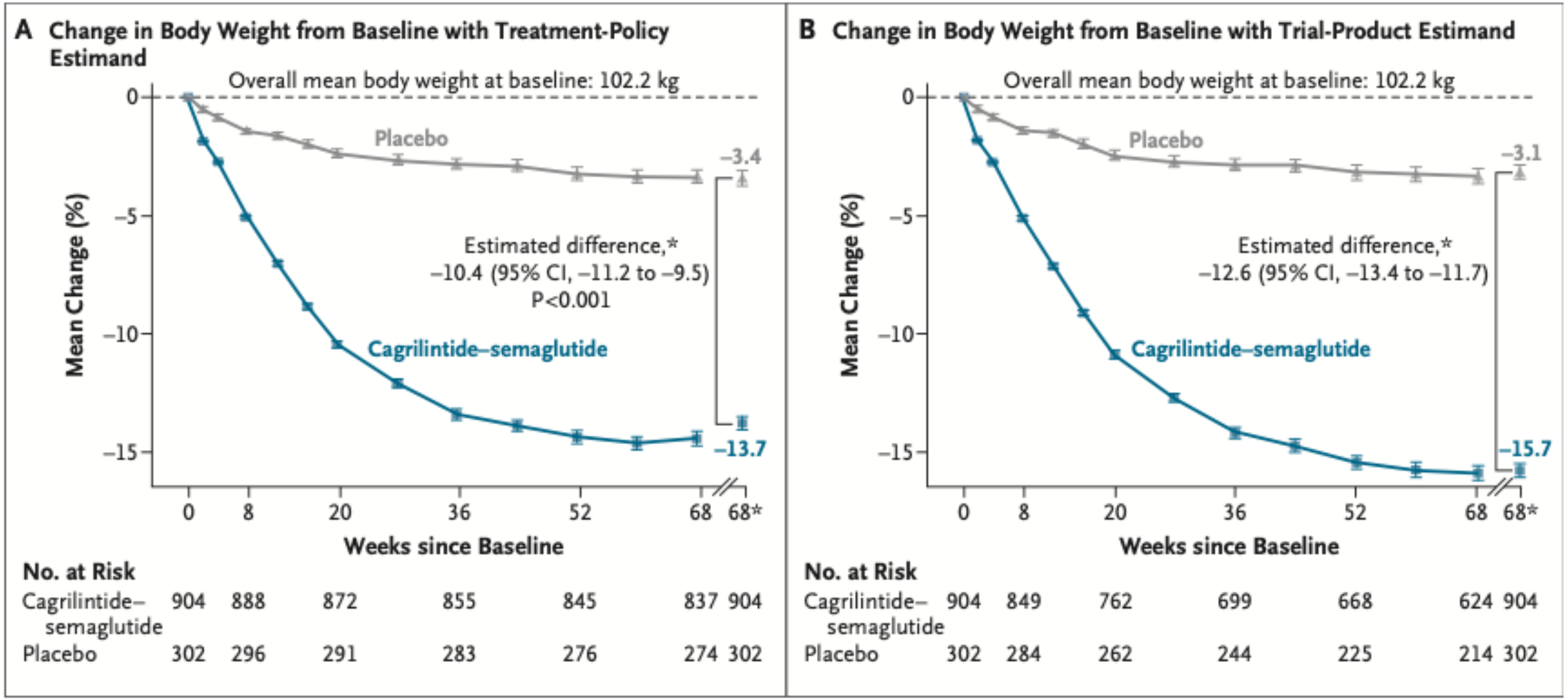
Garvey WT et al.; N Eng J Med 2025

Effects of CagriSema on glucose control in people with obesity (BMI ≈ 36 kg/m^2) and type 2 diabetes



Davies MJ et al.; N Eng J Med 2025

Effects of CagriSema on body weight in people with obesity (BMI ≈ 36 kg/m^2) and type 2 diabetes



Davies MJ et al.; N Eng J Med 2025

Adverse events of CagriSema in people with obesity (BMI 36 kg/m^2) and type 2 diabetes

(Davies MJ et al.; N Eng J Med 2025)

Adverse Events	Cagrilintide–Semaglutide (N=904)			Placebo (N=302)		
	Patients	Events	Event Rate†	Patients	Events	Event Rate†
	no. (%)	*no.*		*no. (%)*	*no.*	
Any	815 (90.2)	6088	477.4	258 (85.4)	1275	301.6
Serious	94 (10.4)	138	10.8	39 (12.9)	51	12.1
Leading to permanent discontinuation						
Any adverse event	76 (8.4)	97	7.6	9 (3.0)	13	3.1
Gastrointestinal adverse event	43 (4.8)	49	3.8	2 (0.7)	3	0.7
Fatal event‡	4 (0.4)	4	0.3	0	—	—
Hypoglycemic episode§						
Alert value: level 1¶	108 (11.9)	328	27.8	24 (7.9)	61	15.6
Clinically significant: level 2¶	54 (6.0)	85	7.2	10 (3.3)	11	2.8
Severe: level 3¶	2 (0.2)	2	0.2	0	—	—
Selected safety event						
Gastrointestinal disorder¶	655 (72.5)	2742	232.4	104 (34.4)	227	58.0
Retinal disorder	75 (8.3)	94	7.4	24 (7.9)	29	6.9
Neoplasm	63 (7.0)	80	6.3	20 (6.6)	26	6.1
Allergic reaction¶	46 (5.1)	55	4.7	18 (6.0)	19	4.9
Injection-site reaction¶	44 (4.9)	65	5.5	0	—	—
Gallbladder-related disorder¶	18 (2.0)	24	2.0	2 (0.7)	2	0.5
Malignant neoplasm‖	14 (1.5)	16	1.3	4 (1.3)	4	0.9
Pancreatitis¶	3 (0.3)	3	0.3	0	—	—
Suicidal ideation or behavior**	8 (0.9)	—	—	4 (1.4)	—	—

Amycretin structure

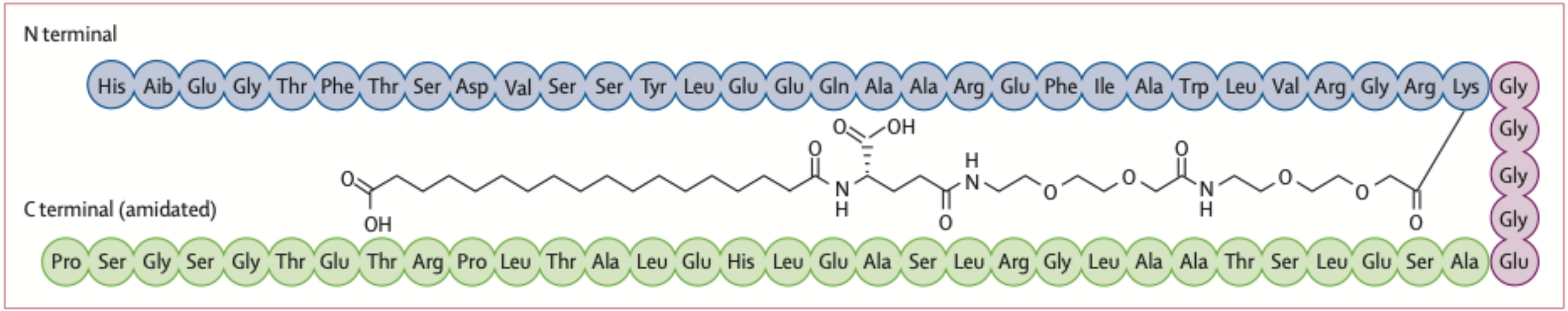


***Figure 1:* Amycretin structure**

Amycretin comprises a GLP-1 receptor agonist peptide (blue) and an amylin receptor agonist peptide (green) connected by a linker (purple). The peptide is acylated with a C18 diacid at position K37.

Gasiorek A et al.; Lancet 2025

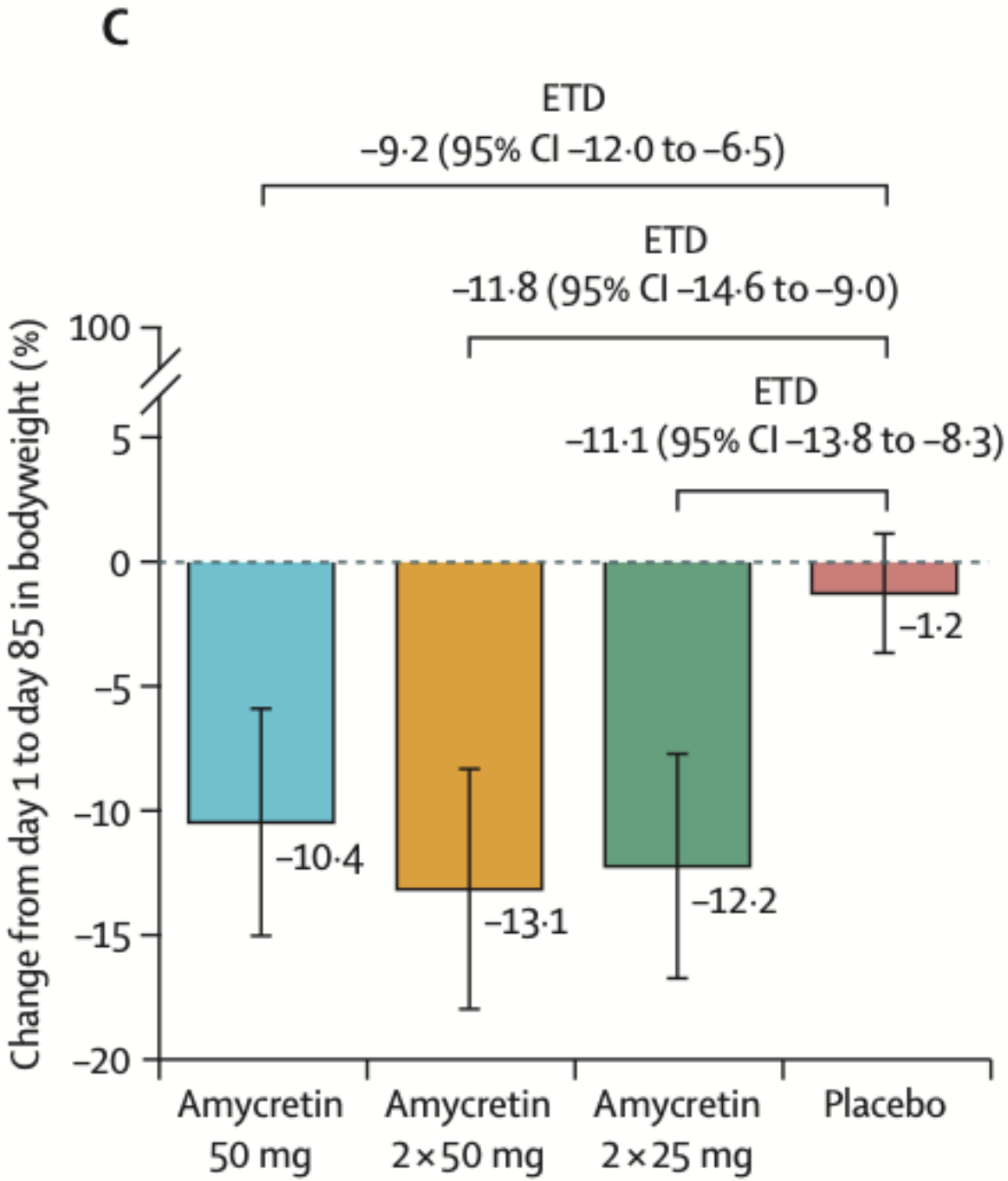
Clinical features of subjects included in part C/D of phase 1 oral amycretin study

	Amycretin 50 mg (n=16)	Amycretin 2 × 50 mg (n=16)	Amycretin 2 × 25 mg (n=16)	Placebo (n=12)
Age, years	38 (10) [19–54]	38 (8) [23–53]	37 (8) [18–49]	42 (4) [34–48]
Sex				
Male	12 (75%)	9 (56%)	4 (25%)	11 (92%)
Female	4 (25%)	7 (44%)	12 (75%)	1 (8%)
Ethnicity				
Hispanic or Latino	4 (25%)	6 (38%)	8 (50%)	6 (50%)
Not Hispanic or Latino	12 (75%)	10 (63%)	8 (50%)	6 (50%)
Race				
White	9 (56%)	8 (50%)	10 (63%)	8 (67%)
Black or African American	6 (38%)	8 (50%)	5 (31%)	3 (25%)
Native Hawaiian or other Pacific Islander	1 (6%)	0	0	1 (8%)
Missing	0	0	1 (6%)	0
Bodyweight, kg	92·3 (10·8) [69·7–114·0]	89·9 (9·8) [73·2–106·0]	89·3 (11·8) [69·5–115·7]	88·4 (7·8) [74·9–100·6]
BMI, kg/m²	30·6 (2·5) [27·5–36·5]	31·6 (2·8) [28·1–38·6]	32·8 (3·7) [27·5–40·2]	30·0 (1·4) [27·9–32·0]

Data are mean (SD) [range] or n (%). Data are for the safety analysis set.

Gasiorek A et al.; Lancet 2025

Changes in body weight of subjects (BMI ≈ 31-33 kg/m^2) included in part C/D of phase 1 oral amycretin study *(Gasiorek A et al.; Lancet 2025)*



Changes in glucose levels in the subjects (BMI ≈ 31-33 kg/m^2) included in part C/D of phase 1 oral amycretin study

	Amycretin 50 mg (n=16)	Amycretin 2 × 50 mg (n=16)	Amycretin 2 × 25 mg (n=16)	Placebo* (n=12)
HbA_{1c} %				
Screening, mean (SD)	5·2 (0·4)	5·2 (0·3)	5·4 (0·4)	5·3 (0·4)
Day 85, mean (SD)	5·0 (0·3)	5·0 (0·2)	5·1 (0·2)	5·3 (0·3)
Change from day 1 to day 85, mean (SD)	−0·2 (0·2)	−0·3 (0·3)	−0·3 (0·2)	0·0 (0·2)
ETD (95% CI) *vs* placebo	−0·3 (−0·4 to −0·1)	−0·3 (−0·5 to −0·1)	−0·3 (−0·4 to −0·1)	..
Fasting plasma glucose, mmol/L				
Day 1, mean (SD)	5·4 (0·3)	5·2 (0·3)	5·3 (0·3)	5·4 (0·4)
Day 85, mean (SD)	4·9 (0·3)	4·8 (0·3)	4·8 (0·3)	5·4 (0·4)
Change from day 1 to day 85, mean (SD)	−0·6 (0·4)	−0·5 (0·3)	−0·5 (0·2)	0·1 (0·3)
ETD (95% CI) *vs* placebo	−0·6 (−0·8 to −0·4)	−0·6 (−0·8 to −0·4)	−0·6 (−0·8 to −0·4)	..

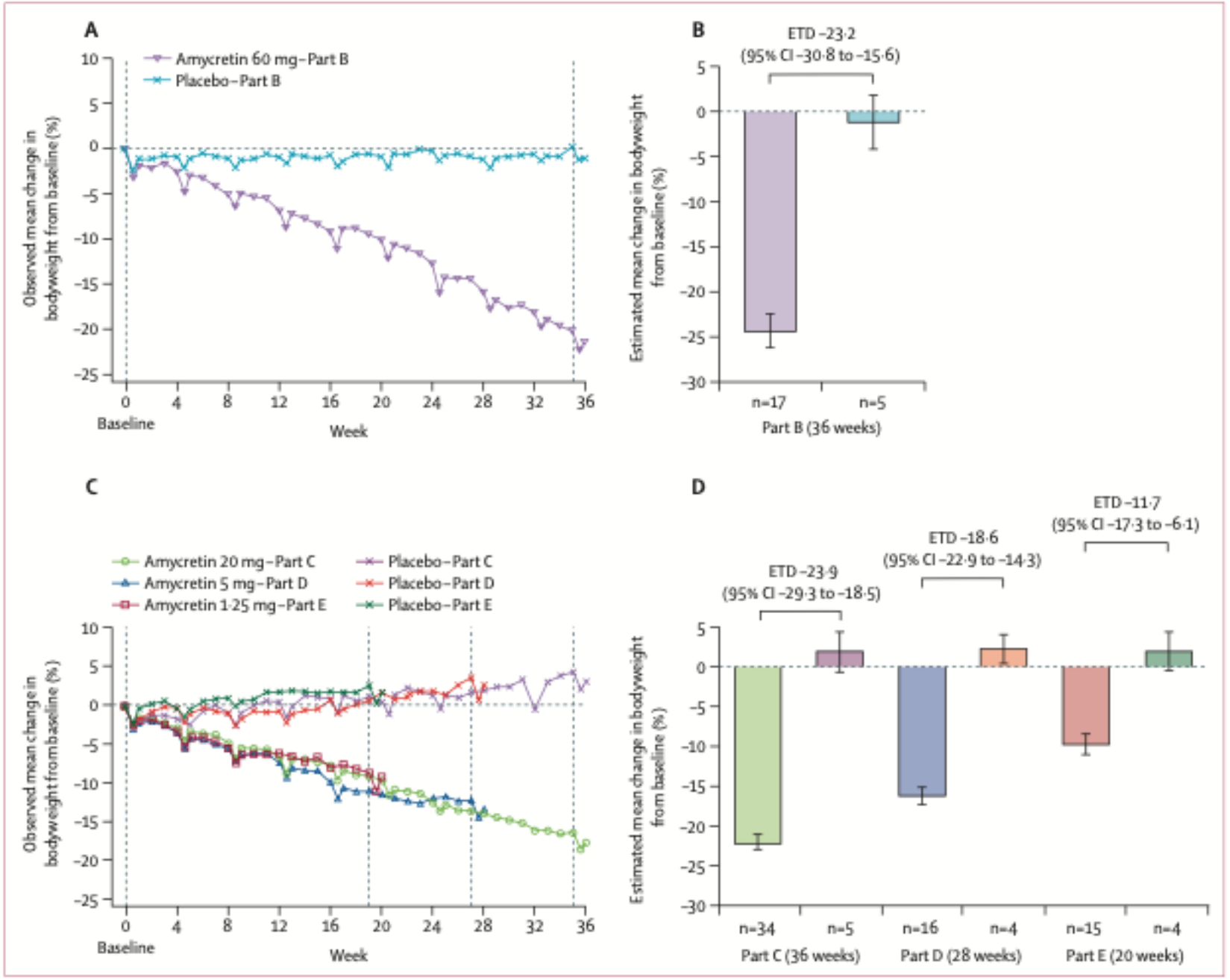
Gasiorek A et al.; Lancet 2025

Changes in lipid levels in the subjects (BMI ≈ 31-33 kg/m^2) included in part C/D of phase 1 oral amycretin study

	Amycretin 50 mg (n=16)	Amycretin 2 × 50 mg (n=16)	Amycretin 2 × 25 mg (n=16)	Placebo* (n=12)
HDL cholesterol, mmol/L				
Day 1, mean (SD)	1·4 (0·3)	1·4 (0·2)	1·5 (0·5)	1·3 (0·4)
Day 85, mean (SD)	1·2 (0·2)	1·1 (0·2)	1·3 (0·2)	1·1 (0·3)
Ratio of day 85 to day 1, mean (SD)	0·9 (0·1)	0·8 (0·1)	0·9 (0·1)	0·9 (0·1)
ETR (95% CI) *vs* placebo	1·0 (0·9 to 1·1)	0·9 (0·9 to 1·0)	1·0 (1·0 to 1·1)	..
LDL cholesterol, mmol/L				
Day 1, mean (SD)	3·6 (0·7)	3·7 (0·8)	4·0 (1·0)	3·7 (0·8)
Day 85, mean (SD)	2·9 (0·7)	3·2 (0·7)	3·1 (0·6)	3·2 (0·7)
Ratio of day 85 to day 1, mean (SD)	0·8 (0·2)	0·8 (0·1)	0·8 (0·1)	0·8 (0·1)
ETR (95% CI) *vs* placebo	0·9 (0·8 to 1·1)	1·0 (0·9 to 1·1)	1·0 (0·9 to 1·1)	..
Triglycerides, mmol/L				
Day 1, mean (SD)	1·4 (0·5)	1·6 (0·8)	1·5 (0·6)	1·9 (0·9)
Day 85, mean (SD)	0·9 (0·3)	1·1 (0·5)	0·9 (0·3)	1·4 (0·6)
Ratio of day 85 to day 1, mean (SD)	0·7 (0·2)	0·7 (0·2)	0·7 (0·3)	0·8 (0·1)
ETR (95% CI) *vs* placebo	0·8 (0·7 to 1·0)	0·8 (0·7 to 1·0)	0·8 (0·7 to 1·0)	..

Gasiorek A et al.; Lancet 2025

Percent changes in body weight in subjects (BMI ≈ 31-33 kg/m^2) of the phase 1b/2a amycretin s.c. RCT *(Dahl K et al., Lancet 2025)*

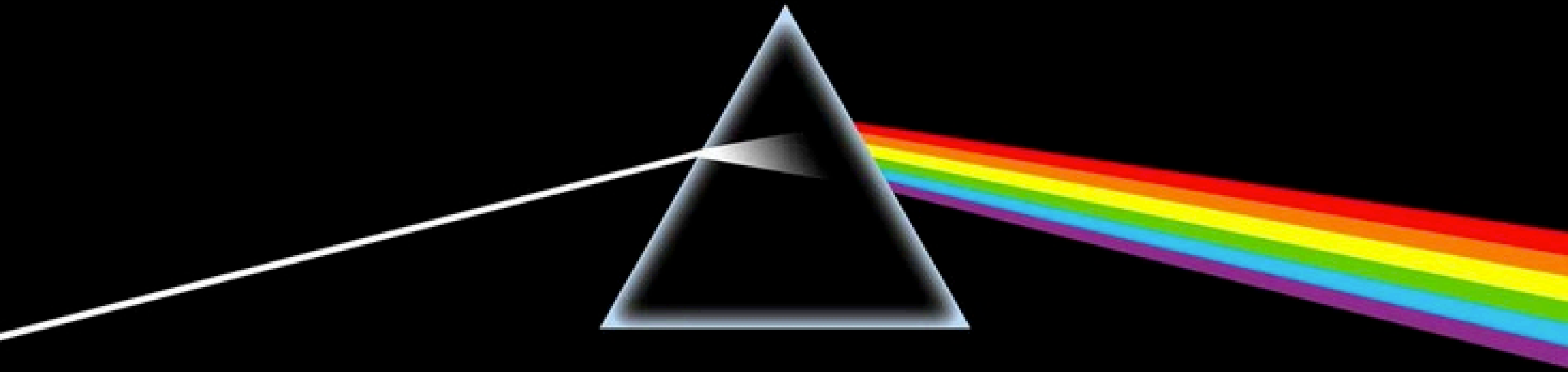


Selected adverse events in the subjects (BMI ≈ 31-33 kg/m^2) recruited in the phase 1b/2a amycretin RCT

	Part B		Part C	
	Amycretin 60 mg (n=17)	Placebo (n=5)	Amycretin 20 mg (n=34)	Placebo (n=5)
Treatment-emergent adverse events	17 (100%), 136	5 (100%), 29	33 (97%), 234	5 (100%), 19
Serious adverse events				
Yes	0	0	1 (3%), 1	0
No	17 (100%), 136	5 (100%), 29	33 (97%), 233	5 (100%), 19
Events leading to withdrawal	6 (35%), 8	0	7 (21%), 15	1 (20%), 1
Severity				
Severe	0	0	1 (3%), 1	0
Moderate	10 (59%), 16	1 (20%), 2	11 (32%), 18	0
Mild	17 (100%), 120	5 (100%), 27	33 (97%), 215	5 (100%), 19

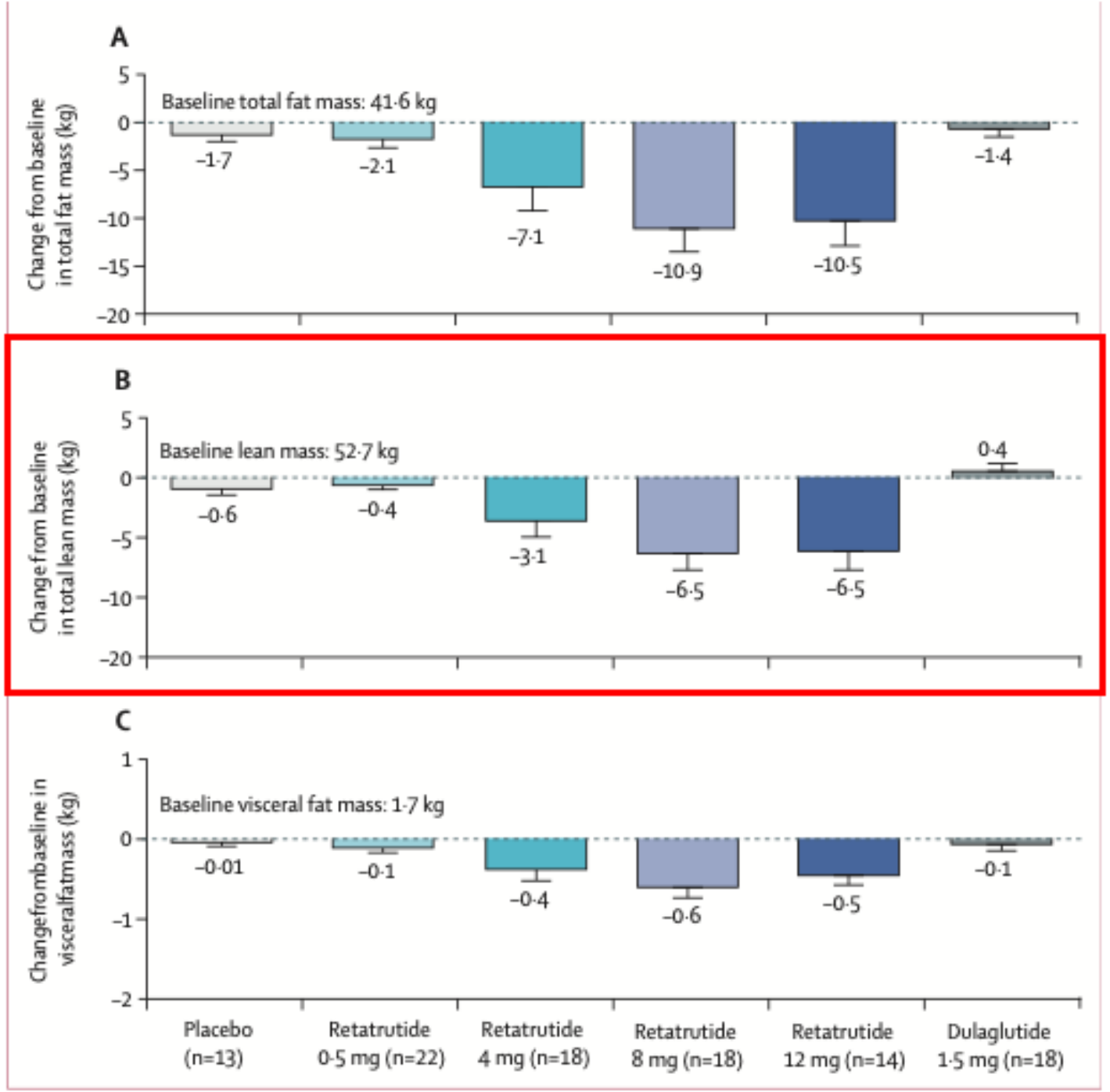
Dahl K et al.; Lancet 2025

The Dark Side of the Moon

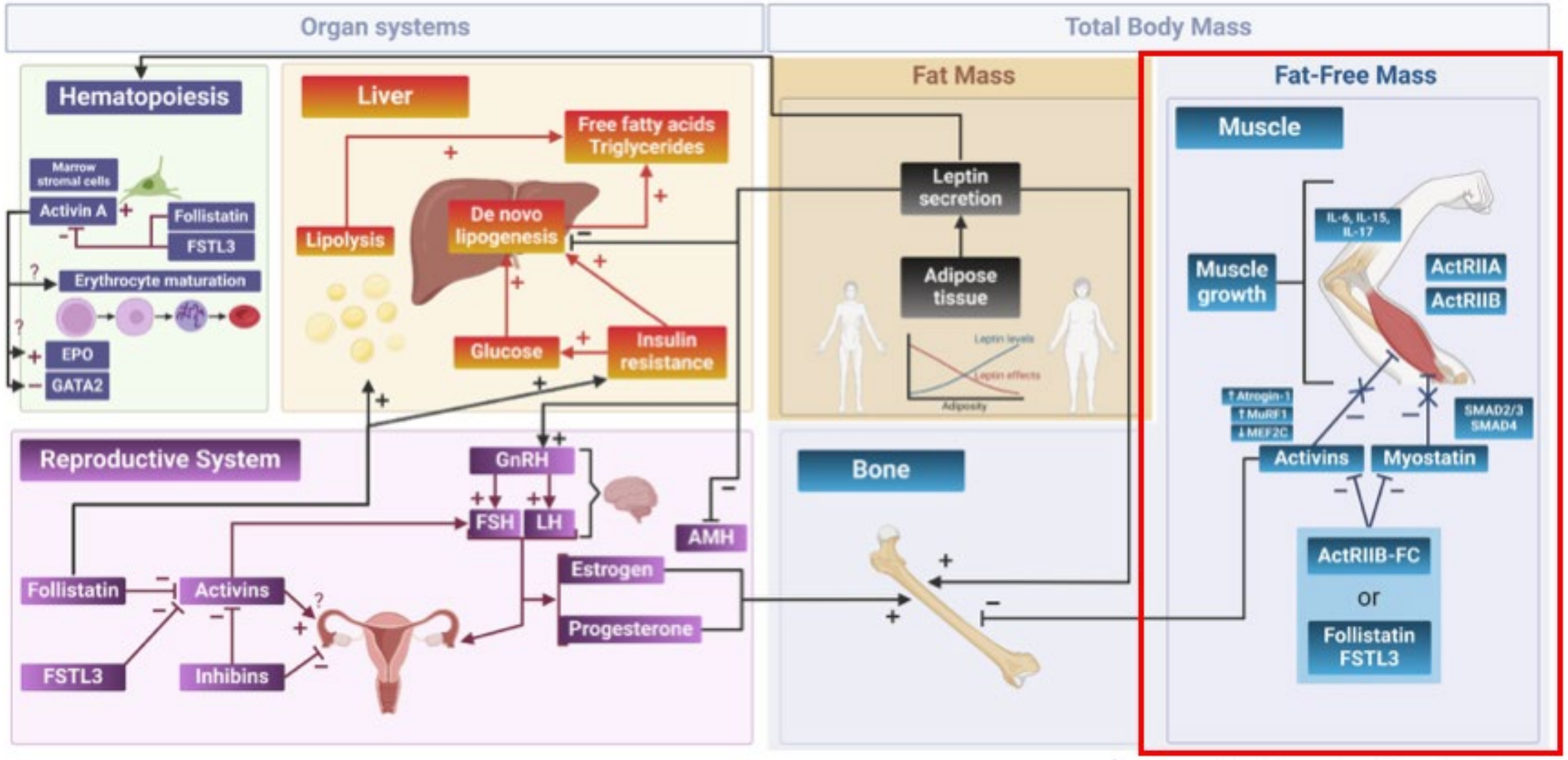


Effects of retatrutide on body composition in people with obesity and type 2 diabetes

(Coskun T et al.; Lancet Diabetes & Endocrinol 2025)

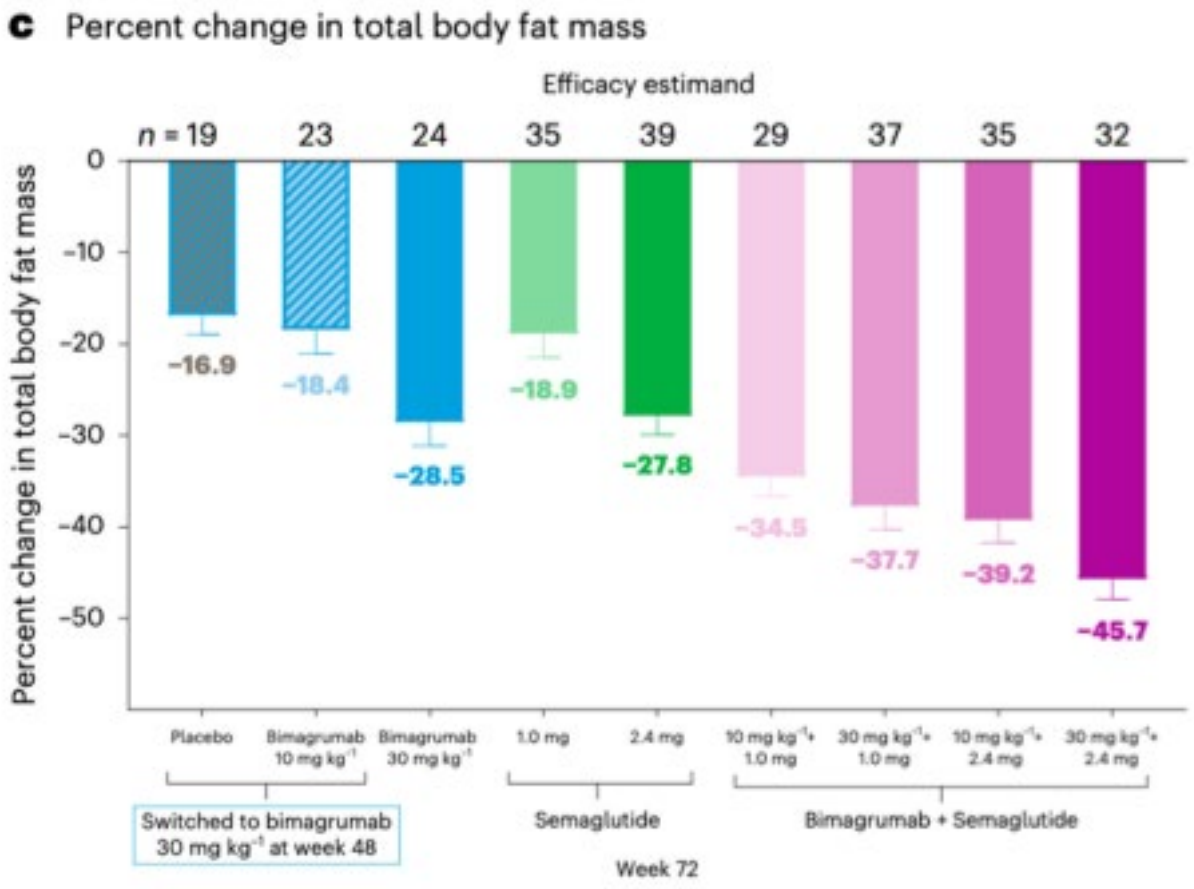


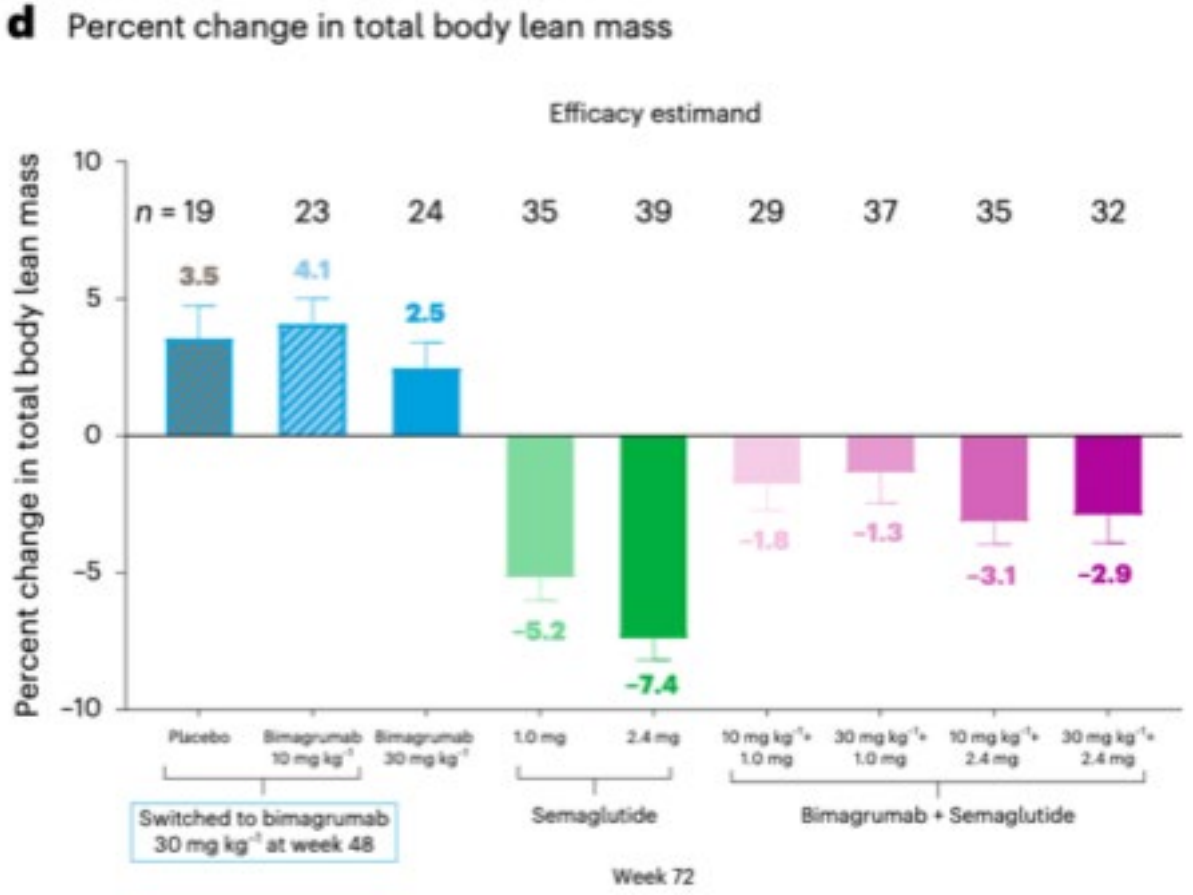
The myostatin-activin-follistatin-inhibin (MAFI) system and its influence on fat mass, fat free mass (muscle and bone), and metabolic regulation



Stefanakis K et al.; Metabolism 2025

Bimagrumab, an inhibitor of activin type II receptors, synergizes semaglutide body fat lowering action, restrains semaglutide lean body mass lowering effect in people with obesity





Heymsfield SM et al.; Nat Med 2026

Riflessioni finali

- L’ingaggio farmacologico del recettore del glucagone mediante peptidi multi-agonisti sembra conferire un’ulteriore efficacia nei confronti degli effetti desiderati (e.g. survodutide > semaglutide 1 mg/settimana)
- Retatrutide, pur in assenza di un confronto diretto con il «best performer», sembra essere il peptide multi-agonista noto con la massima attività di riduzione del peso corporeo nell’obesità e dell’iperglicemia nel diabete di tipo 2
- L’ingaggio simultaneo del recettore del GLP-1 dei recettori di amilina/calcitonina conferisce un’ulteriore efficacia in termini di riduzione di peso e HbA1c rispetto a semaglutide, e forse potrebbe in futuro rivelarsi anche pari a retatrutide
- In presenza di multi-agonisti tutti dotati di grandissima efficacia su peso corporeo e controllo glicemico la tollerabilità diventerà sempre di più un fattore discriminante
- Tutti questi ligandi, mono- e multi-agonisti, riducono il peso con rilevanti riduzioni della massa magra.
- Lo studio BELIEVE riporta risultati di efficacia straordinaria sul peso corporeo, con preservazione della massa magra, proponendo un nuovo paradigma e un nuovo «benchmark» nel trattamento farmacologico dell’obesità con l’inibizione della miostatina e delle activine: il **disaccoppiamento** della perdita di massa grassa e della perdita di massa magra durante la riduzione del peso.

Grazie per l'attenzione