使用降糖或減重藥物來控制體重
內分泌醫師觀點

台北榮總 內分泌新陳代謝科
胡啟民 醫師

GLP-1RAs and Beyond: FDA Approved Indications

Dose$_{max}$: 3.0 mg sc QD

Table 1
Incretin-based therapies: generic names, brand names and adult indications.

Generic	Brand	Indication	Year approved
Dulaglutide	Trulicity	T2DM, CV event risk reduction in pts. w/DM and CVD	2014
Exenatide[a]	Byetta	T2DM	2005
Exenatide	Bydureon BCise	T2DM	2017
Liraglutide	Victoza	T2DM, CV event risk reduction in pts. w/DM and CVD	2010
Liraglutide	Saxenda	Obesity/overweight	2014
Lixisenatide[a]	Adlyxin	T2DM	2016
Semaglutide	Ozempic	T2DM, CV event risk reduction in pts. w/DM and CVD	2017
Semaglutide	Rybelsus	T2DM	2019
Semaglutide	Wegovy	Obesity/overweight, CV event risk reduction in pts. w/overweight/obesity and CVD	2021
Tirzepatide	Mounjaro	T2DM	2022
Tirzepatide	Zepbound	Obesity/overweight	2023

Dose$_{max}$: 2 mg sc QW

Dose$_{max}$: 15 mg sc QW

CV: cardiovascular, T2DM: Type 2 Diabetes, CVD = cardiovascular disease.
[a] Discontinued, no longer available in US market.
Source: https://www.fda.gov/drugs/drug-safety-and-availability/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type#:%C3%BC:text=GLP%252D1%2520receptors%2520are%2520also,Wegovy. Accessed July 4, 2024.

Dose$_{max}$: 14 mg po QD

Dose$_{max}$: 2.4 mg sc QW

Reddy TK, et al. Am Heart J Plus 46:100455, 2024

2025/7/5 凌晨4:55 控糖減重 張毓哲醫師 - 【新知分享】 Mounjaro猛健樂取得台灣衛福部核准「體重控制」適應症👍... | Facebook

【新知分享】 Mounjaro猛健樂取得台灣衛福部核准「體重控制」適應症👍

💡仿單適應症:

●作為飲食及運動療法之外的輔助治療，用於改善第二型糖尿病成人病人之血糖控制。說明:
MOUNJARO 可做為單一療法或與其他糖尿病治療藥物合併使用。

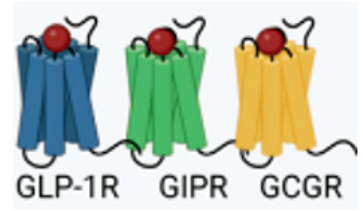
●用於體重控制，做為低熱量飲食及增加體能活動之輔助療法，適用對象為成人且初始身體質量指數 (BMI) 為≥ 30 kg/m2 (肥胖)，或≥ 27kg/m2 至 < 30 kg/m2 (過重) 且至少患有一項體重相關共病，例如高血壓、血脂異常、糖尿病前期或第二型糖尿病、阻塞性睡眠呼吸中止或心血管疾病。

Mounjaro dosing schedule

Week	1-4	5-8	9-12	13-16	17-20	21+
Dose	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg

GLP-1RAs and Beyond (1G, 2G, 3G, and Others)

- GLP-1R monoagonist: Semaglutide 降糖(+)或減重 (+)
- GLP-1R multiagonist
  - GLP-1R/GIP-R dual agonist: Tirzepatide 降糖(++)或減重 (++)
  - GLP-1R/GCG-R dual agonist: Survodutide (BI 456906)、Mazdutide 減重 (++)
  - GLP-1R/GIP-R/GCG-R triple G agonist: Retatrutide 減重 (++)
- GLP-1R agonist/GIPR antagonist
  - AMG 133 (maridebart cafraglutide) (MariTide) 減重 (+++)
- GLP-1R/Amylin agonist
  - Cagrilintide/Semaglutide (CagriSema) 減重 (++)
  - Amycretin
- GIPRA-LA II (Macupatide)
- Others: Bimagrumab



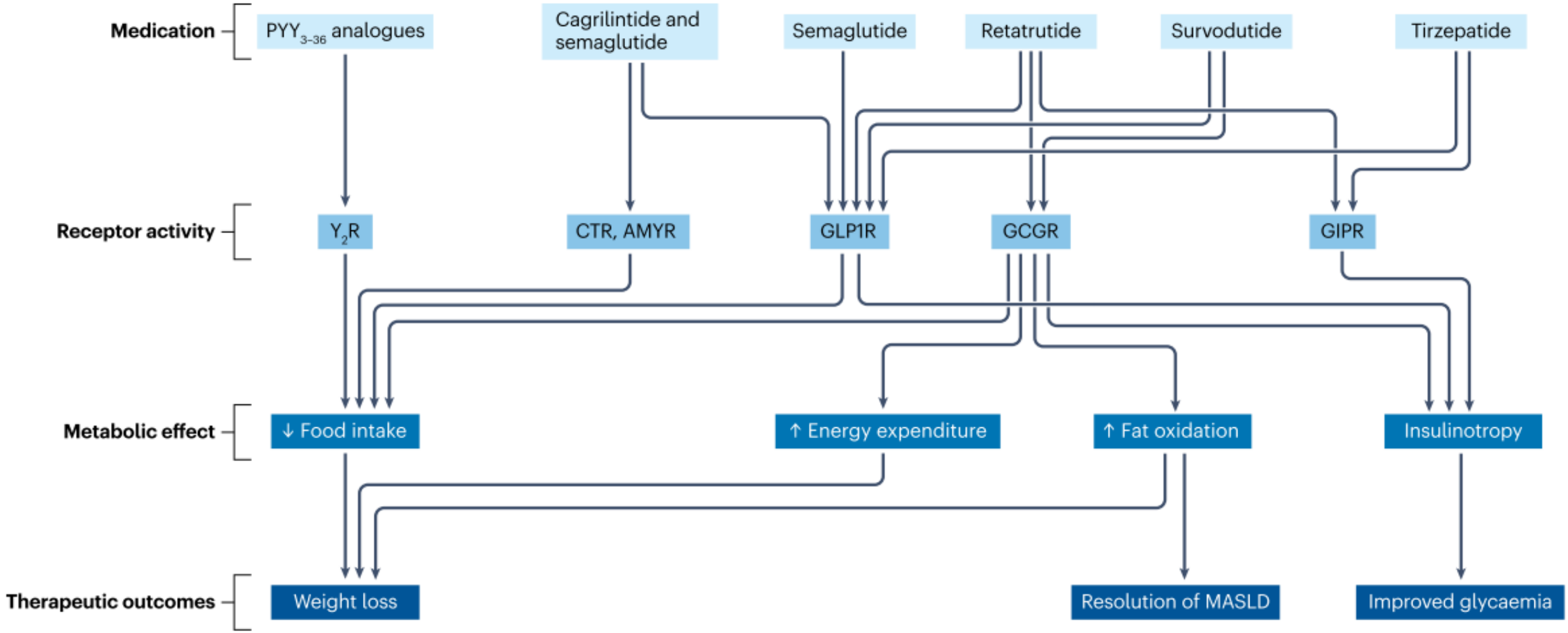


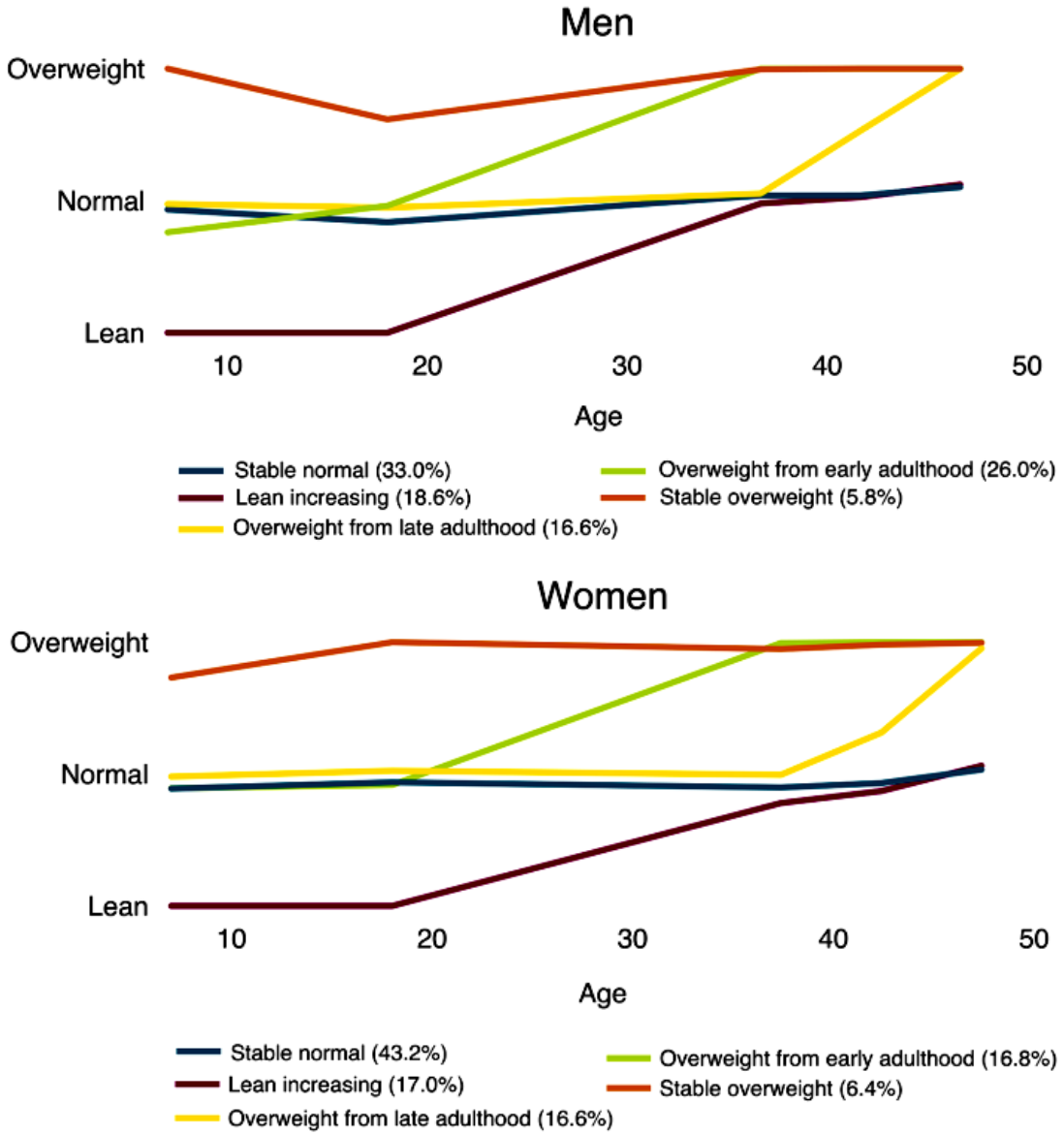
Fig. 1 | Therapies based on incretin hormones. Medications that contain the activities of endogenous incretins and related hormones are shown together with their respective receptor activities, metabolic effects and therapeutic outcomes. AMYR, amylin receptor; CTR, calcitonin receptor; GCGR, glucagon receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide 1 receptor; MASLD, metabolic dysfunction-associated steatotic liver disease; PYY, peptide YY; Y2R, neuropeptide Y2 receptor.

Ansari S et al. Nat Rev Endocrinol 20:447-459, 2024

觀點：（體重控制）

- 肥胖與第2型糖尿病均為「終身」「慢性疾病」：減重與"對作"
- 用藥治療需考慮
  - ✓治療的目的：用在誰？體重控制？血糖控制？預防(併生)疾病？
  - ✓藥物劑量：減重劑量 vs. 控糖劑量
  - ✓用藥效果：個案、"專家"意見、實證→Level of Evidence
  - ✓用藥策略：Debulking→Maintenance
  - ✓藥效持續/用藥多久問題：停藥後會如何？
    - ➢Cure? Remission? Recurrence? active surveillance (watchful waiting)
  - ✓藥物分配(公平)問題：誰可以用？誰用了最好？(效益最大化)
- 背後的科學原理：Why↓BW? 作用機轉?
- 未來趨勢：戰國→平衡

Life-Course Trajectories of Weight and Risk of T2DM



Stockholm Diabetes Prevention Program (SDPP) —20 years F/U

n =7203 (4820 women and 2383 men)

Self-Reported weight status

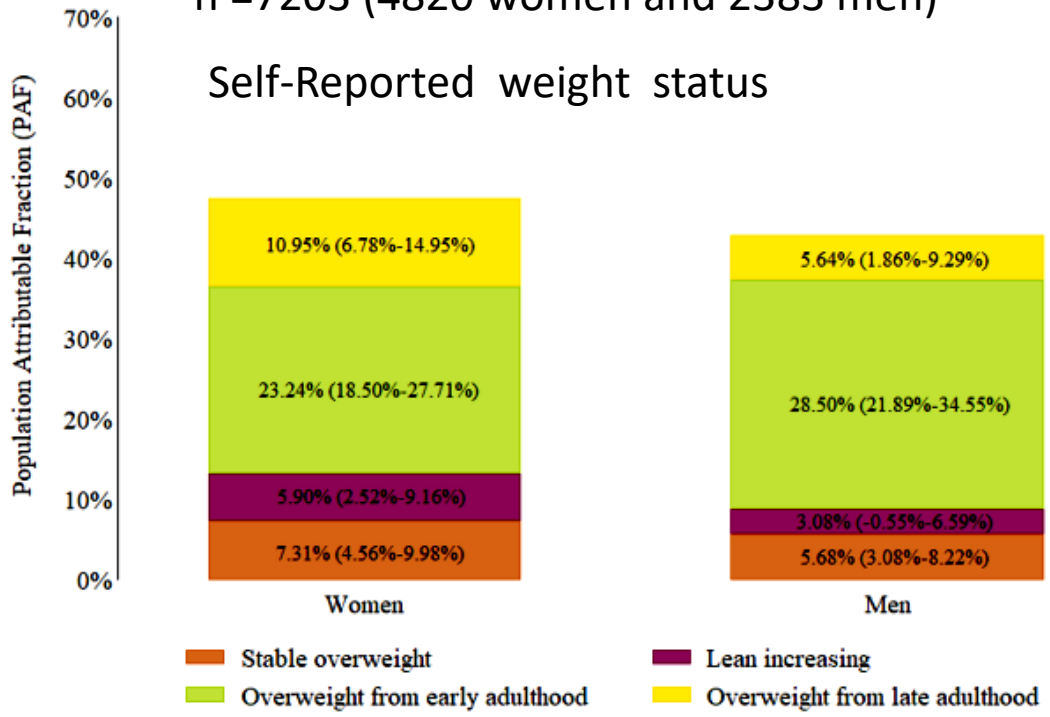


Figure 3. Population attributable fractions (PAF) of trajectory groups by sex. Compared to the stable normal trajectory group, the overall proportion of type 2 diabetes cases attributable to any of the life-course weight trajectories was 47.40% (95% CI 38.06–55.34%) for women and 42.91% (95% CI 31.47–52.45%) for men.

Yacamán-Méndez D, et al. Sci Rep 11:12494, 2021

Long-Term Persistence of Hormonal Adaptations to Weight Loss

METHODS

We enrolled 50 overweight or obese patients without diabetes in a 10-week weight-loss program for which a very-low-energy diet was prescribed.

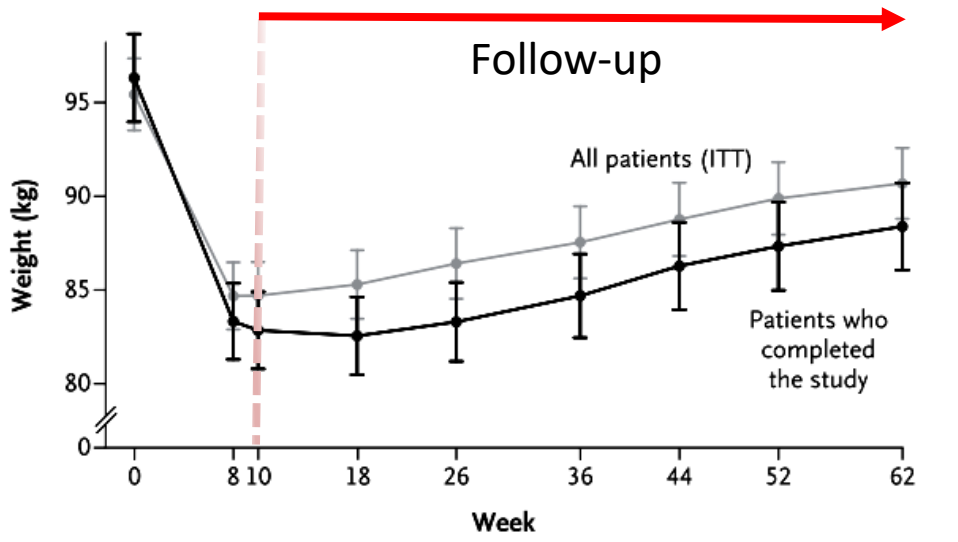


Figure 1. Mean (±SE) Changes in Weight from Baseline to Week 62.

The weight-loss program was started at week 0 and completed at week 10. ITT denotes intention to treat.

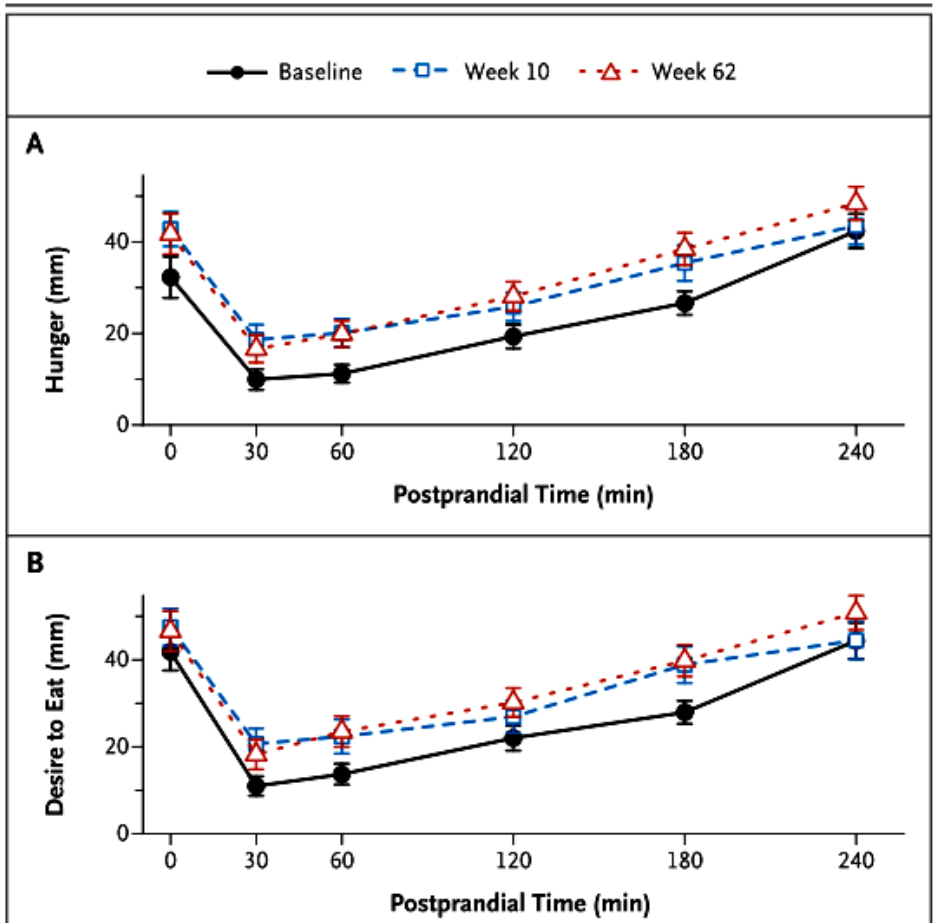
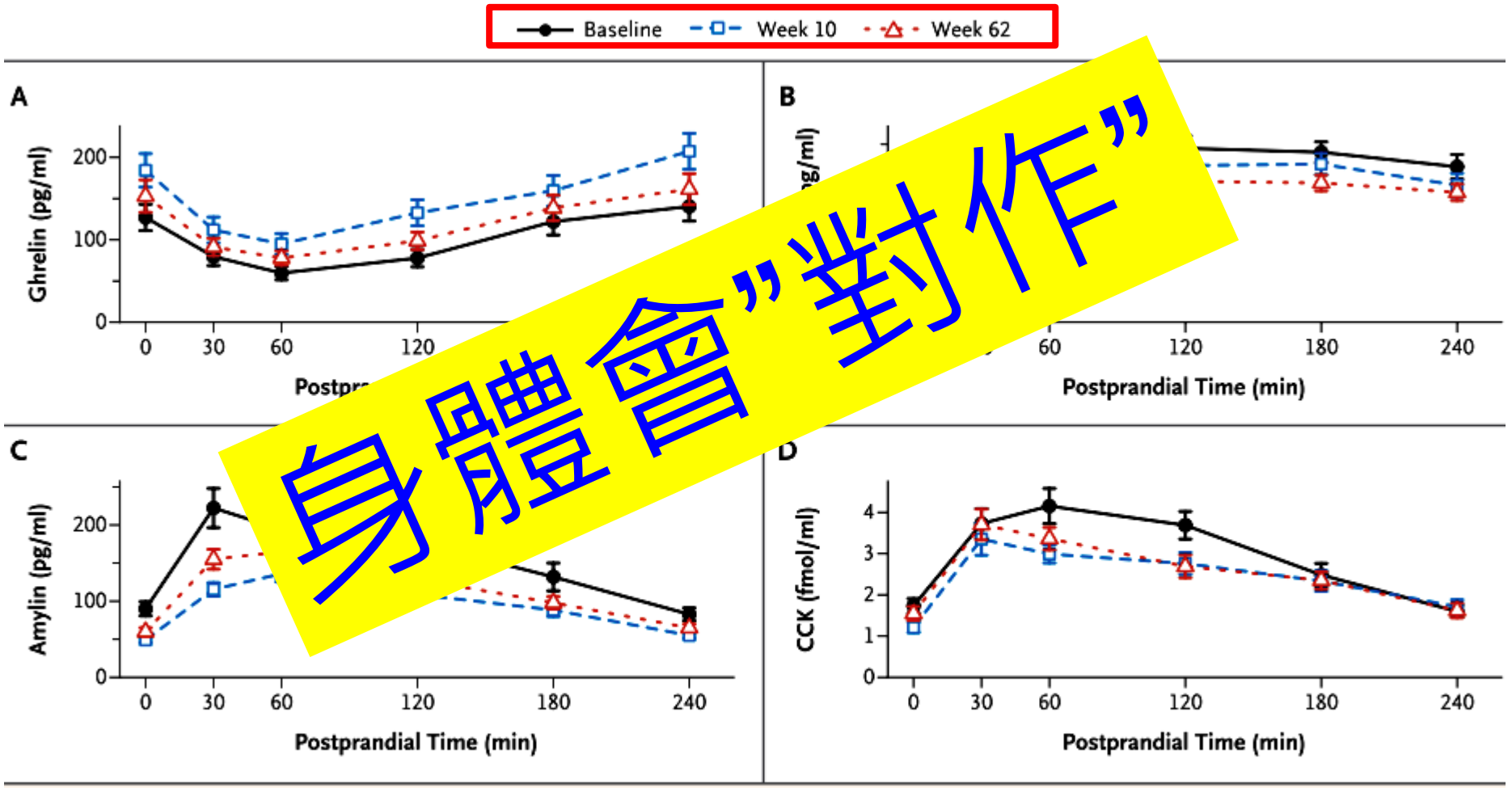


Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.

Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.

Sumithran P, et al. Nat Metab N Engl J Med 365: 1597-604, 2021

Long-Term Persistence of Hormonal Adaptations to Weight Loss



身體會"對作"

Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

Sumithran P, et al. Nat Metab N Engl J Med 365: 1597-604, 2021

The Dilemma of Weight Loss in Diabetes

- **People with diabetes have a harder time loosing weight.**

Not all weight reduction interventions in patients with increased adiposity have head-to-head comparisons of efficacy among those with type 2 diabetes mellitus, versus those without type 2 diabetes mellitus. However, a general overview of the data suggests that weight reduction interventions are less effective among those with type 2 diabetes mellitus than without type 2 diabetes mellitus [8]. While the quality of the data, as well as statistic and clinical significance vary, the amount of weight reduction and/or success of weight reduction maintenance appears less among those with type 2 diabetes mellitus treated with dietary intervention, physical activity, behavior modification [9,10],orlistat [11], phentermine [12], phentermine/topiramate [13,14], naltrexone/bupropion [13,15–17], liraglutide [13,18], semaglutide [19], as well as bariatric surgery [20]. It may also be relevant that in the tirzepatide SURMOUNT program [21], SURMOUNT 1 demonstrated weight reduction up to 21% among patients with overweight/obesity and without diabetes mellitus [22], while preliminary reports suggest that in SURMOUNT 2, tirzepatide reduced weight up to 16% among patients with overweight/obesity and type 2 diabetes mellitus (https://investor.lilly.com/node/48776/pdf).

Bays HE. Obes Pillars 7:100076, 2023

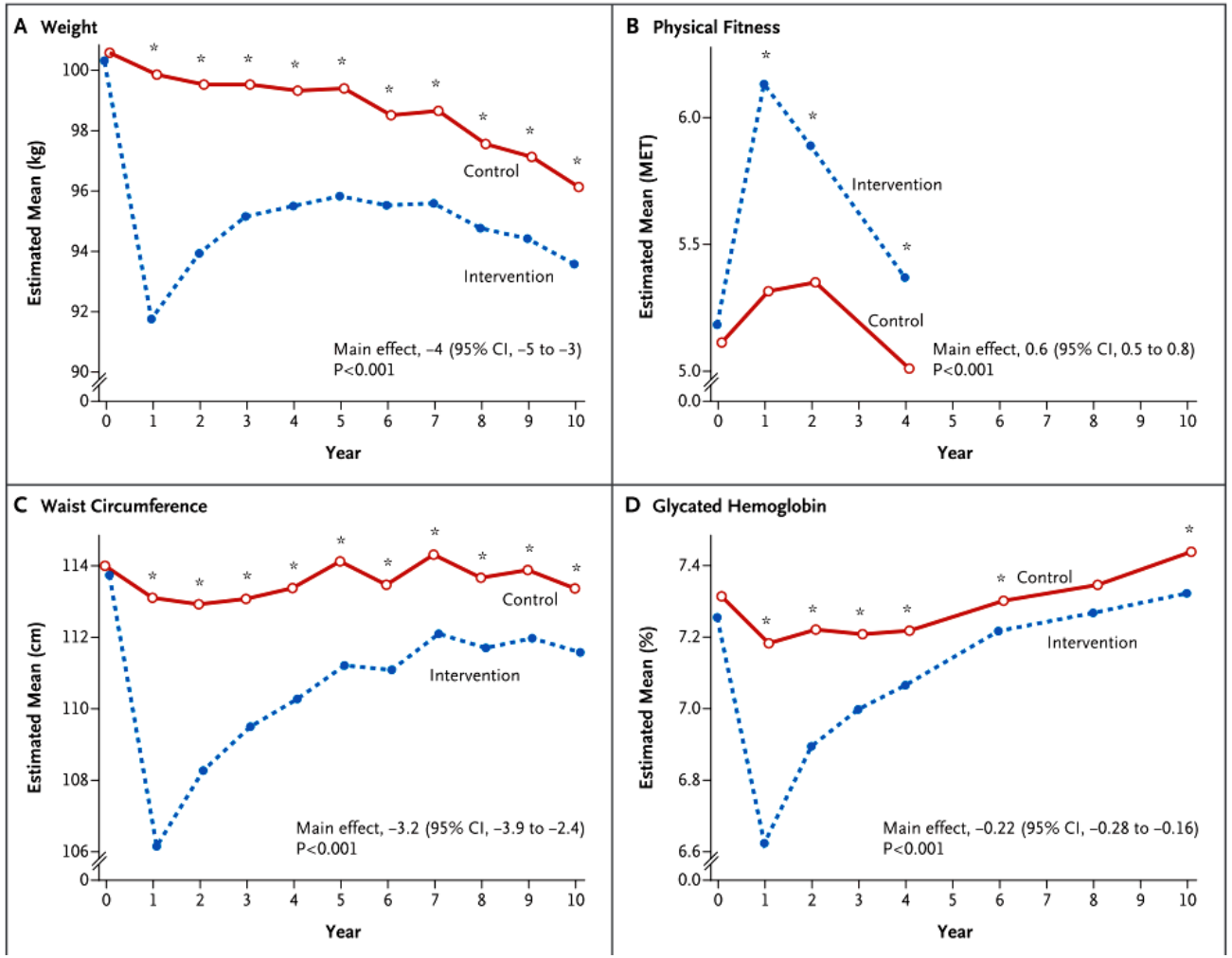
The Dilemma of Weight Loss in Diabetes

- Why people with diabetes have a harder time loosing weight.
  - **Some medications that control blood sugar can cause weight gain.**
  - **Stopping loss of sugar in the urine with treatment.**
  - **Low blood sugars (hypoglycemia).**
  - **Stress.**
  - **Unhealthy relationship with food.**
  - **Complications of diabetes can limit physical activity.**
  - **Insulin resistance.**

Posted by Dr. Sue Pedersen | Mar 14, 2021
https://drsue.ca/2021/03/why-do-people-with-diabetes-have-a-harder-time-losing-weight/

The Dilemma of Weight Loss in Diabetes

- Lessons Learned From the Look AHEAD Trial –**Satisfaction Not Guaranteed!**



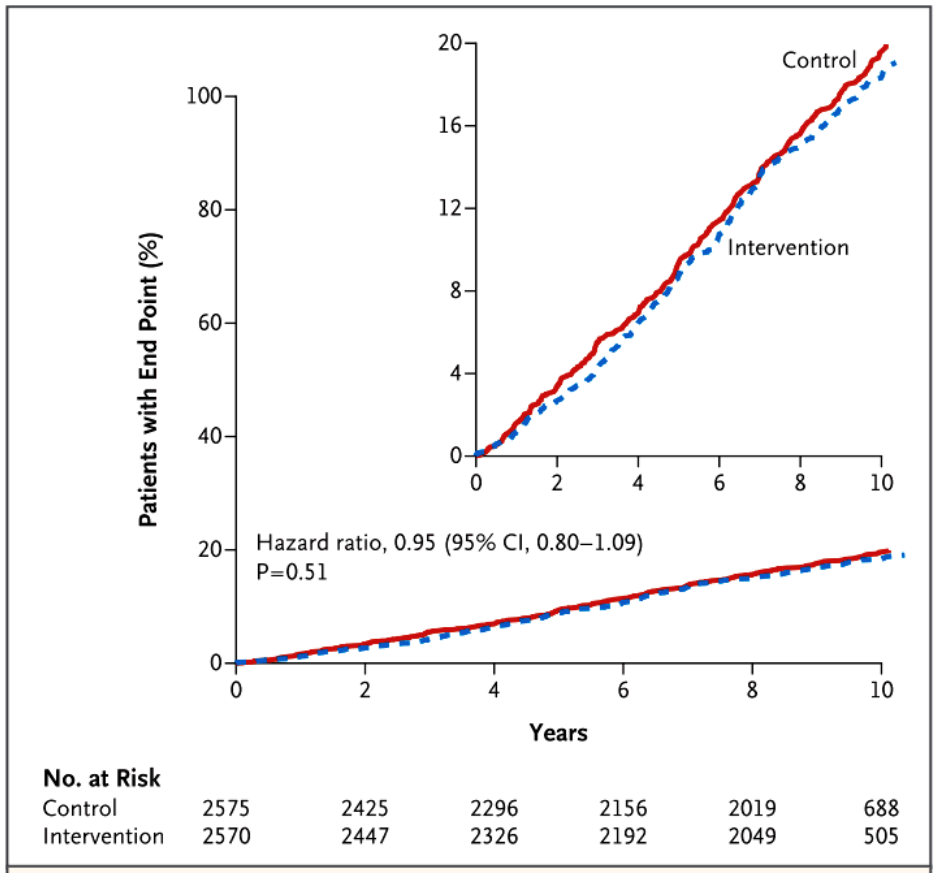


Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.
Shown are Kaplan–Meier estimates of the cumulative proportion of patients with a primary event. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina. The numbers below the graph are the numbers of patients at risk in each study group at years 2, 4, 6, and 8 and at 10.4 years, when the last observed event occurred. The inset shows the same data on an expanded y axis.

The Look AHEAD Research Group. N Engl J Med 369:145-54, 2013

The Dilemma of Weight Loss in Diabetes

- **Satisfaction Not Guaranteed!**

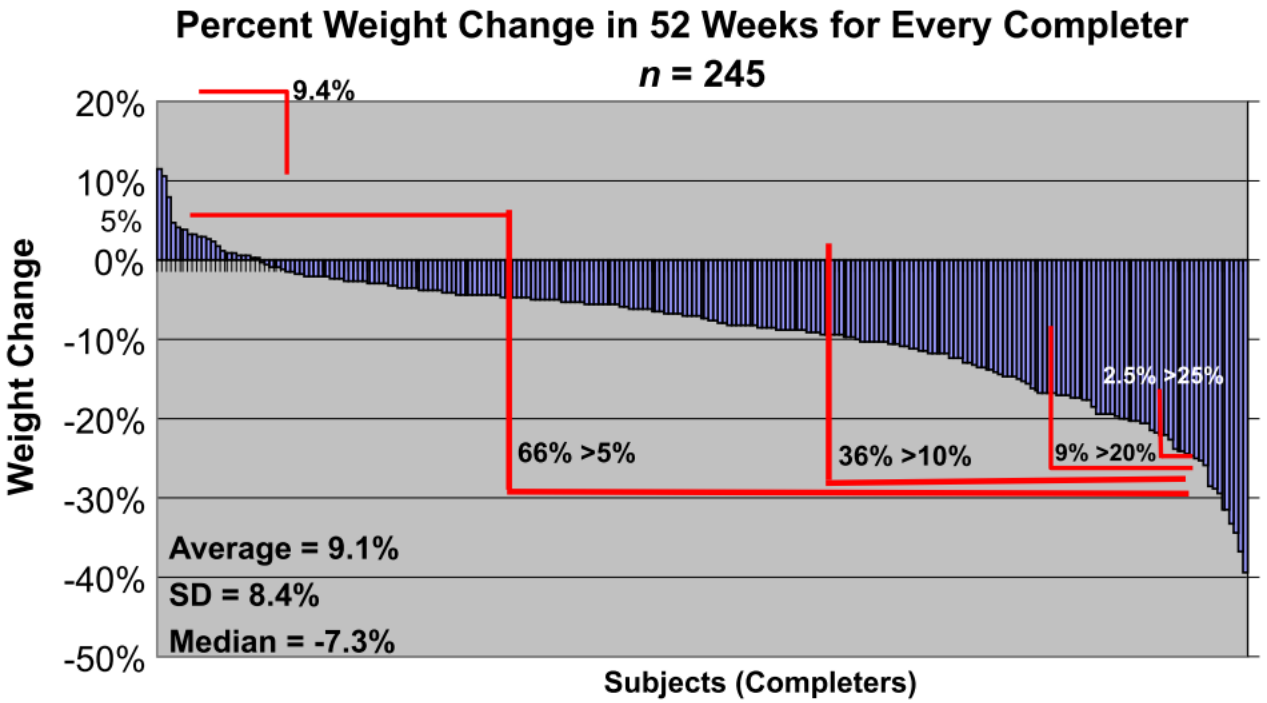


Figure 3—Percentage of weight change by subject (n = 245) at week 52 of the NYORC weight-loss program. Courtesy of Richard Weil, MEd, CDE (Columbia University, New York, NY); Betty Kovacs, MS, RD (Columbia University, New York, NY); and F.X.P.-S.

Table 2—Effects of weight-loss medications on glycemic control and the need for oral antidiabetes agents in people with type 2 diabetes

	Orlistat (163)	Lorcaserin (149)	Phentermine/ topiramate (164,165)	Naltrexone/ bupropion (166)	Liraglutide 3 mg (167)
Weight loss (%)					
Drug	6.2	4.5	9.6	5.0	6.0
Placebo	4.3	1.5	2.6	1.8	2.0
Initial A1C (%)	8.1	8.1	8.6	8.0	8.0
A1C change (%)					
Drug	−0.3	−0.9	−1.6	−0.6	?
Placebo	+0.2	−0.4	−1.2	−0.1	?
Patients reaching an A1C ≤7% (%)					
Drug	?	50.4	53	44	69
Placebo	?	26.3	40	26	27
Need for oral antidiabetes agents	↓	↓	↓	↓	?

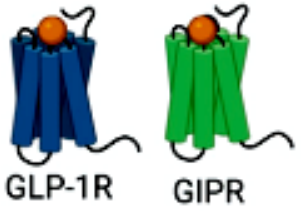
Cefalu WT. Diabetes Care 38:1567-82, 2015

用藥策略: Debulking → Maintenance

Bariatric Surgeries

Vertical Sleeve Gastrectomy (VSG)	Roux-en-Y Gastric Bypass (RYGB)	Biliopancreatic diversion with Duodenal Switch (BDP-DS)
		
• 22% Weight Loss • 14-86% T2DM Remission	• 25-28% Weight Loss • 50-84% T2DM Remission	• 36-55% Weight Loss • 90-100% T2DM Remission

GLP-1RA-Based Pharmacotherapy

GLP-1 Receptor Agonist	GLP-1/GIP Receptor Dual Agonist	GLP-1/GIP/GCG Receptor Tri-Agonist
		
• 6-10% weight loss • 56-68% reached HbA1c ≤6.5% • 69-79% reached HbA1c <7%	• 12% Weight Loss • 69-80% reached HbA1c ≤6.5% • 82-96% reached HbA1c <7%	• 16% Weight Loss • 80% reached HbA1c ≤6.5% • 80% reached HbA1c <7%

Which comes first? Surgery or Medical

Comorbidities (定義) vs Simple Obesity

Stage: Debulking or Maintenance

起跑體重: 100kg→150kg→250kg
復胖體重: 100kg→150kg→200kg

Morissette A, Mulvihill EE. J Pharm Pharm Sci 6;27:13065. 2024

Results of Example Major Phase III Clinical Trials Using Semaglutide in T2DM and Obesity

T2DM

Trial	Intervention	Study duration (weeks)	Number of participants (% female)	Age (years) (±s.d.)	BMI (kg/m^2) (±s.d.)	HbA_{1c} (%) (±s.d.)	Dose (mg)	Mean reduction in HbA_{1c} (%)	Proportion of participants achieving HbA_{1c} ≤7.0% (%)	Mean weight loss vs baseline (%)
AWARD 11 (ref. 78)	Dulaglutide (weekly, s.c.)	36	1,842 (48.8)	57.1±10.0	34.2±6.3	8.6±1.0	1.5	1.55	49.7	3.0
							3.0	1.64	55.8	NR
							4.5	1.77	62.2	4.6
SUSTAIN FORTE (ref. 79)	Semaglutide (weekly, s.c.)	40	961 (41.0)	58.0±10.0	34.6±7.0	8.9±0.6	1.0	1.9	57.5	7.0
							2.0	2.1	67.6	6.0
PIONEER PLUS (ref. 136)	Semaglutide (daily, oral)	68	535 (41.7)	58.2±10.2	33.8±6.3	9.0±0.8	14	1.5	39	4.7
							25	1.8	51	7.3
							50	2.0	63	8.5

Obesity

Trial	Intervention	Study duration (weeks)	Number of participants (% female)	Age (years) (±s.d.)[a]	BMI (kg/m^2) (±s.d.)[a]	Number of cardiovascular or metabolic complications for inclusion in study	Dose (mg)	Placebo-subtracted mean weight loss (%)[b]	Proportion of patients achieving ≥15% body weight loss (%)[b]
STEP 1 (ref. 84)	Semaglutide (weekly, s.c.)	68	1,961 (74.1)	46	37.9	≥1	2.4	12.4	50.5
STEP 5 (ref. 89)	Semaglutide (weekly, s.c.)	104	304 (77.6)	47.3	38.5	≥1	2.4	12.6	52.1
OASIS 1 (ref. 138)	Semaglutide (daily, oral)	68	667 (73)	50±13	37.5±6.5	≥1	50	12.7	54

Ansari S et al. Nat Rev Endocrinol 20:447-459, 2024

藥效持續/用藥多久問題

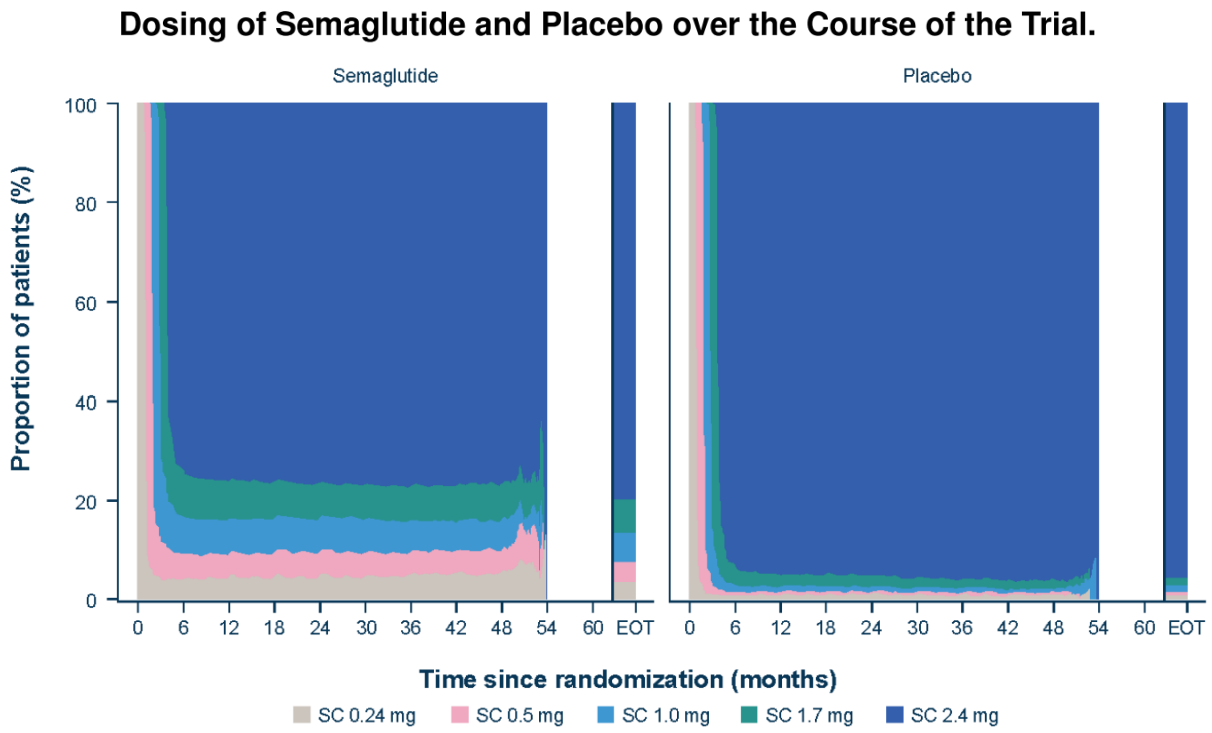
GLP-1 Receptor agonist: Semaglutide

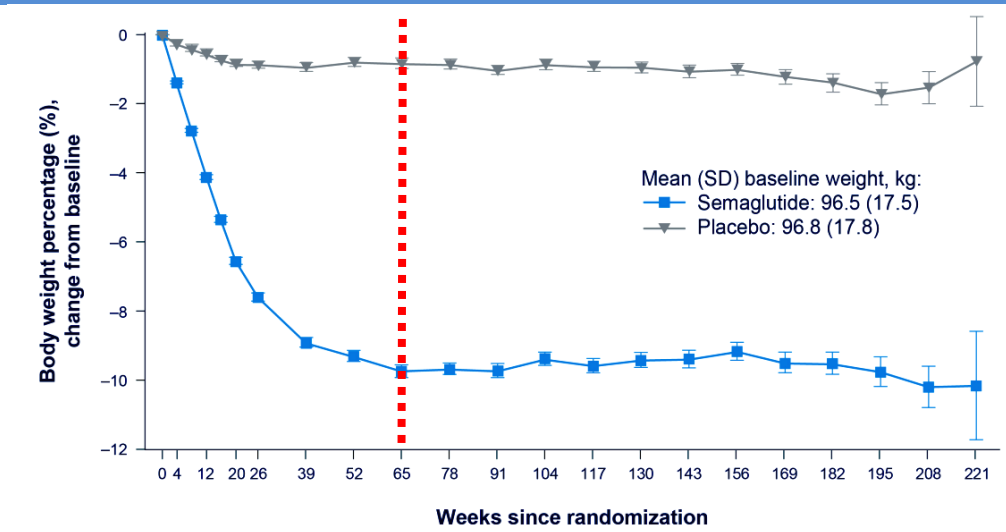
SELECT (Obesity only)

METHODS

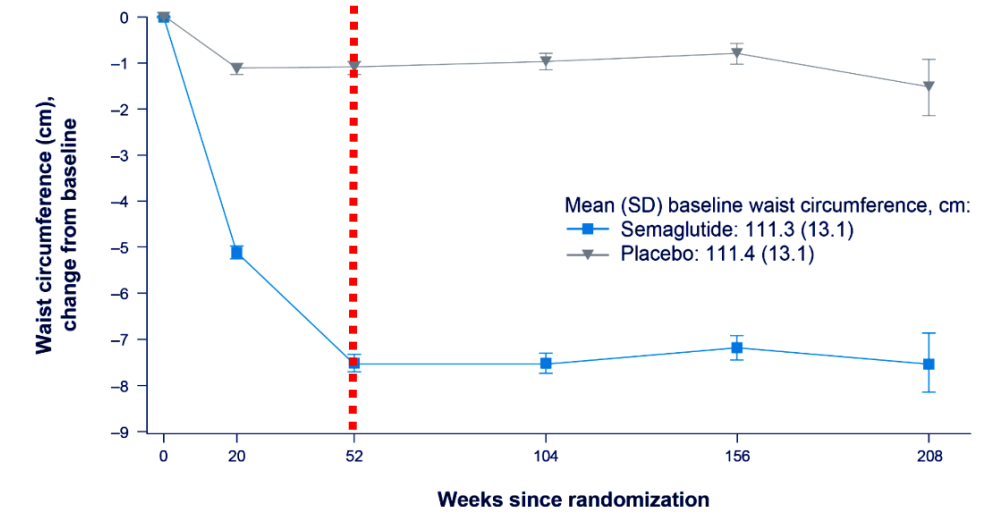
In a multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial, we enrolled patients 45 years of age or older who had preexisting cardiovascular disease and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27 or greater but no history of diabetes. Patients were randomly assigned in a 1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis. Safety was also assessed.

Lincoff AM, et al. N Engl J Med 389:2221-32, 2023





Semaglutide, N	8,803	7,647	7,493	6,690	7,290	6,447	7,282	6,460	7,474	5,991	5,898	4,686	5,085	3,650	2,954	1,737	921	157
Placebo, N	8,801	7,715	7,516	6,704	7,269	6,340	7,272	6,392	7,378	5,871	5,879	4,583	5,014	3,560	2,890	1,698	898	152



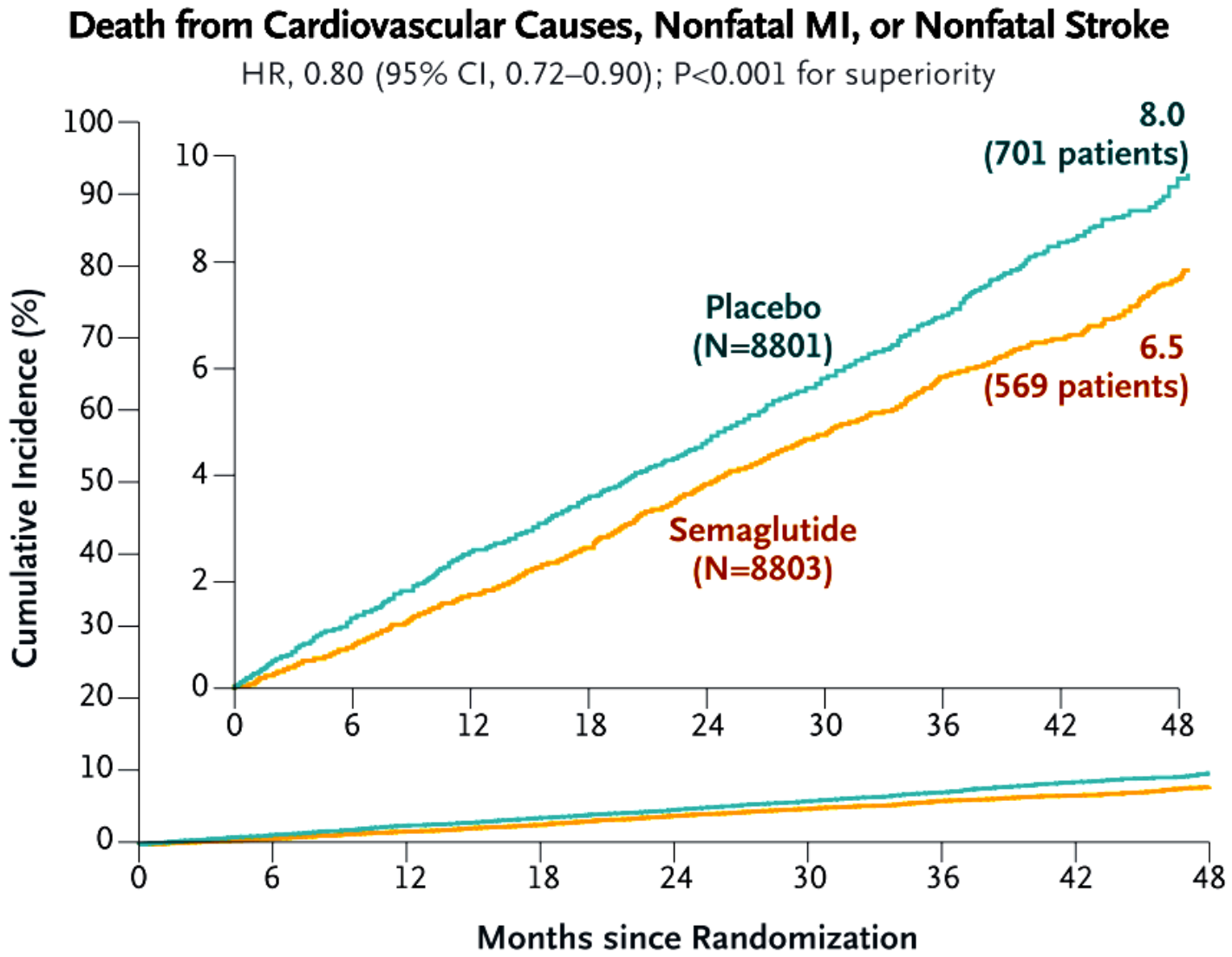
Semaglutide, N	8,759	7,507	7,193	7,373	5,013	912
Placebo, N	8,756	7,533	7,182	7,273	4,950	887

藥效持續/用藥多久問題

SELECT (Obesity only)

GLP-1 Receptor agonist: Semaglutide

Mean duration of follow-up 39.8±9.4 months.



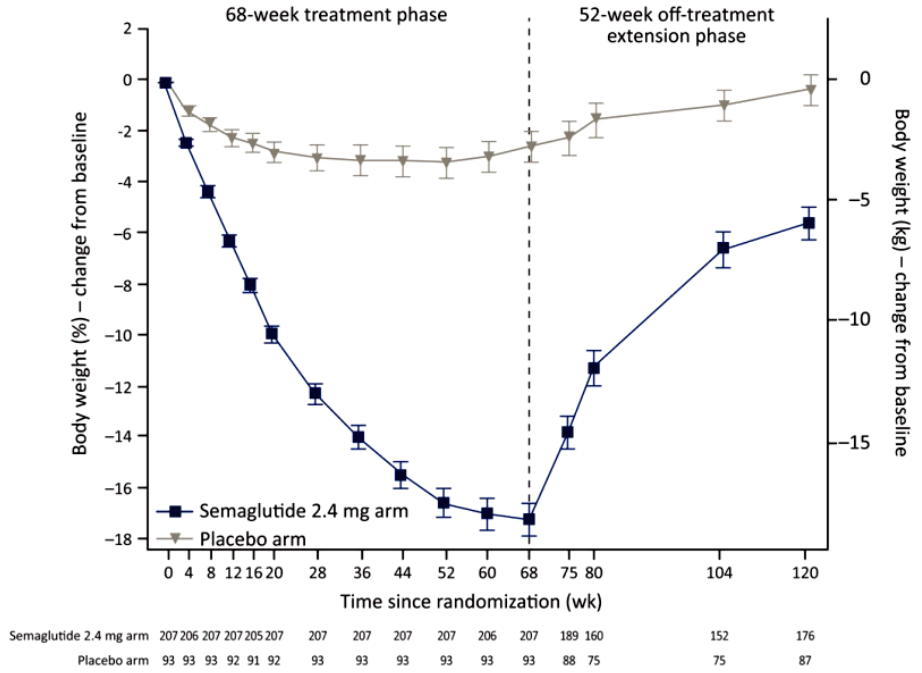
Lincoff AM, et al. N Engl J Med 389:2221-32, 2023

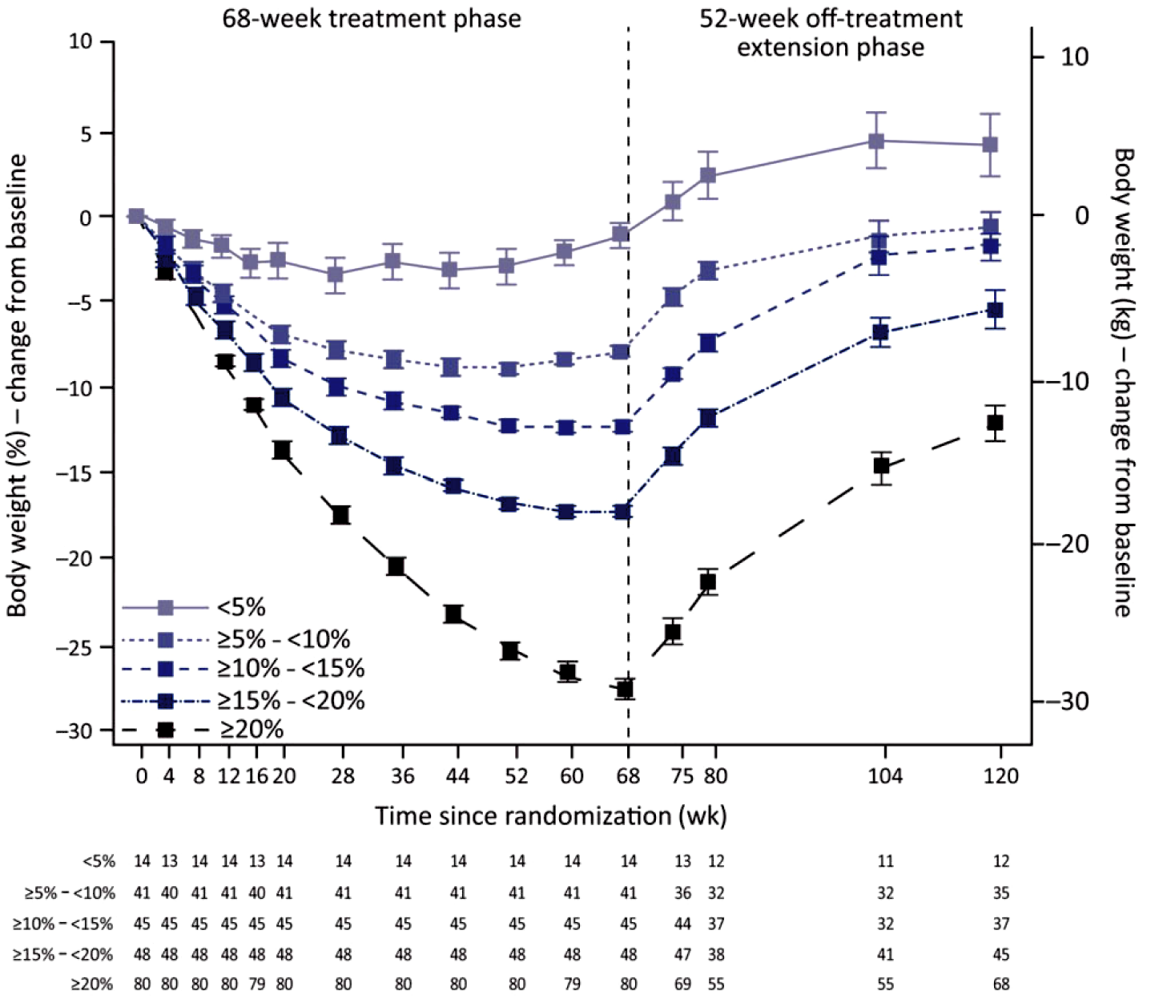
Is Semaglutide Another Yo-Yo Diet?

Unfortunately, semaglutide can end up being a yo-yo diet if you are not careful!!!

STEP 1 extension (Obesity only)

Materials and Methods: STEP 1 (NCT03548935) randomized 1961 adults with a body mass index ≥ 30 kg/m^2 (or ≥ 27 kg/m^2 with ≥ 1 weight-related co-morbidity) without diabetes to 68 weeks of once-weekly subcutaneous semaglutide 2.4 mg (including 16 weeks of dose escalation) or placebo, as an adjunct to lifestyle intervention. At week 68, treatments (including lifestyle intervention) were discontinued.

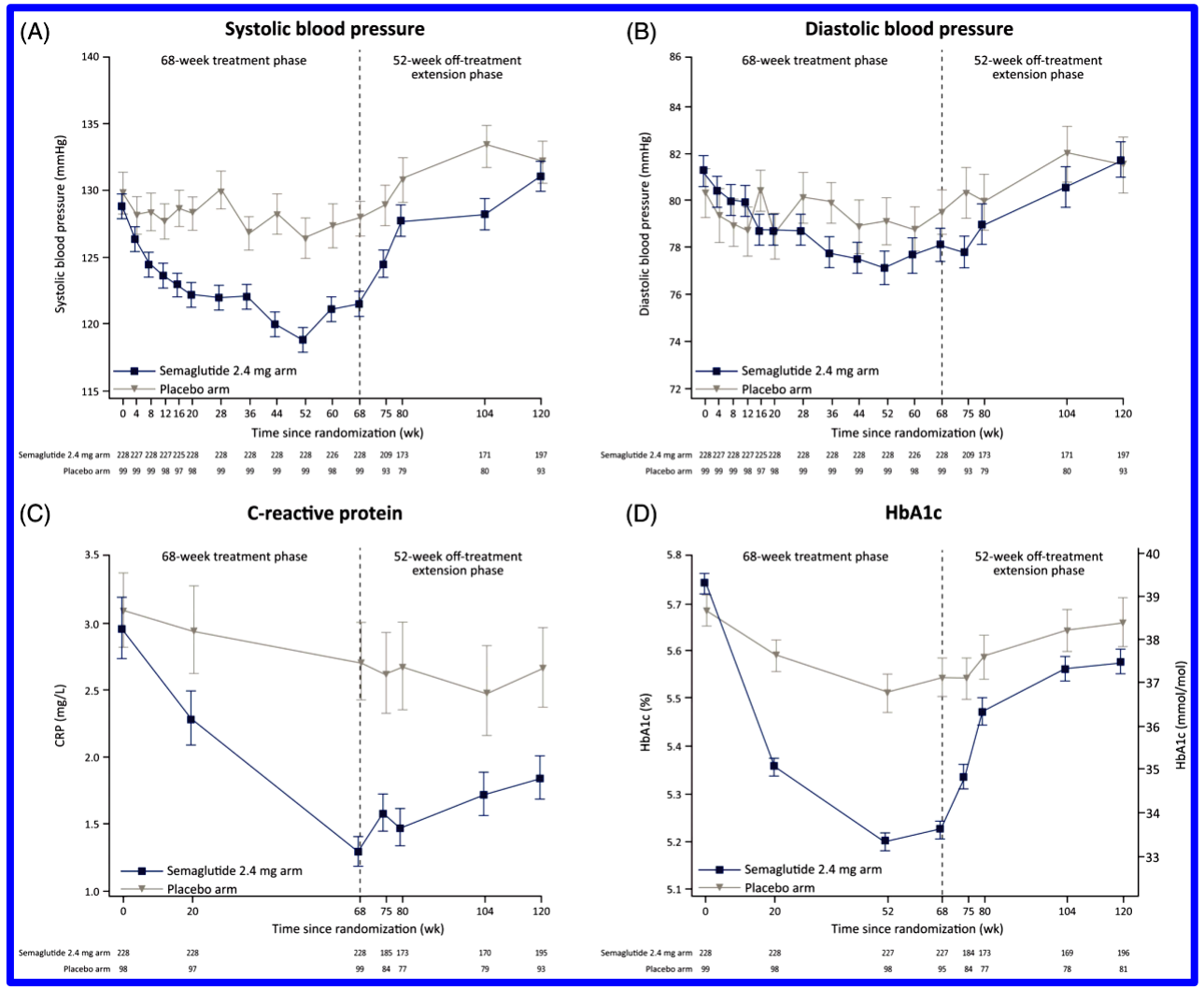


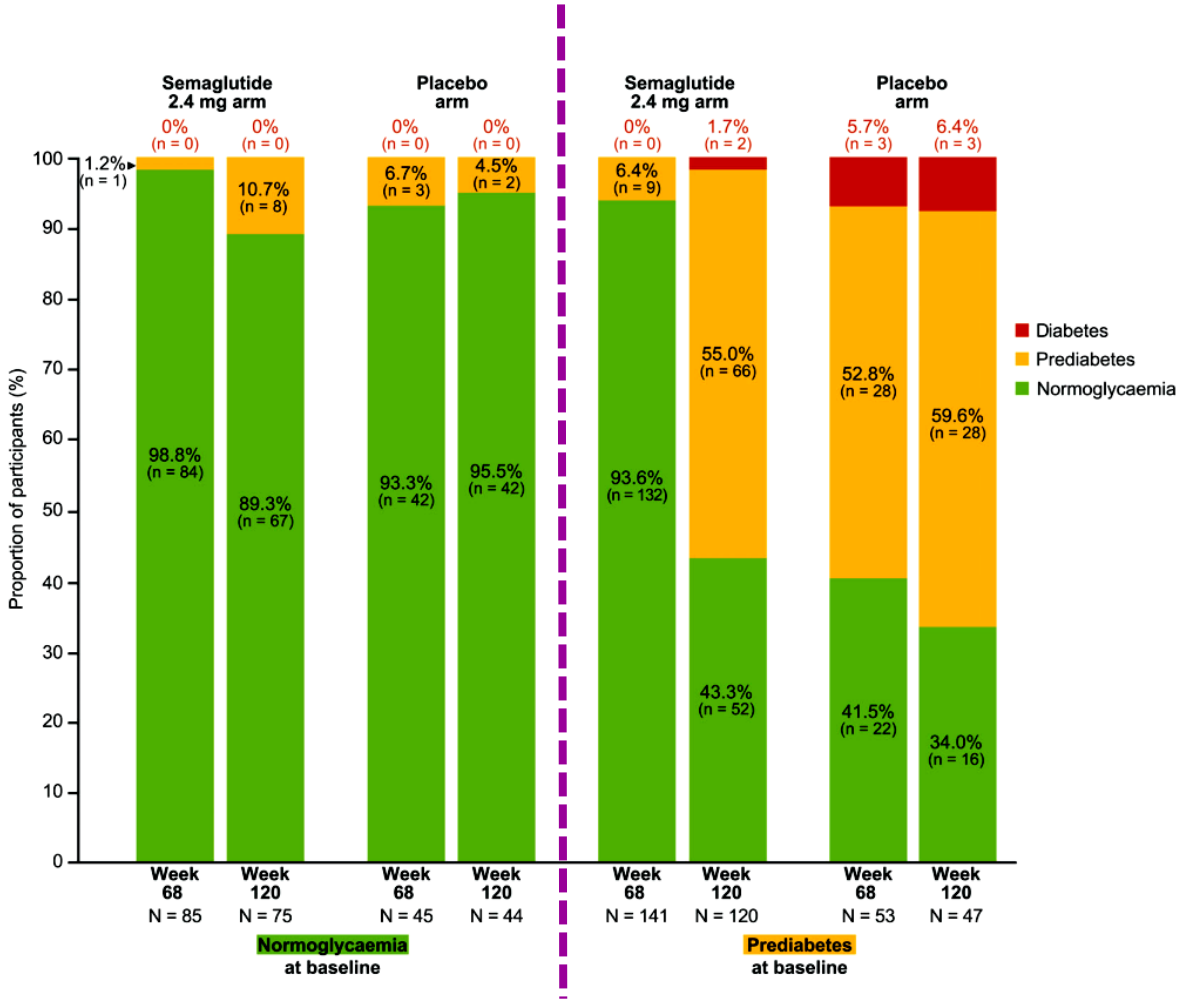


Wilding JPH, et al. Diabetes Obes Metab. 24:1553-1564, 2022

Is Semaglutide Another Yo-Yo Diet?

Unfortunately, semaglutide can end up being a yo-yo diet if you are not careful!!!





Wilding JPH, et al. Diabetes Obes Metab. 24:1553-1564, 2022

Mechanisms of Weight Regain After Semaglutide

1. Metabolic Adaptation and Hormonal Changes
2. The Muscle Mass Effect: Weight loss contributes to the loss of significant weight loss, resulting in:
   - Limited Caloric Burn: Muscle burns greater calories than fat when energy is stored (i.e. when there is no activity).
   - Limited muscle mass reduces energy usage.
   - Less Activity: Less muscle mass often decreases exercise levels, further reducing caloric expenditure.

What You Need to Do to Stop Weight Regain After Taking Semaglutide?

1. Moderate Your Carbohydrates
2. Make a Plan to Move More
3. Make Sleep a Priority
4. Intermittent Fasting
5. Find Foods That Fill You Up
6. Focus on Health, Not on Weight

Posted by Dr. MK Mazaheri | Updated: June 14th, 2024 Published: September 19, 2023
https://drmazaheri.com/how-to-stop-rebound-weight-gain-after-taking-semaglutide/

SCALE Kids Trial (Obesity only)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide for Children 6 to <12 Years of Age with Obesity — A Randomized Trial

BACKGROUND

No medications are currently approved for the treatment of nonmonogenic, nonsyndromic obesity in children younger than 12 years of age. Although the use of liraglutide has been shown to induce weight loss in adults and adolescents with obesity, its safety and efficacy have not been established in children.

METHODS

In this phase 3a trial, which consisted of a 56-week treatment period and a 26-week follow-up period, we randomly assigned children (6 to <12 years of age) with obesity, in a 2:1 ratio, to receive either once-daily subcutaneous liraglutide at a dose of 3.0 mg (or the maximum tolerated dose) or placebo, plus lifestyle interventions. The primary end point was the percentage chanfge in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters). The confirmatory secondary end points were the percentage change in body weight and a reduction in BMI of at least 5%.

RESULTS

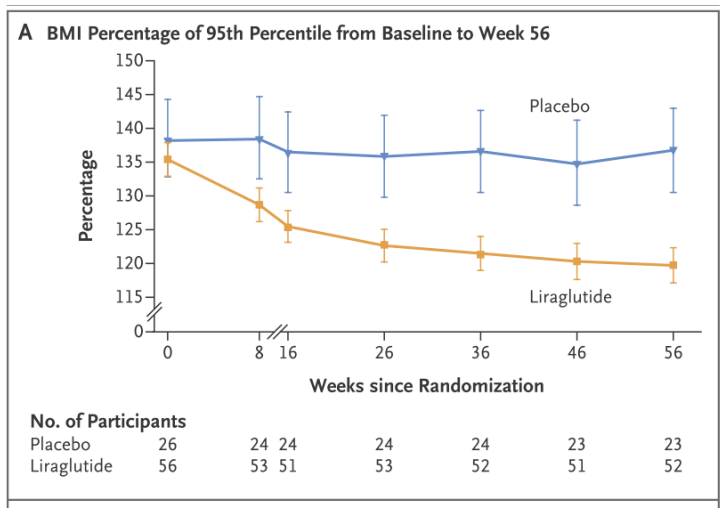
A total of 82 participants underwent randomization; 56 were assigned to the liraglutide group and 26 to the placebo group. At week 56, the mean percentage change from baseline in BMI was –5.8% with liraglutide and 1.6% with placebo, representing an estimated difference of –7.4 percentage points (95% confidence interval [CI], –11.6 to –3.2; P<0.001). The mean percentage change in body weight was 1.6% with liraglutide and 10.0% with placebo, representing an estimated difference of –8.4 percentage points (95% CI, –13.4 to –3.3; P=0.001), and a reduction in BMI of at least 5% occurred in 46% of participants in the liraglutide group and in 9% of participants in the placebo group (adjusted odds ratio, 6.3 [95% CI, 1.4 to 28.8]; P=0.02). Adverse events occurred in 89% and 88% of participants in the liraglutide and placebo groups, respectively. Gastrointestinal adverse events were more common in the liraglutide group (80% vs. 54%); serious adverse events were reported in 12% and 8% of participants in the liraglutide and placebo groups, respectively.

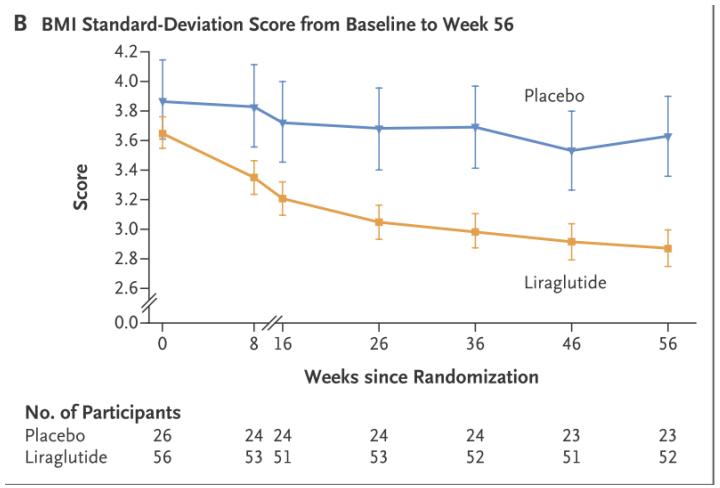
CONCLUSIONS

Among children (6 to <12 years of age) with obesity, treatment with liraglutide for 56 weeks plus lifestyle interventions resulted in a greater reduction in BMI than placebo plus lifestyle interventions. (Funded by Novo Nordisk; SCALE Kids ClinicalTrials.gov number, NCT04775082.)

Table 2. End Points at Week 56 (Treatment Policy Estimand).*

End Point	Liraglutide (N=56)	Placebo (N=26)	Difference (95% CI)	P value
Primary end point				
Percentage change in BMI	–5.8	1.6	–7.4 (–11.6 to –3.2)	<0.001
Confirmatory secondary end points				
Percentage change in body weight	1.6	10.0	–8.4 (–13.4 to –3.3)	0.001
BMI reduction of ≥5% — % of participants	46	9	6.3 (1.4 to 28.8)†	0.02
Supportive secondary end points				
Change in body weight — kg	1.1	7.1	–6.0 (–9.3 to –2.7)	
Change in BMI percentage of 95th percentile — percentage points‡	–14.0	–4.0	–10.0 (–15.1 to –4.8)	
Change in BMI standard-deviation score	–0.7	–0.3	–0.4 (–0.6 to –0.2)	
BMI reduction of ≥10% — % of participants	35	4	8.2 (1.0 to 65.3)†	
Change in waist circumference — cm	–2.0	1.3	–3.4 (–9.4 to 2.7)	
Change in blood pressure — mm Hg				
Systolic	–1.7	1.7	–3.4 (–8.9 to 2.0)	
Diastolic	–1.2	3.0	–4.2 (–8.4 to 0.0)	
Change in glycated hemoglobin level — %	–0.2	–0.1	–0.1 (–0.2 to 0.0)	





Fox CK, et al. N Engl J Med 392: 555-565, 2025

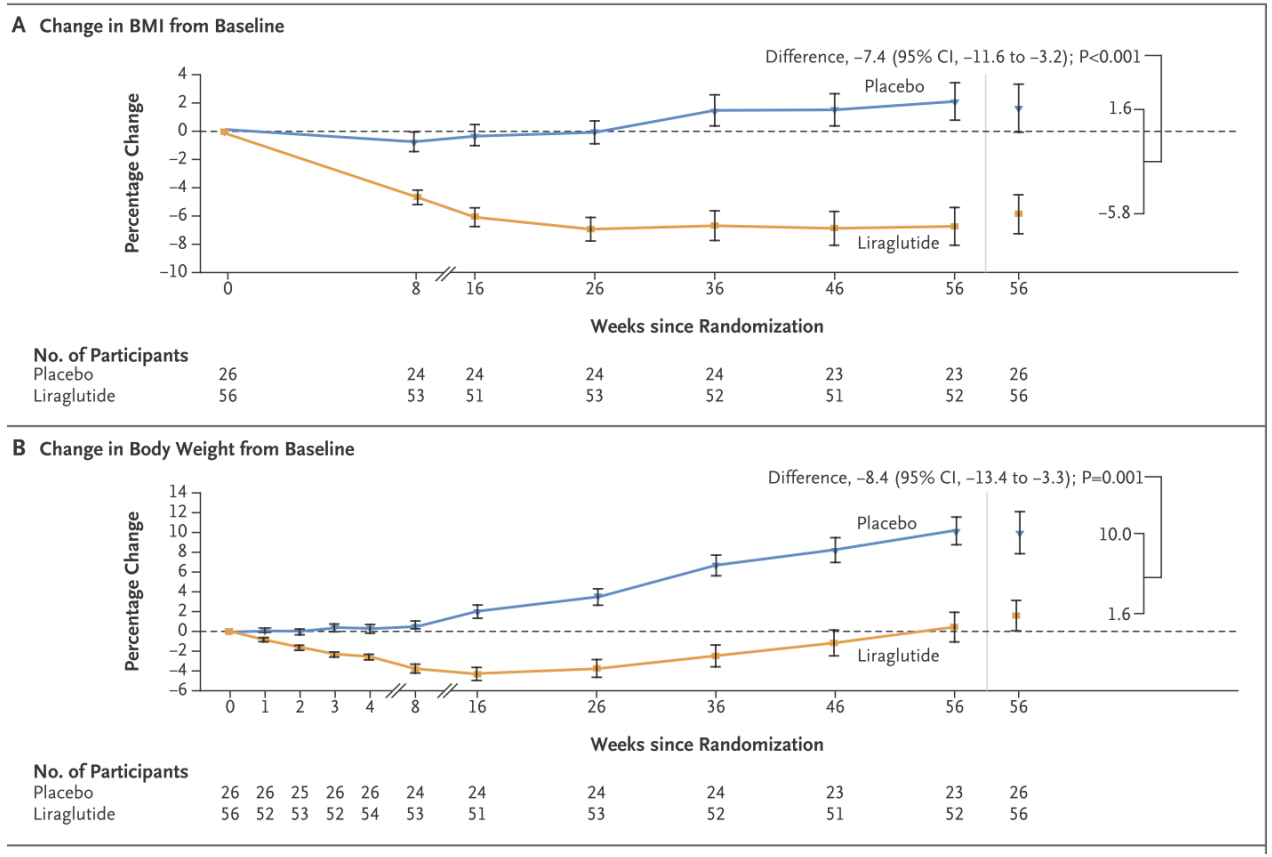
SCALE Kids Trial (Obesity only)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide for Children 6 to <12 Years of Age with Obesity — A Randomized Trial

full analysis



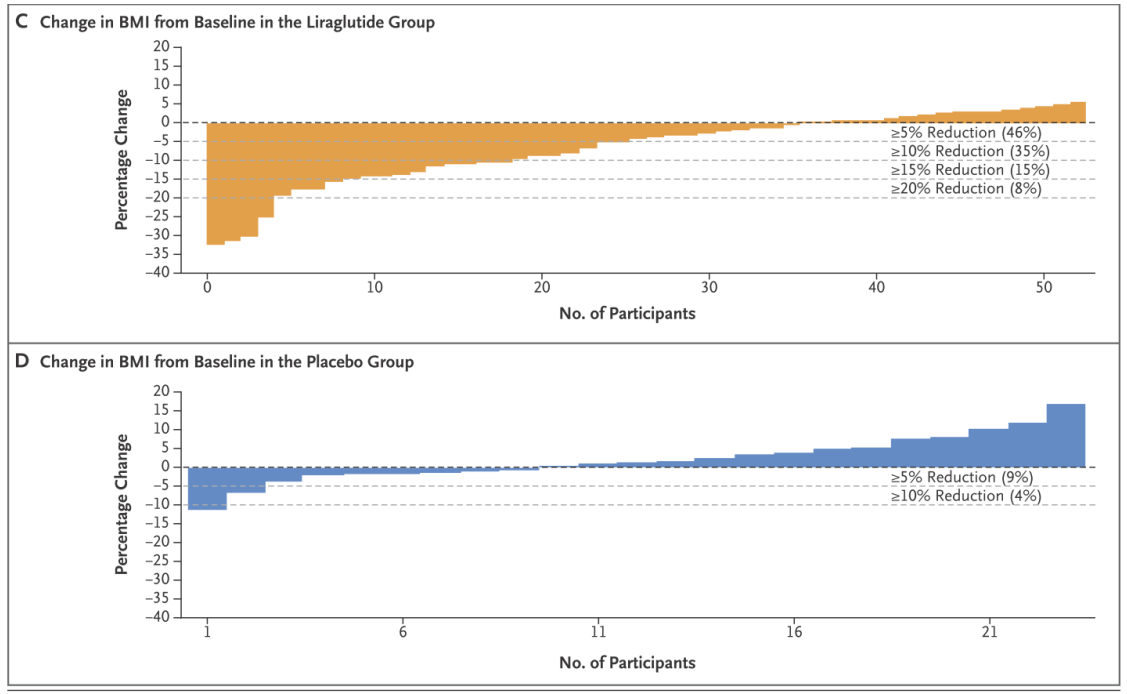


Table 3. Adverse Events.*

Event	Liraglutide (N=56) %	Liraglutide (N=56) no. of events	Liraglutide (N=56) events/100 person-yr	Placebo (N=26) %	Placebo (N=26) no. of events	Placebo (N=26) events/100 person-yr
Adverse event						
Any	89	50	801.1	88	23	582.7
Gastrointestinal	80	45	428.1	54	14	156.9
Serious adverse event						
Any	12	7	22.0	8	2	7.5
Gastrointestinal	7	4	9.2	0	0	0
Adverse event leading to treatment discontinuation†						
Any	11	6	11.0	0	0	0
Gastrointestinal	5	3	5.5	0	0	0
Fatal adverse event	0	0	0	0	0	0

Fox CK, et al. N Engl J Med 392: 555-565, 2025

GIP/GLP-1 Receptor Coagonist: Tirzepatide

Chavda VP, et al. Molecules 27:4315, 2022

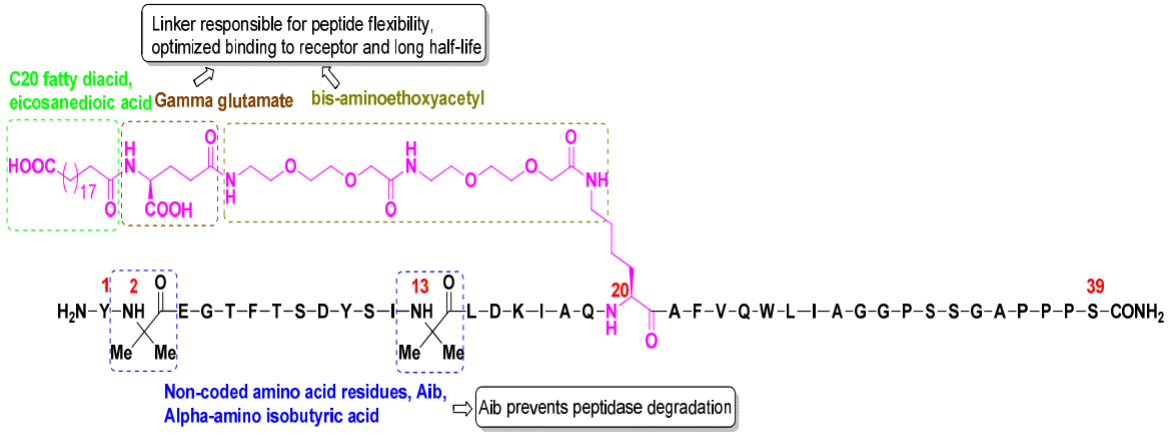
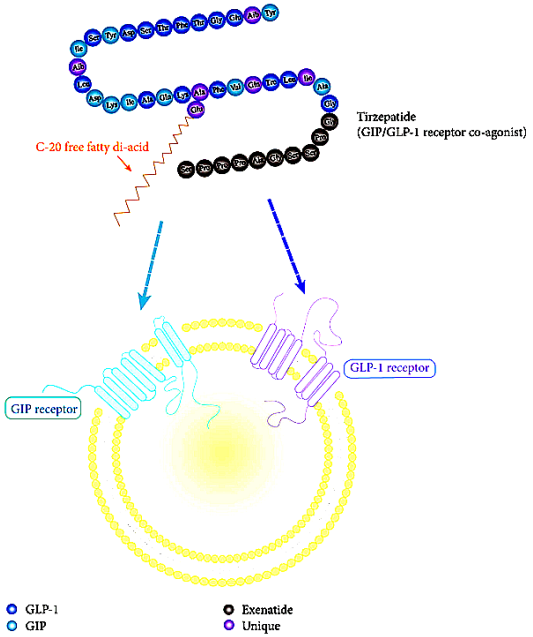


Figure 2. Structural features of tirzepatide, amino acids are denoted as single-letter codes.



Ma Z, et al. J Diabetes Res 2023:5891532, 2023

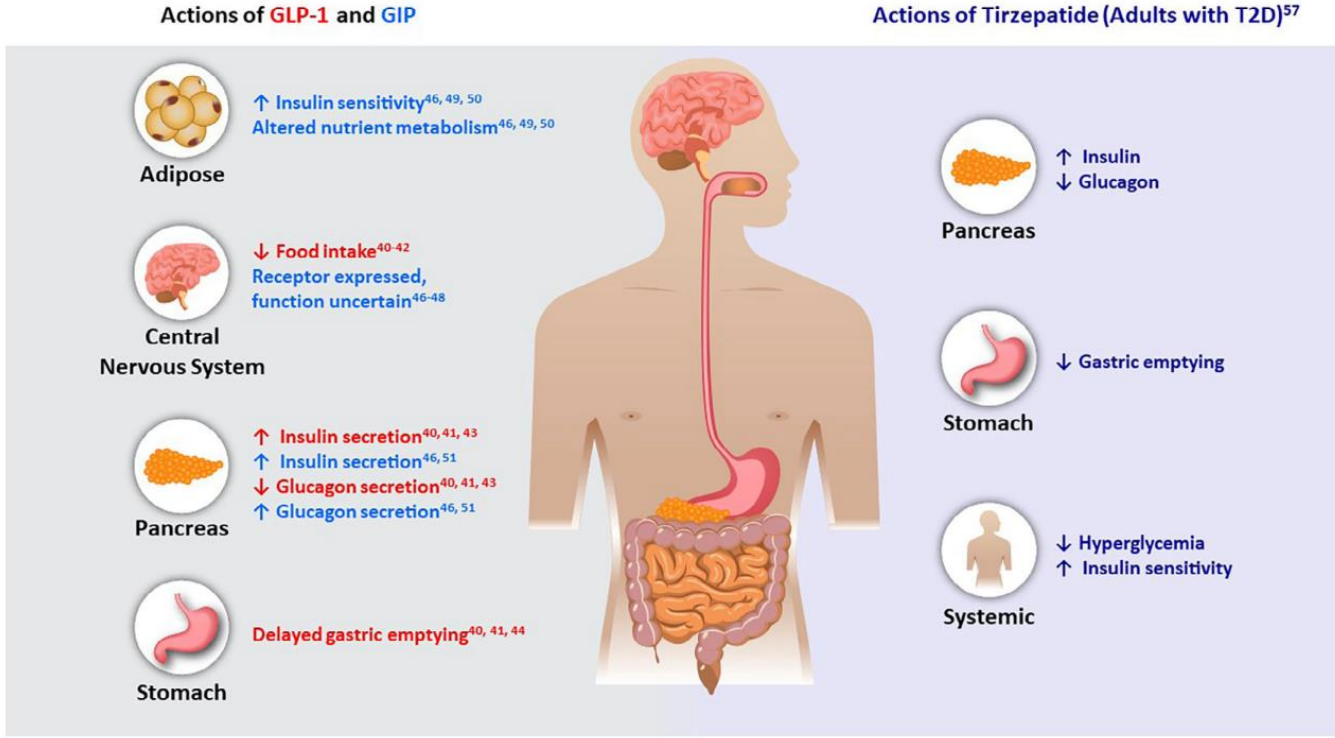


FIGURE 1 Gluco-regulatory actions of GIP and GLP-1 proposed based on preclinical and clinical studies, and actions of tirzepatide in adults with type 2 diabetes. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes

De Block C, et al. Diabetes Obes Metab 25: 3-17, 2023

GIP/GLP-1 Receptor Coagonist: Tirzepatide

Tirzepatide binds with high affinity to human GLP-1 and GIP receptors expressed on transfected HEK293 cells.[54]

Binding affinity [Ki +/−SEM (nM)]

- GIP receptors: 0.135 +/−0.020
- GLP-1 receptors: 4.23 +/−0.23

Tirzepatide potently stimulates cAMP accumulation by human GLP-1 and GIP receptors expressed on transfected HEK293 cells.[54]

Intracellular cAMP accumulation [EC_{50} +/−SEM (nM)]

- GIP receptors: 0.0224 +/−0.0053
- GLP-1 receptors: 0.934 +/−0.068

Tirzepatide stimulated cAMP accumulation in differentiated human adipocytes that express GIP receptors but not GLP-1 receptors. The effect was comparable with that of GIP alone.[54]

Pharmacokinetics below are average values from healthy single ascending dose cohorts administered 0.25-8.0 mg doses subcutaneously. Pharmacokinetics in healthy participants are comparable with those with type 2 diabetes[54]

- Geometric mean maximum observed drug concentration (C_{max}) for 5.0 mg: 397 ng/ml
  - Intersubject variability for C_{max} ≤30% across doses
- $t_{1/2}$: ~5 days
- CL/F: 0.056 L/h
- Vz/F: 9.5 L

Pharmacokinetics appear dose proportional, C_{max} reached within 24-48 h post-dose.

Average accumulation following four weekly doses: 1.58.

Tirzepatide delays gastric emptying; e greatest after 1 dose and undergoes tachyphylaxis with repeated once-weekly dosing.[64]

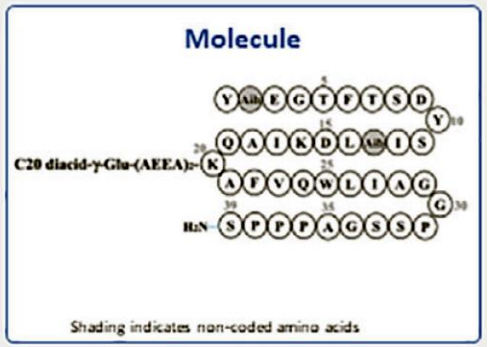
Intrinsic factors

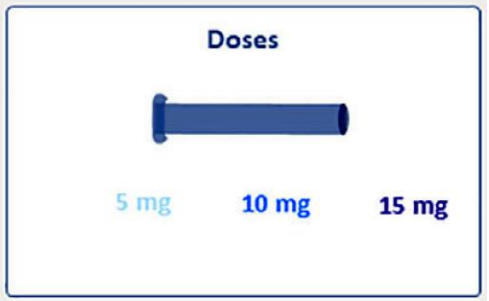
- no clinically meaningful effect of renal or hepatic impairment[62,63];
- dose adjustment may not be required in patients with renal impairment;
- dose adjustment may not be required in patients with hepatic impairment.

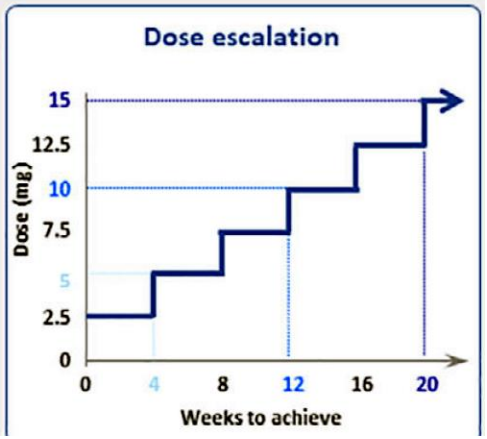
De Block C, et al. Diabetes Obes Metab 25: 3-17, 2023

GIP/GLP-1 Receptor Coagonist: Tirzepatide

	Monotherapy	2-Drug Combination	2-3 Drug Combinations	2-4 Drug Combinations	Combination With Insulin
	SURPASS-1	SURPASS-2	SURPASS-3	SURPASS-4	SURPASS-5
Population	Inadequately controlled by diet and exercise alone. Recently diagnosed patients	Inadequately controlled with metformin ≥1500 mg/day	Insulin-naïve, inadequately controlled with metformin ± SGLT-2i	Receiving ≥1 to ≤3 OAMs. Reflective of higher comorbidity burden and CV risk	Receiving titrated insulin glargine ± metformin
Add-on to	Drug-naïve or washout from any OAM	Metformin	Metformin ± SGLT-2i	Any combination of metformin, SGLT-2i, or SU	Insulin glargine ± metformin
Comparator	Placebo	Semaglutide 1 mg	Insulin degludec (titrated to fasting blood glucose <90 mg/dL)	Insulin glargine 100 U/mL (titrated to fasting blood glucose <100 mg/dL)	Placebo
Baseline Characteristics					
Diabetes duration, y	4.7	8.6	8.4	11.8	13.3
HbA1c, (%)	7.94	8.28	8.17	8.52	8.31
BMI, kg/m²	31.9	34.2	33.5	32.6	33.4
Medication use (%)					
Metformin	-	100	100	94.9	82.9
SGLT-2i	-	-	31.9	25.1	-
SU	-	-	-	54.5	-







De Block C, et al. Diabetes Obes Metab 25: 3-17, 2023

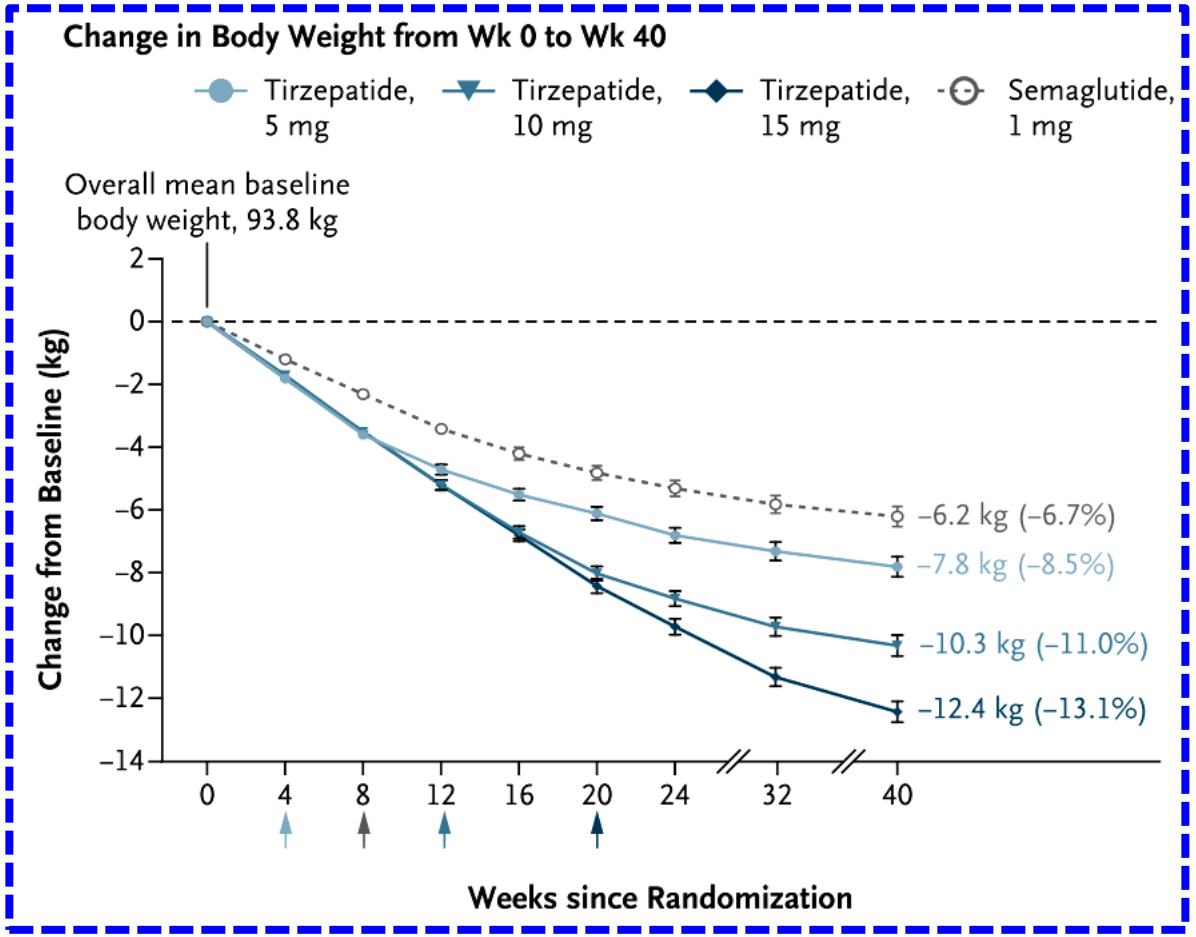
藥效持續/用藥多久問題

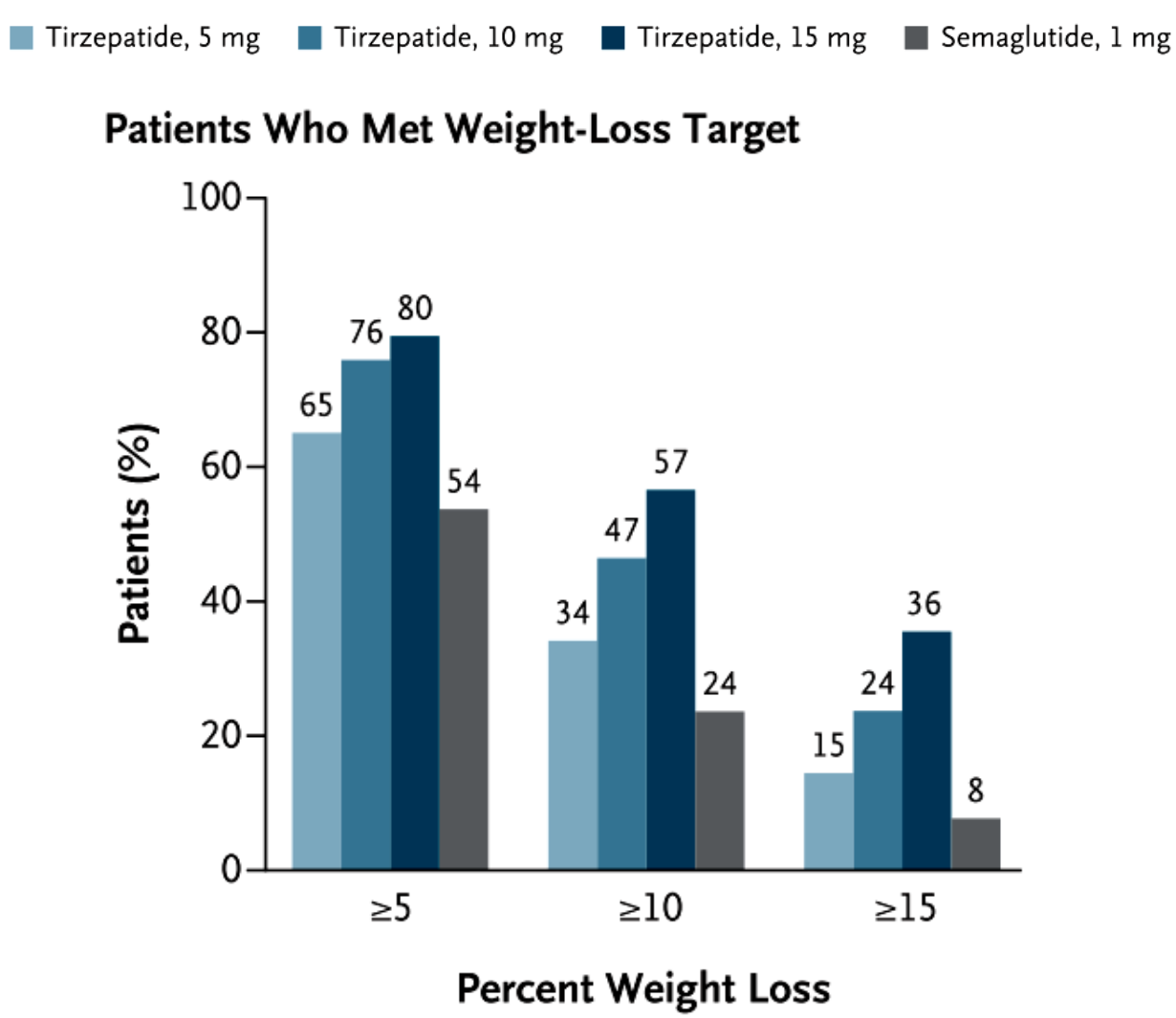
GIP/GLP-1 Receptor Coagonist: Tirzepatide

SURPASS-2 (T2DM only)

METHODS

In an open-label, 40-week, phase 3 trial, we randomly assigned 1879 patients, in a 1:1:1:1 ratio, to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg. At baseline, the mean glycated hemoglobin level was 8.28%, the mean age 56.6 years, and the mean weight 93.7 kg. The primary end point was the change in the glycated hemoglobin level from baseline to 40 weeks.





Frías JP, et al. N Engl J Med 385:503-15, 2021

SURMOUNT-5 (Obesity only)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide as Compared with Semaglutide for the Treatment of Obesity

BACKGROUND

Tirzepatide and semaglutide are highly effective medications for obesity management. The efficacy and safety of tirzepatide as compared with semaglutide in adults with obesity but without type 2 diabetes is unknown.

METHODS

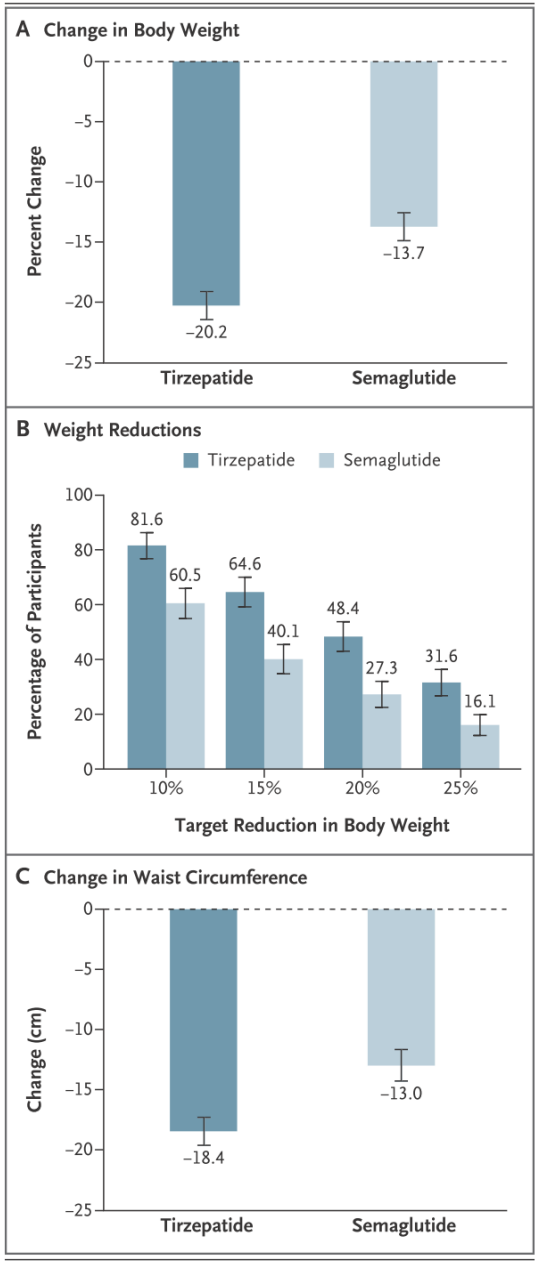
In this phase 3b, open-label, controlled trial, adult participants with obesity but without type 2 diabetes were randomly assigned in a 1:1 ratio to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. The primary end point was the percent change in weight from baseline to week 72. Key secondary end points included weight reductions of at least 10%, 15%, 20%, and 25% and a change in waist circumference from baseline to week 72.

RESULTS

A total of 751 participants underwent randomization. The least-squares mean percent change in weight at week 72 was –20.2% (95% confidence interval [CI], –21.4 to –19.1) with tirzepatide and –13.7% (95% CI, –14.9 to –12.6) with semaglutide (P<0.001). The least-squares mean change in waist circumference was –18.4 cm (95% CI, –19.6 to –17.2) with tirzepatide and –13.0 cm (95% CI, –14.3 to –11.7) with semaglutide (P<0.001). Participants in the tirzepatide group were more likely than those in the semaglutide group to have weight reductions of at least 10%, 15%, 20%, and 25%. The most common adverse events in both treatment groups were gastrointestinal, and most were mild to moderate in severity and occurred primarily during dose escalation.

CONCLUSIONS

Among participants with obesity but without diabetes, treatment with tirzepatide was superior to treatment with semaglutide with respect to reduction in body weight and waist circumference at week 72. (Funded by Eli Lilly; SURMOUNT-5 ClinicalTrials.gov number, NCT05822830.)



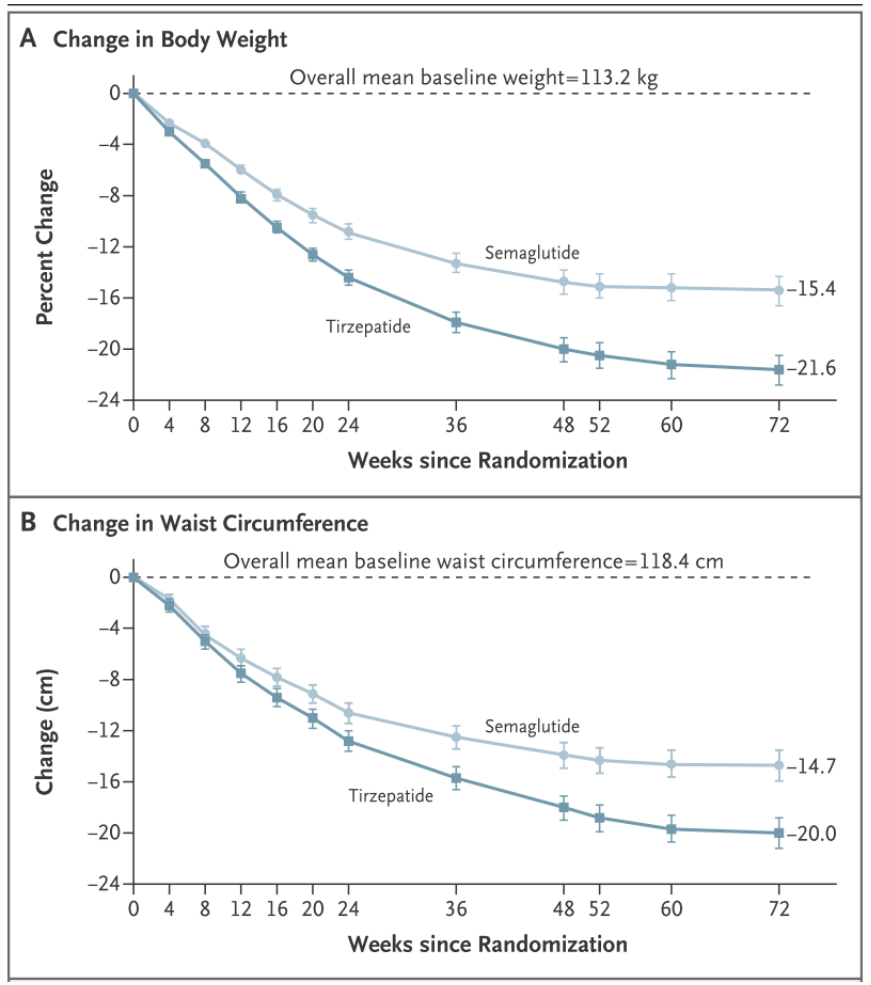


Figure 2. Change in Body Weight and Waist Circumference from Baseline to Week 72 (Efficacy Estimand).

Shown are the least-squares mean percent changes in body weight (Panel A) and the least-squares mean changes in waist circumference (Panel B) according to weeks since randomization. Values were derived with the use of a mixed-model-for-repeated-measures analysis for the efficacy estimand (described in the Supplementary Appendix). I bars indicate 95% confidence intervals.

Aronne LJ, et al. N Engl J Med 393:26-36, 2025

SURMOUNT-5 (Obesity only)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide as Compared with Semaglutide for the Treatment of Obesity

Overall, 85.0% of the participants completed the trial (85.1% in the tirzepatide group and 84.8% in the semaglutide group) and 80.2% completed the 72 weeks of trial treatment (81.6% in the tirzepatide group and 78.7% in the semaglutide group). The trial treatment was discontinued because of adverse events by 6.1% of the participants in the tirzepatide group and 8.0% of those in the semaglutide group. In the tirzepatide group, 89.3% of the participants received at least one 15-mg dose, and in the semaglutide group, 92.8% received at least one 2.4-mg dose.

Table 3. Adverse Events and Safety.*

Variable	Tirzepatide (N=374)	Semaglutide (N=376)	Total (N=750)
	number of participants (percent)		
Adverse events that occurred or worsened during the treatment period	287 (76.7)	297 (79.0)	584 (77.9)
Serious adverse events	18 (4.8)	13 (3.5)	31 (4.1)
Adverse events leading to death	0	0	0
Discontinuation from the trial because of adverse events	6 (1.6)	6 (1.6)	12 (1.6)
Discontinuation of the trial treatment because of adverse events	23 (6.1)	30 (8.0)	53 (7.1)
Discontinuation of the trial treatment because of gastrointestinal adverse events	10 (2.7)	21 (5.6)	31 (4.1)
Adverse events occurring in ≥5% of participants in either group†			
Nausea	163 (43.6)	167 (44.4)	330 (44.0)
Constipation	101 (27.0)	107 (28.5)	208 (27.7)
Diarrhea	88 (23.5)	88 (23.4)	176 (23.5)
Vomiting	56 (15.0)	80 (21.3)	136 (18.1)
Coronavirus disease 2019	51 (13.6)	47 (12.5)	98 (13.1)
Fatigue	39 (10.4)	46 (12.2)	85 (11.3)
Eructation	37 (9.9)	29 (7.7)	66 (8.8)
Injection-site reaction	32 (8.6)	1 (0.3)	33 (4.4)
Upper respiratory tract infection	32 (8.6)	43 (11.4)	75 (10.0)
Alopecia	31 (8.3)	23 (6.1)	54 (7.2)
Abdominal distention	27 (7.2)	24 (6.4)	51 (6.8)
Headache	27 (7.2)	27 (7.2)	54 (7.2)
Abdominal pain	24 (6.4)	26 (6.9)	50 (6.7)
Dizziness	24 (6.4)	18 (4.8)	42 (5.6)
Gastroesophageal reflux disease	23 (6.1)	40 (10.6)	63 (8.4)
Dyspepsia	22 (5.9)	28 (7.4)	50 (6.7)
Decreased appetite	17 (4.5)	19 (5.1)	36 (4.8)
Nasopharyngitis	17 (4.5)	23 (6.1)	40 (5.3)
Sinusitis	11 (2.9)	21 (5.6)	32 (4.3)
Adverse events leading to discontinuation of the trial treatment‡			
Nausea	5 (1.3)	7 (1.9)	12 (1.6)
Vomiting	3 (0.8)	4 (1.1)	7 (0.9)
Constipation	1 (0.3)	2 (0.5)	3 (0.4)
Diarrhea	1 (0.3)	2 (0.5)	3 (0.4)
Fatigue	1 (0.3)	1 (0.3)	2 (0.3)
Cholelithiasis	0	2 (0.5)	2 (0.3)

Aronne LJ, et al. N Engl J Med 393:26-36, 2025

降糖試驗 (T2D only)

ARTICLE

Check for updates

Dose–response effects on HbA_{1c} and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial

Methods This Phase II, multicentre, randomised, double-blind, parallel-group, placebo-controlled study, conducted in clinical research centres, assessed survodutide in participants aged 18–75 years with type 2 diabetes, an HbA_{1c} level of 53–86 mmol/mol (7.0–10.0%) and a BMI of 25–50 kg/m^2 on a background of metformin therapy. Participants were randomised via interactive response technology to receive survodutide (up to 0.3, 0.9, 1.8 or 2.7 mg once weekly [qw; dose group (DG) 1–4, respectively] or 1.2 or 1.8 mg twice weekly [DG 5 and 6, respectively]), placebo or semaglutide (up to 1.0 mg qw). Participants and all those involved in the trial conduct/analysis were blinded; the semaglutide arm was open-label. The primary endpoint was absolute change from baseline in HbA_{1c} after 16 weeks' treatment. The key secondary endpoint was relative change from baseline in bodyweight after 16 weeks' treatment.

Research in context

What is already known about this subject?

- Glucagon-like peptide-1 receptor (GLP-1R) agonists are approved for the treatment of type 2 diabetes and obesity
- Glucagon receptor (GCGR) agonism can increase energy expenditure and lipolysis
- GCGR/GLP-1R dual agonists can reduce bodyweight by reducing food intake and increasing energy expenditure and may be more efficacious than GLP-1R mono-agonists

What is the key question?

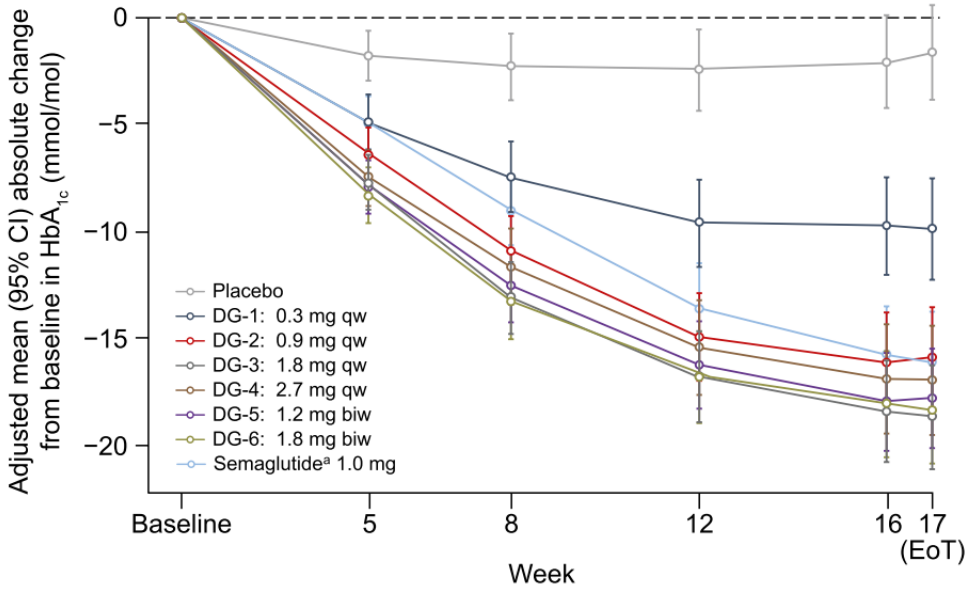
- Are multiple rising doses of the GCGR/GLP-1R dual agonist survodutide tolerated and efficacious in participants with type 2 diabetes compared with placebo or open-label semaglutide?

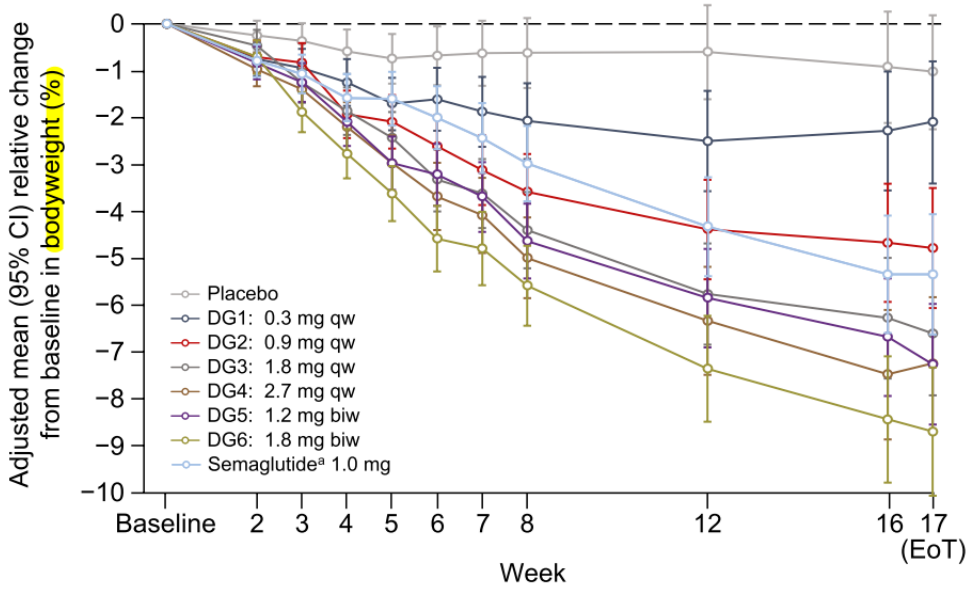
What are the new findings?

- After 16 weeks, survodutide produced greater HbA_{1c} and bodyweight reductions than placebo or semaglutide
- High dose survodutide (≥1.2 mg twice weekly) reduced bodyweight by ≥5% in >50% of participants and by ≥10% in >25% of participants
- The survodutide tolerability profile was as expected for the mechanism of action; gastrointestinal-related adverse events were most frequently reported

How might this impact on clinical practice in the foreseeable future?

- GCGR/GLP-1R dual agonism shows potential for greater therapeutic efficacy than GLP-1R mono-agonism, supporting the development of survodutide for the treatment of type 2 diabetes and obesity





Blüher M, et al. Diabetologia 67:470-482, 2024

Evaluating the efficacy and safety of survodutide for obesity: a systematic review and meta-analysis of randomized controlled trials

Table 2. Summary of the included studies

Study ID	Roux 2024[15]	Yazawa 2023[16]	Jungnik 2022[17]	Blüher 2023[18]
Phase (NCT number)	Phase 2 (NCT04667377)	Phase I (NCT04384081)	Phase 1b (NCT03591718)	NCT04153929
Sample size	384	36	125	411
Country	USA, Australia, Belgium, Canada, China, Germany, South Korea, Netherlands, New Zealand, Poland, Sweden, and UK	Japan	Germany	Germany
Treatment doses (mg)	0.6, 2.4, 3.6, 4.8	1.8, 4.8	Multiple rising doses	0.3 qw, 0.9 qw, 1.8 qw, 2.[illegible] qw, 1.2 biw, 1.8 biw
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Frequency of administration	Once weekly	Once weekly, twice weekly	Once weekly	Once weekly, twice weekly
Treatment duration	46 weeks	16 weeks	Part A: 6 weeks; Part B: 16 weeks	16 weeks
Follow-up duration	3 weeks			4 weeks
Main inclusion criteria	Adults (≥18 to <75 years) with a BMI ≥ 27 kg/m^2, a stable body weight ≥ 70 kg (females) or ≥80 kg (males), and with HbA1c < 6.5% (without diabetes) at screening	Men 20 to 45 years, with a BMI of 23–40 kg/m^2, stable (≤5% change within 3 months) body weight of ≥65 kg, and glycated hemoglobin (HbA1c) < 6.5%	Adults (18–70 years) with a BMI of 27–40 kg/m^2 and stable body weight (≤5% change within 3 months prior to screening) of ≥70 kg (females) or ≥80 kg (males)	Adults 18–75 years, diagnosed with type 2 diabetes for ≥6 months, had HbA1c value of 53–86 mmol/mol (7.0–10.0%) and a BMI of 25–50 kg/m^2 at screening, treated with a stable dose of metformin of ≥1000 mg/day (immediate or extended-release) for ≥3 months before screening; exclusion criteria listed in the Methods
Conclusion	All tested survodutide doses significantly reduced body weight in a dose-dependent manner relative to placebo in participants with a BMI ≥27 kg/m^2	No unexpected tolerability concerns; reduced placebo-corrected body weight by up to 12.37% in Japanese men with overweight/obesity after 16 weeks of treatment	Produced a placebo-corrected body weight loss of 13.8% (week 16), highlighting its potential to promote clinically meaningful body weight loss in people with overweight/obesity	Reduced HbA1c levels and body weight after 16 weeks of treatment in participants with type 2 diabetes; dose-related gastrointestinal AEs could be mitigated with slower dose escalations

AE indicates adverse event; biw, twice weekly; BMI, body mass index; HbA1c, hemoglobin A1c; qw, once weekly.

Meta-analysis (Obesity only)

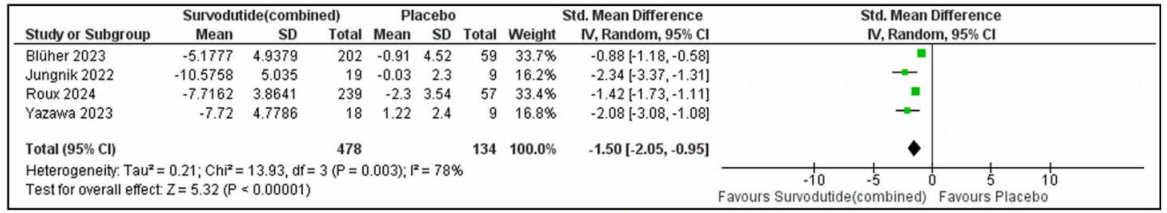


Figure 2. A forest plot showing the relative change in body weight from baseline (%).

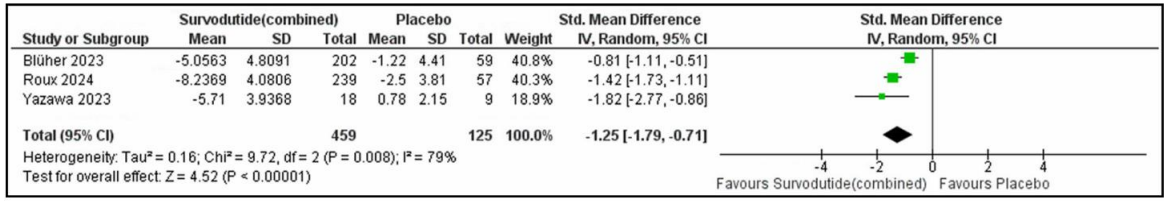
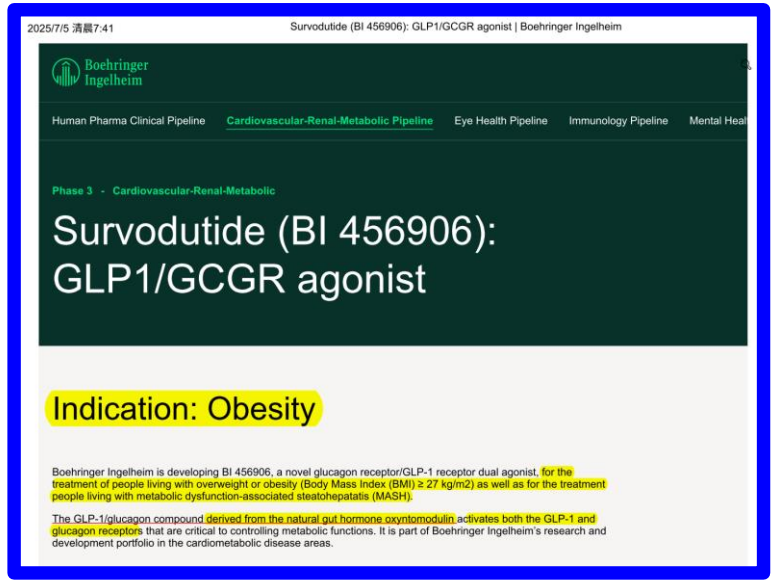


Figure 3. A forest plot showing the absolute change from baseline in body weight (kg).



Awad AA, et al. Proc (Bayl Univ Med Cent) 38:514-522, 2025

GLORY-1 (Obesity only) (Chinese only)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Weekly Mazdutide in Chinese Adults with Obesity or Overweight

BACKGROUND

Evidence suggests that incretin-based dual agonist pharmacotherapy is helpful in persons with obesity. Mazdutide, a glucagon-like peptide-1 and glucagon receptor dual agonist, may have efficacy in persons with overweight or obesity.

METHODS

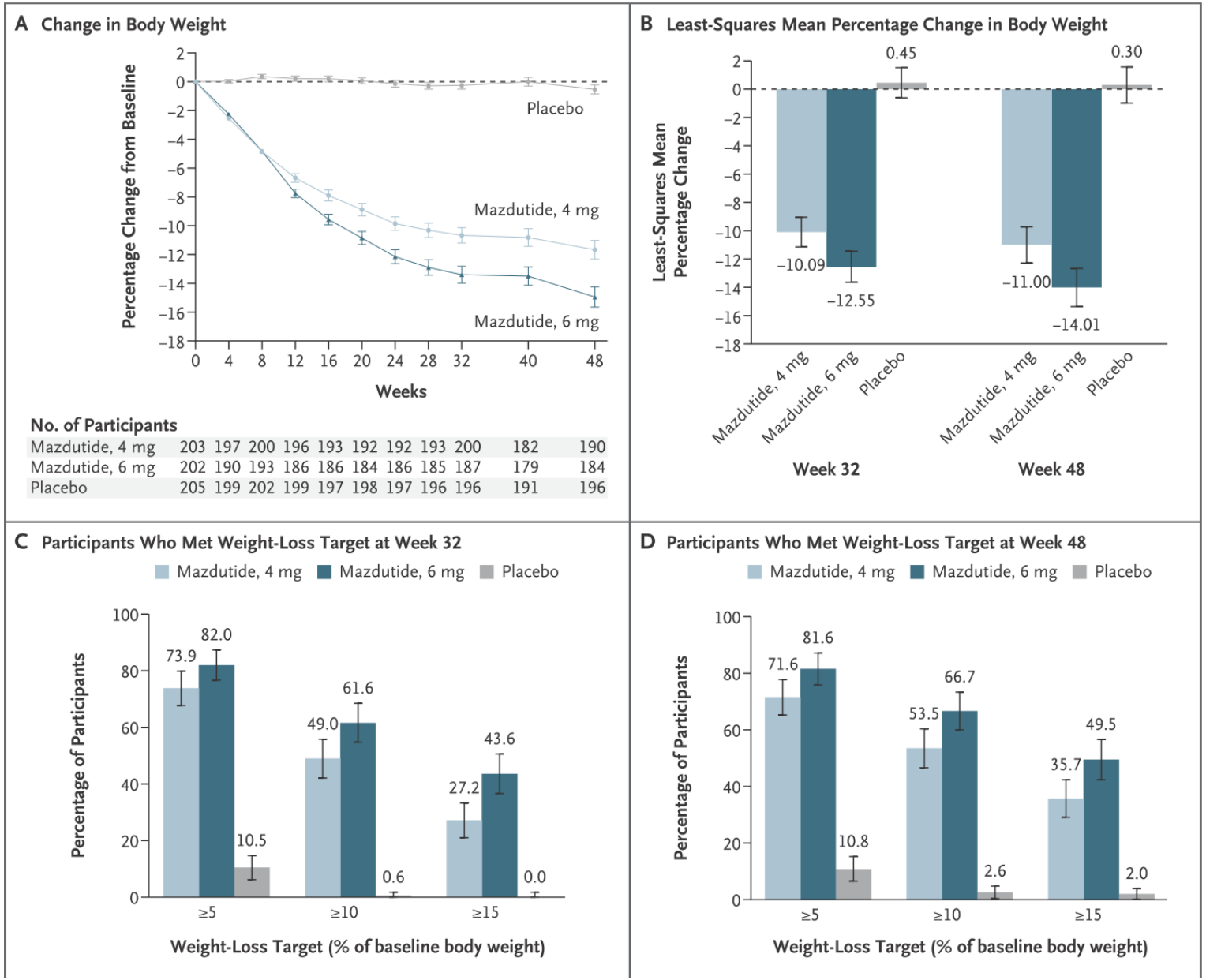
In a phase 3, double-blind, placebo-controlled trial in China, we randomly assigned, in a 1:1:1 ratio, adults 18 to 75 years of age who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 28 or had a BMI of 24 to less than 28 plus at least one weight-related coexisting condition to receive 4 mg of mazdutide, 6 mg of mazdutide, or placebo for 48 weeks. The two primary end points were the percentage change in body weight from baseline and a weight reduction of at least 5% at week 32, as assessed in a treatment-policy estimand analysis (which assessed effects regardless of early discontinuation of mazdutide or placebo and the initiation of new antiobesity therapies).

RESULTS

Among 610 participants, the mean body weight was 87.2 kg and the mean BMI was 31.1 at baseline. At week 32, the mean percentage change in body weight from baseline was –10.09% (95% confidence interval [CI], –11.15 to –9.04) in the 4-mg mazdutide group, –12.55% (95% CI, –13.64 to –11.45) in the 6-mg mazdutide group, and 0.45% (95% CI, –0.61 to 1.52) in the placebo group, and 73.9%, 82.0%, and 10.5% of the participants, respectively, had a weight reduction of at least 5% (P<0.001 for all comparisons with placebo). At week 48, the mean percentage change in body weight from baseline was –11.00% (95% CI, –12.27 to –9.73) in the 4-mg mazdutide group, –14.01% (95% CI, –15.36 to –12.66) in the 6-mg mazdutide group, and 0.30% (95% CI, –0.98 to 1.58) in the placebo group, and 35.7%, 49.5%, and 2.0% of the participants, respectively, had a weight reduction of at least 15% (P<0.001 for all comparisons with placebo). Beneficial effects on all prespecified cardiometabolic measures were seen with mazdutide. The most frequently reported adverse events were gastrointestinal and mostly mild to moderate in severity. The incidence of adverse events leading to discontinuation of the trial regimen was 1.5% with the 4-mg mazdutide dose, 0.5% with the 6-mg mazdutide dose, and 1.0% with placebo.

CONCLUSIONS

In Chinese adults with overweight or obesity, once-weekly mazdutide at a dose of 4 mg or 6 mg for 32 weeks led to clinically relevant reductions in body weight. (Funded by Innovent Biologics; GLORY-1 ClinicalTrials.gov number, NCT05607680.)



Ji L, et al. N Engl J Med 392:2215-2225, 2025

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

BACKGROUND

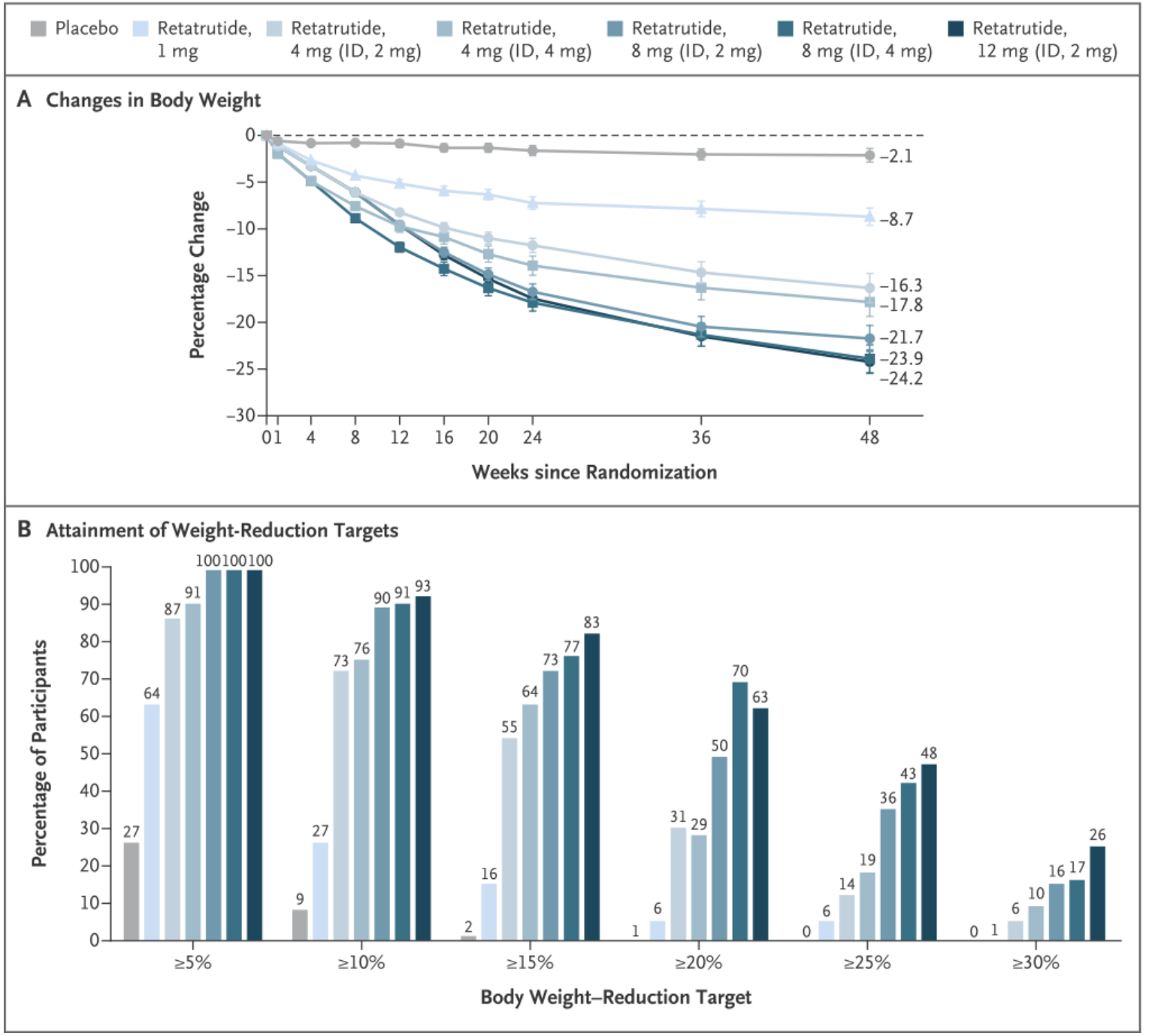
Retatrutide (LY3437943) is an agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors. Its dose–response relationships with respect to side effects, safety, and efficacy for the treatment of obesity are not known.

METHODS

We conducted a phase 2, double-blind, randomized, placebo-controlled trial involving adults who had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or higher or who had a BMI of 27 to less than 30 plus at least one weight-related condition. Participants were randomly assigned in a 2:1:1:1:1:2:2 ratio to receive subcutaneous retatrutide (1 mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], or 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks. The primary end point was the percentage change in body weight from baseline to 24 weeks. Secondary end points included the percentage change in body weight from baseline to 48 weeks and a weight reduction of 5% or more, 10% or more, or 15% or more. Safety was also assessed.

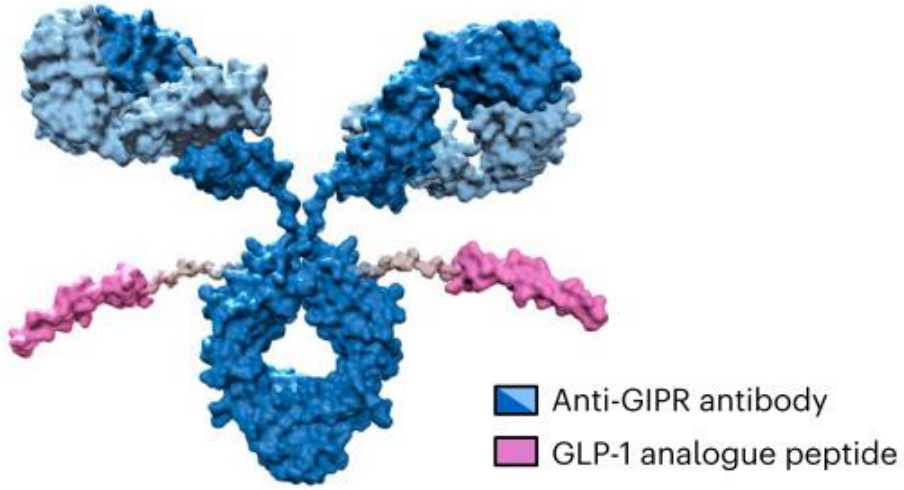
Jastreboff AM, et al. N Engl J Med 389:514-26, 2023

ID denotes initial dose



AMG 133 (maridebart cafraglutide)
GIPR antagonist and GLP-1R agonist

Fusion Molecule



AMG 133	GIPR recombinant cells	IC_{50} (nM)
GIPR antagonist assay	Human	42.4
	Cynomolgus monkey	26.5
	Rat	822.3
	Mouse	–
AMG 133	**GLP-1R recombinant cells**	**EC_{50} (pM)**
GLP-1R agonist assay	Human	24.4
	Cynomolgus monkey	5.7
	Rat	2.4
	Mouse	123

Phase 1 data
multiple ascending doses of placebo and AMG 133

	Placebo (*n*=6)	140 mg (*n*=6)	280 mg (*n*=6)	420 mg (*n*=8)
Number of individuals reporting TEAEs	3 (50.0)	6 (100.0)	6 (100.0)	8 (100.0)
GI disorders				
Diarrhoea	0 (0.0)	1 (16.7)	0 (0.0)	2 (25.0)
Dyspepsia	0 (0.0)	1 (16.7)	0 (0.0)	1 (12.5)
Abdominal distension	0 (0.0)	1 (16.7)	0 (0.0)	1 (12.5)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Constipation	0 (0.0)	2 (33.3)	1 (16.7)	0 (0.0)
Nausea	1 (16.7)	5 (83.3)	4 (66.7)	8 (100.0)
Vomiting	0 (0.0)	4 (66.7)	5 (83.3)	6 (75.0)
GI safety laboratory				
Amylase elevation	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Lipase elevation	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)

Data show number (%) of participants with the event of interest.

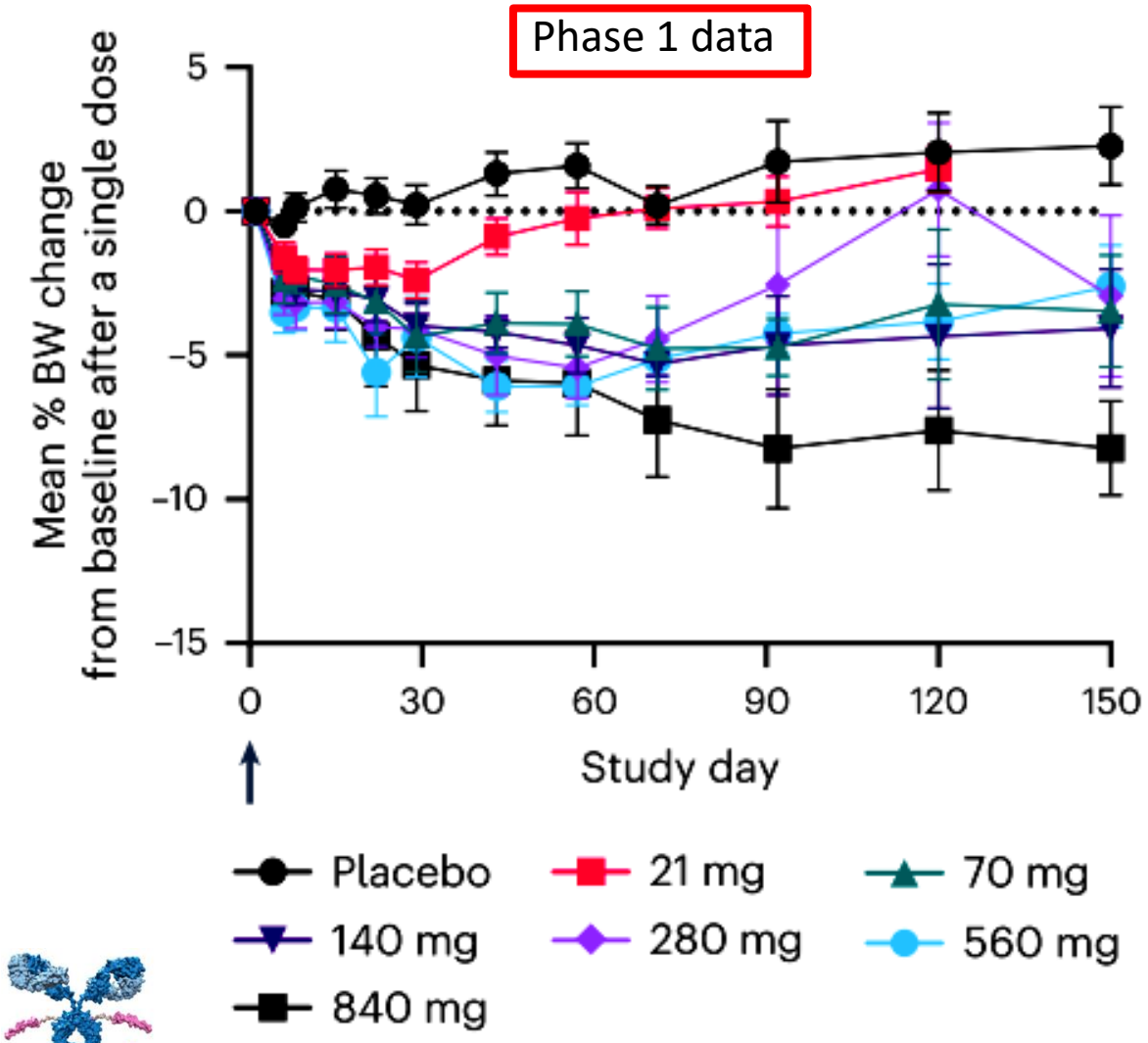
Véniant MM, et al. Nat Metab 6: 290-303, 2024

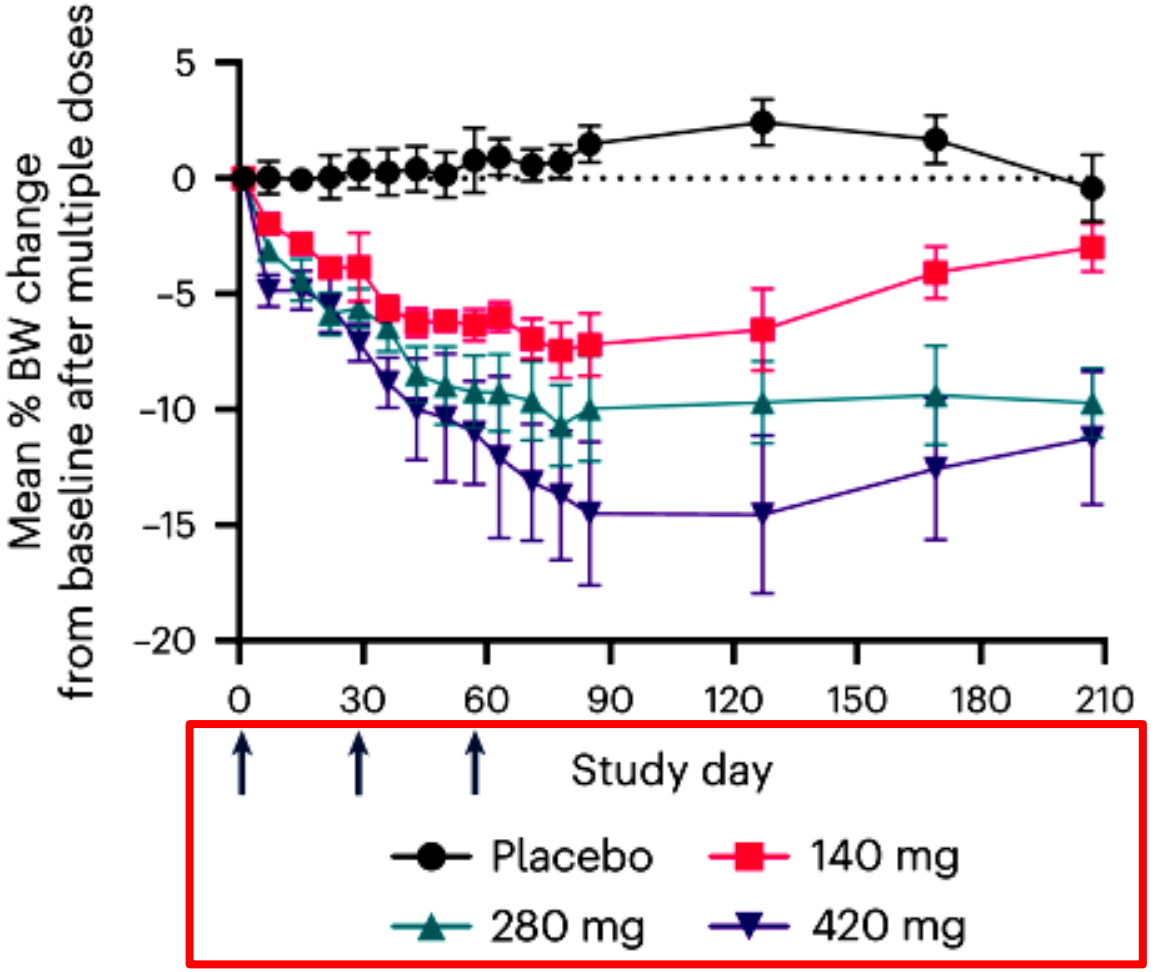
AMG 133 (maridebart cafraglutide)

GIPR antagonist and GLP-1R agonist

In a phase 1, randomized, double-blind, placebo-controlled clinical study in participants with obesity (NCT04478708), AMG 133 had an acceptable safety and tolerability profile along with pronounced dose-dependent weight loss. In the multiple ascending dose cohorts, weight loss was maintained for up to 150 days after the last dose. These findings support continued clinical evaluation of AMG 133.

Phase 1 data

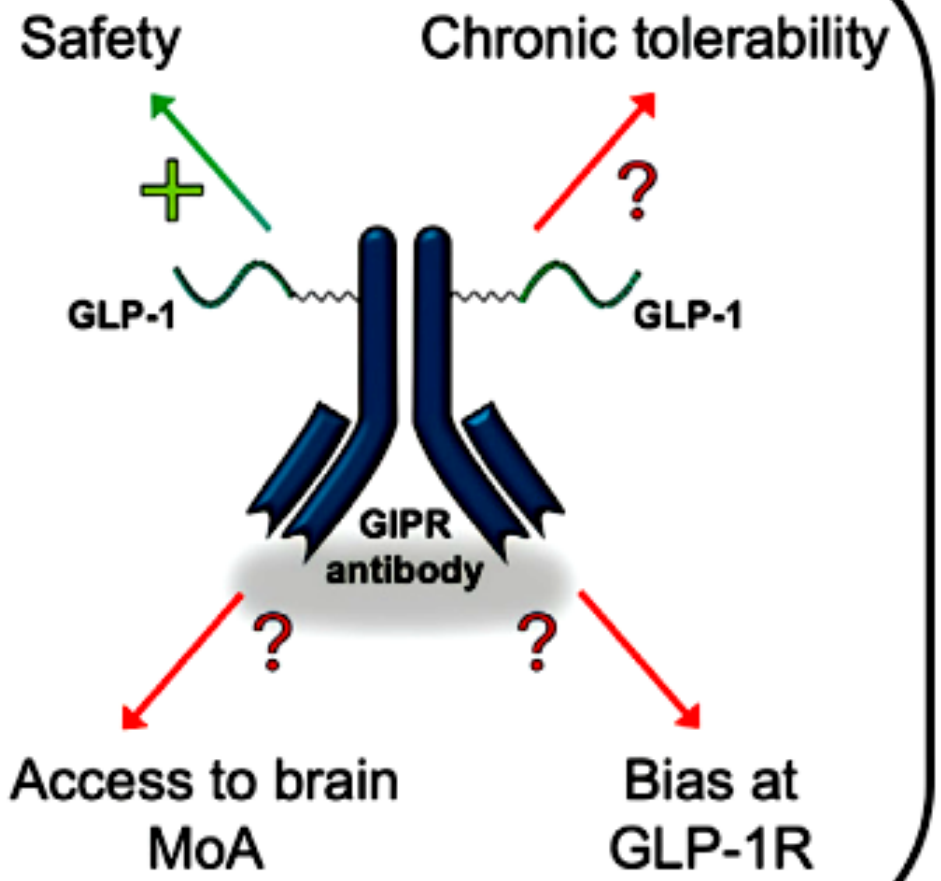




Véniant MM, et al. Nat Metab 6: 290-303, 2024

GLP-1RAs and Beyond

Drug	Semaglutide (2.4 mg)	Tirzepatide (15 mg)	Retatrutide (8 mg)	AMG 133 (420 mg)
Targets	GLP-1R Ag.	GLP-1R/GIPR Dual Ag.	GLP-1R/ GIPR/GcgR Triple Ag.	GLP-1R Ag. / GIPR Ant.
Δ% BW (week 12-13)	-6%	-8%	-12%	-14%
Δ% BW (end of trial)	-15% *68 weeks*	-23% *72 weeks*	-24% *48 weeks*	-14% *12 weeks*
Target dosage achieved (at week 12)	No	No	No	Yes
Clinical trial phase	3	3	3	1
Participant criteria	Obesity w/o T2D	Obesity w/o T2D	Obesity w/o T2D	Obesity w/o T2D



Novikoff A, Müller TD. Trends Endocrinol Metab 35:566-568, 2024

The NEW ENGLAND JOURNAL of MEDICINE

(Obesity ± T2DM)

ORIGINAL ARTICLE

Once-Monthly Maridebart Cafraglutide for the Treatment of Obesity — A Phase 2 Trial

BACKGROUND

Maridebart cafraglutide (known as MariTide) is a long-acting peptide–antibody conjugate that combines glucagon-like peptide-1 receptor agonism and glucose-dependent insulinotropic polypeptide receptor antagonism and that is intended for the treatment of obesity.

METHODS

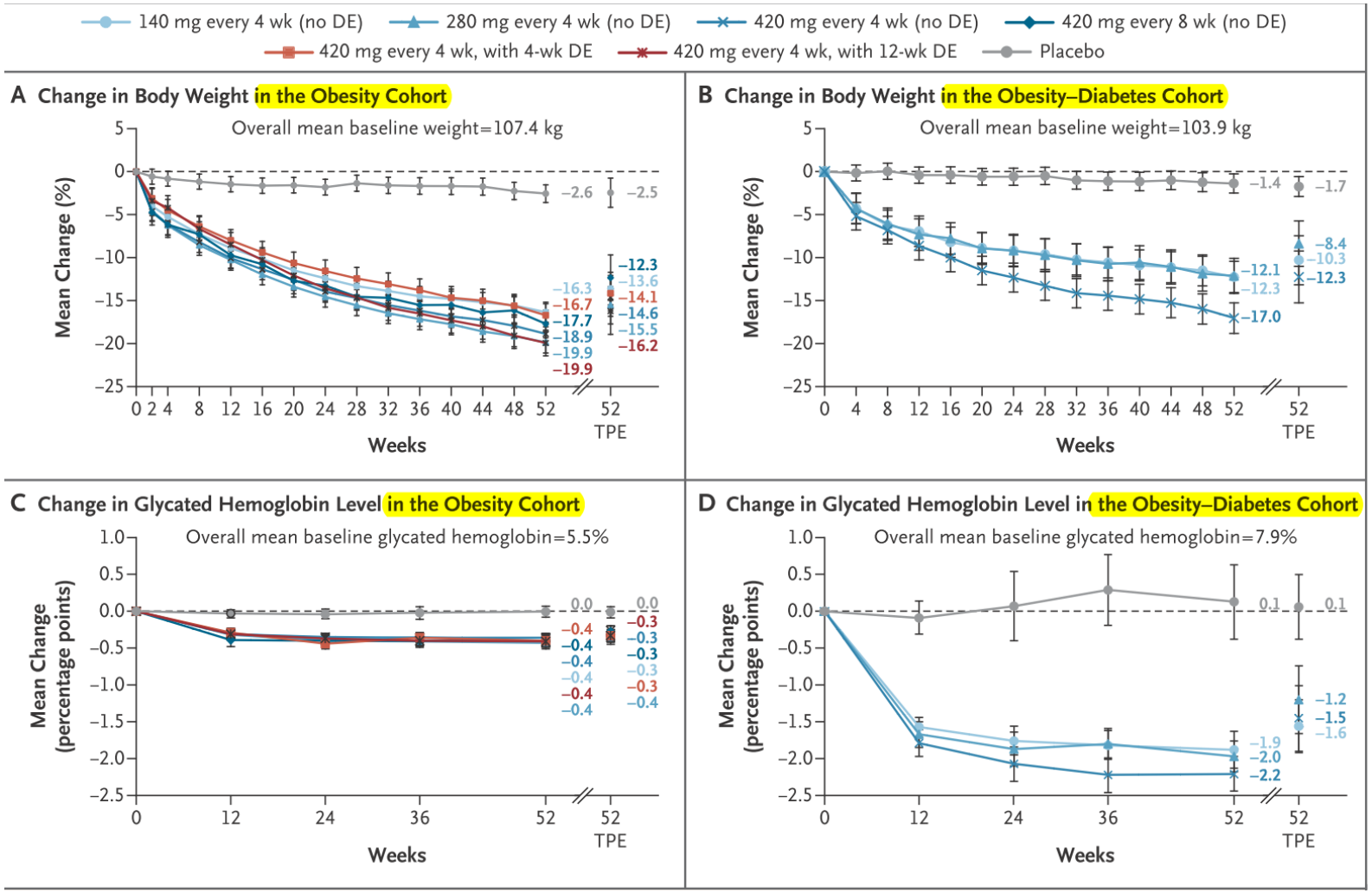
We conducted a phase 2, double-blind, randomized, placebo-controlled, dose-ranging trial that included 11 groups as two cohorts. Participants with obesity (obesity cohort) were randomly assigned in a 3:3:3:2:2:2:3 ratio to receive maridebart cafraglutide subcutaneously at a dose of 140, 280, or 420 mg every 4 weeks without dose escalation; 420 mg every 8 weeks without dose escalation; 420 mg every 4 weeks with 4-week dose escalation; 420 mg every 4 weeks with 12-week dose escalation; or placebo. Participants with obesity with type 2 diabetes (obesity–diabetes cohort) were randomly assigned in a 1:1:1:1 ratio to receive maridebart cafraglutide at a dose of 140, 280, or 420 mg every 4 weeks (all without dose escalation) or placebo. The primary end point was the percent change in body weight from baseline to week 52.

RESULTS

We enrolled 592 participants. In the obesity cohort (465 participants; female sex, 63%; mean age, 47.9 years; mean body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], 37.9), the mean percent change in body weight from baseline to week 52 on the basis of the treatment policy estimand (intention-to-treat approach) ranged from −12.3% (95% confidence interval [CI], −15.0 to −9.7) to −16.2% (95% CI, −18.9 to −13.5) with maridebart cafraglutide, as compared with −2.5% (95% CI, −4.2 to −0.7) with placebo. In the obesity–diabetes cohort (127 participants; female sex, 42%; mean age, 55.1 years; mean BMI, 36.5), the mean percent change in body weight from baseline to week 52 on the basis of the treatment policy estimand ranged from −8.4% (95% CI, −11.0 to −5.7) to −12.3% (95% CI, −15.3 to −9.2) with maridebart cafraglutide, as compared with −1.7% (95% CI, −2.9 to −0.6) with placebo. The mean change in the glycated hemoglobin level on the basis of the treatment policy estimand in this cohort was −1.2 to −1.6 percentage points in the maridebart cafraglutide groups and 0.1 percentage points in the placebo group. Gastrointestinal adverse events were common with maridebart cafraglutide, although less frequent with dose escalation and a lower starting dose. No unexpected safety signals emerged.

CONCLUSIONS

In this phase 2 trial, once-monthly maridebart cafraglutide resulted in substantial weight reduction in participants with obesity with or without type 2 diabetes. (Funded by Amgen; ClinicalTrials.gov number, NCT05669599.)



Jastreboff AM, et al. N Engl J Med. 2025 Jun 23. Epub ahead of print. PMID: 40549887

Amylin and Beyond

Anti-obesity peptides

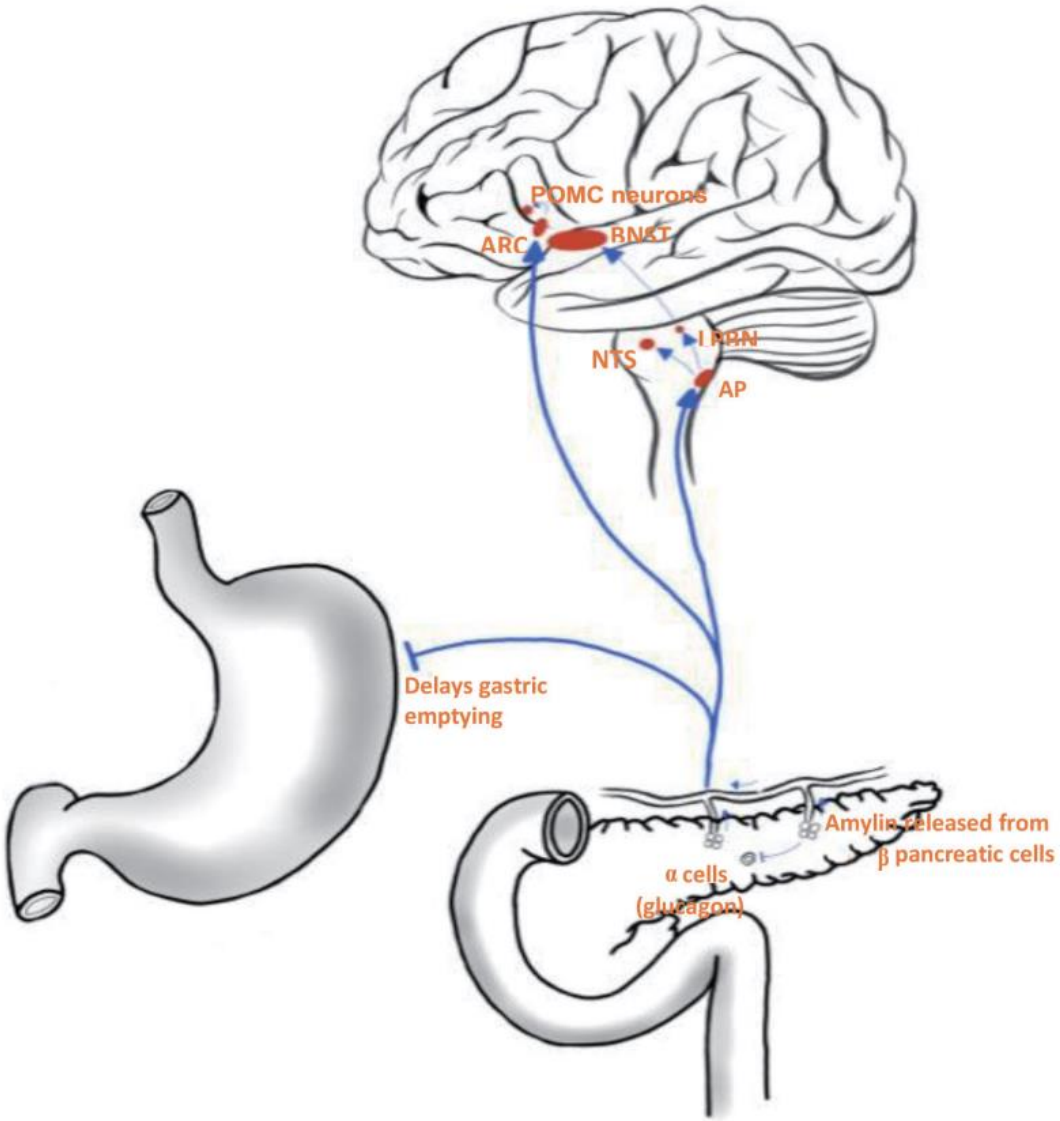
In addition to the weight-reducing effects of the peptides described above, several other peptides are under investigation specifically for

Amylin	KCNTATCATQ RLANFLVHSSNNFGAILSSTNVGSNTY.NH_2
Pramlintide	KCNTATCATQ RLANFLVHSSNNFGPILPPTNVGSNTY.NH_2
Cagrilintide	**K**CNTATCATQ RLAEFLRHSSNNFGPILPPTNVGSNTP.NH_2

Fig. 2. A comparison of the primary structure of cagrilintide with naturally occurring amylin and the proline-substituted analogue pramlintide. **K** denotes the site of attachment of a C-20 fatty di-acid via a γ-glutamyl spacer. Amino acid residues that differ from amylin are shown as shaded.

Bailey CJ, et al. Peptides 161:170939, 2023

Mechanism of Action of Cagrilintide



Amylin functions as a satiety hormone.

Released into the bloodstream by pancreatic β cells, amylin act on 3 primary targets:

(1) the brain to activate various homeostatic and hedonic reward centers to suppress appetite and reduce food intake;

(2) the stomach as an inhibitory signal to delay gastric emptying;

(3) α-cells of the pancreas to suppress glucagon release.

POMC, proopiomelanocortin; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; NTS, nucleus tractus solitarius; LPBN, lateral parabrachial nucleus; AP, area postrema.

Dehestani B, et al. J Obes Metab Syndr 30:320-325, 2021

Cagrilintide Plus Semaglutide for Obesity Management

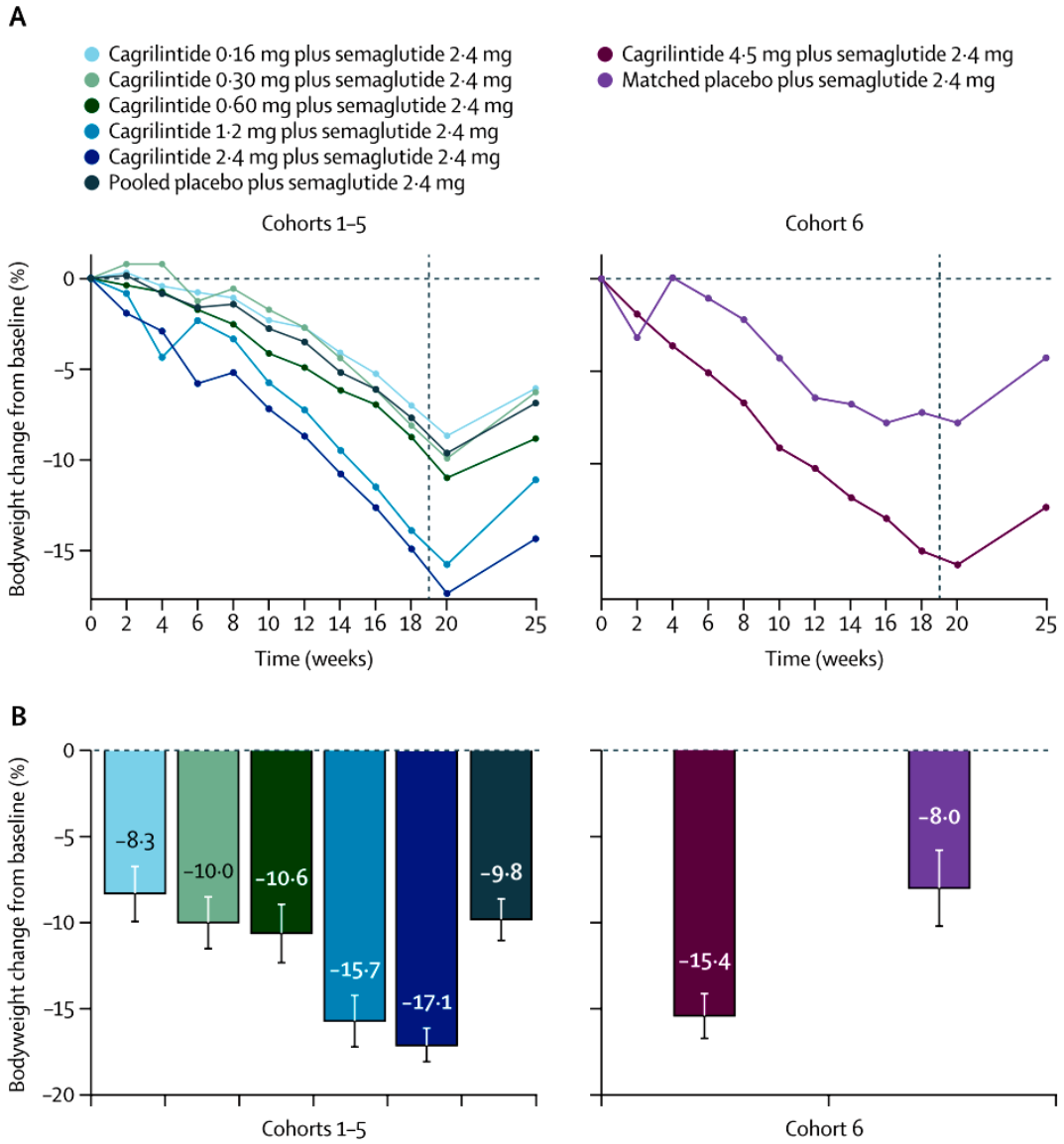
Summary

Background Cagrilintide, a long-acting amylin analogue, and semaglutide 2·4 mg, a glucagon-like peptide-1 analogue, are both being investigated as options for weight management. We aimed to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of this drug combination.

Methods In this randomised, placebo-controlled, multiple-ascending dose, phase 1b trial, individuals aged 18–55 years with a body-mass index 27·0–39·9 kg/m² and who were otherwise healthy were recruited from a single centre in the USA. The trial included six sequential overlapping cohorts, and in each cohort eligible participants were randomly assigned (3:1) to once-weekly subcutaneous cagrilintide (0·16, 0·30, 0·60, 1·2, 2·4, or 4·5 mg) or matched placebo, in combination with once-weekly subcutaneous semaglutide 2·4 mg, without lifestyle interventions. In each cohort, the doses of cagrilintide and semaglutide were co-escalated in 4-week intervals to the desired dose over 16 weeks, participants were treated at the target dose for 4 weeks, and then followed up for 5 weeks. Participants, investigators, and the sponsor were masked to treatment assignment. The primary endpoint was number of treatment-emergent adverse events from baseline to end of follow-up. Secondary pharmacokinetic endpoints assessed from day of last dose (week 19) to end of treatment (week 20) were area under the plasma concentration-time curve from 0 to 168 h ($AUC_{0–168\ h}$) and maximum concentration [C_{max}] of cagrilintide and semaglutide; exploratory pharmacokinetic endpoints were half-life, time to C_{max} [t_{max}], plasma clearance, and volume of distribution of cagrilintide and semaglutide; and exploratory pharmacodynamic endpoints were changes in bodyweight, glycaemic parameters, and hormones. Safety, pharmacokinetic, and pharmacodynamic endpoints were assessed in all participants who were exposed to at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03600480, and is now complete.

Enebo LB, et al. Lancet 397: 1736-1748, 2021

Cagrilintide Plus Semaglutide for Obesity Management



	Cohort 1: cagrilintide 0·16 mg plus semaglutide 2·4 mg (n=12)		Cohort 2: cagrilintide 0·30 mg plus semaglutide 2·4 mg (n=12)		Cohort 3: cagrilintide 0·60 mg plus semaglutide 2·4 mg (n=12)		Cohort 4: cagrilintide 1·2 mg plus semaglutide 2·4 mg (n=12)		Cohort 5: cagrilintide 2·4 mg plus semaglutide 2·4 mg (n=12)		Cohort 6: cagrilintide 4·5 mg plus semaglutide 2·4 mg (n=11)		Pooled placebo cohorts 1–6: placebo plus semaglutide 2·4 mg (n=24)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Adverse event	11 (92%)	37	12 (100%)	84	11 (92%)	88	12 (100%)	60	12 (100%)	89	11 (100%)	76	23 (96%)	132
Severity														
Mild	11 (92%)	36	12 (100%)	77	11 (92%)	80	12 (100%)	53	12 (100%)	82	11 (100%)	66	23 (96%)	116
Moderate	1 (8%)	1	4 (33%)	7	4 (33%)	8	5 (42%)	6	4 (33%)	7	4 (36%)	10	8 (33%)	15
Severe*	0	0	0	0	0	0	1 (8%)	1	0	0	0	0	1 (4%)	1
Serious adverse event†	0	0	0	0	0	0	1 (8%)	1	0	0	0	0	0	0
Participants with ≥1 adverse event leading to withdrawal	1 (8%)	1	0	0	0	0	1 (8%)	1	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adverse events of gastrointestinal disorders system organ class	7 (58%)	12	10 (83%)	38	7 (58%)	30	10 (83%)	19	11 (92%)	33	9 (82%)	25	19 (79%)	50
Most common events by preferred term‡§														
Injection-site reaction	4 (33%)	7	4 (33%)	8	2 (17%)	19	2 (17%)	4	6 (50%)	17	3 (27%)	7	7 (29%)	10
Nausea	6 (50%)	6	9 (75%)	13	6 (50%)	10	6 (50%)	7	10 (83%)	12	8 (73%)	10	8 (33%)	9
Decreased appetite	7 (58%)	8	8 (67%)	9	7 (58%)	7	6 (50%)	6	12 (100%)	12	9 (82%)	9	14 (58%)	14
Early satiety	1 (8%)	1	3 (25%)	3	4 (33%)	4	8 (67%)	8	8 (67%)	8	10 (91%)	10	9 (38%)	9
Vomiting	0	0	4 (33%)	8	2 (17%)	5	1 (8%)	2	9 (75%)	12	4 (36%)	11	3 (13%)	5
Headache	1 (8%)	1	6 (50%)	7	3 (25%)	4	2 (17%)	2	2 (17%)	3	2 (18%)	8	6 (25%)	9
Dyspepsia	2 (17%)	3	4 (33%)	4	5 (42%)	5	2 (17%)	2	4 (33%)	4	2 (18%)	2	8 (33%)	12
Diarrhoea	0	0	2 (17%)	6	2 (17%)	4	1 (8%)	2	2 (17%)	2	0	0	9 (38%)	14
Abdominal pain	1 (8%)	1	3 (25%)	4	1 (8%)	2	1 (8%)	1	1 (8%)	1	0	0	2 (8%)	2
Fatigue	0	0	0	0	3 (25%)	3	3 (25%)	3	0	0	3 (27%)	3	1 (4%)	1
Dizziness	0	0	3 (25%)	3	2 (17%)	3	0	0	0	0	0	0	2 (8%)	2

Data are n (%), where n is participants with one or more adverse event, and number of events. Data for participants receiving treatment with placebo in combination with semaglutide 2·4 mg were pooled across cohorts; subset analyses of placebo groups for cohorts 1–5 (n=20) and cohort 6 (n=4) did not identify any differences in frequency of adverse events (data not shown). *Severe adverse events included meningitis (cohort 4) and serum creatinine increased (pooled placebo). †The serious adverse event was meningitis (cohort 4). ‡Adverse events occurring in at least 20% of participants in any group. §Adverse event definitions are listed in the protocol (appendix pp 97–98).

Table 2: **Treatment-emergent adverse events**

Enebo LB, et al. Lancet 397: 1736-1748, 2021

REDEFINE 1 (Obesity only)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity

BACKGROUND

Semaglutide at a dose of 2.4 mg has established weight-loss and cardiovascular benefits, and cagrilintide at a dose of 2.4 mg has shown promising results in early-phase trials; the efficacy of the combination (known as CagriSema) on weight loss in persons with either overweight and coexisting conditions or obesity is unknown.

METHODS

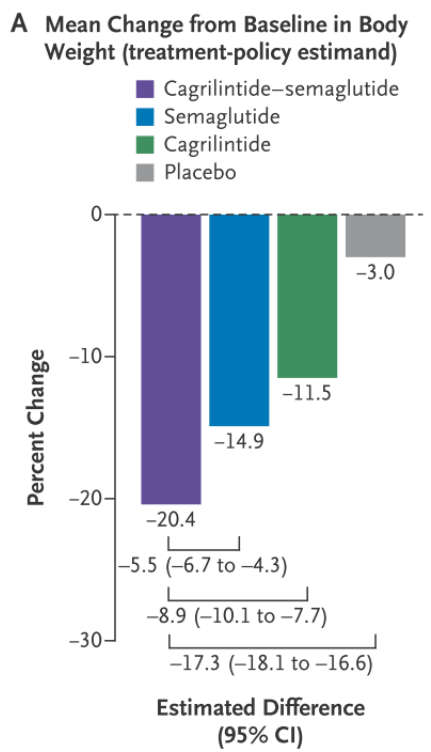
In a phase 3a, 68-week, multicenter, double-blind, placebo-controlled and active-controlled trial, we enrolled adults without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher with at least one obesity-related complication. Participants were randomly assigned in a ratio of 21:3:3:7 to receive the combination of semaglutide at a dose of 2.4 mg and cagrilintide at a dose of 2.4 mg, semaglutide alone at a dose of 2.4 mg, cagrilintide alone at a dose of 2.4 mg, or placebo, plus lifestyle interventions for all groups. The coprimary end points were the relative change in body weight and a reduction of 5% or more in body weight from baseline to week 68 with cagrilintide–semaglutide as compared with placebo. Body-weight reductions of 20% or more, 25% or more, and 30% or more were assessed as confirmatory secondary end points. Effect estimates were assessed with the treatment-policy estimand (consistent with the intention-to-treat principle). Safety was assessed.

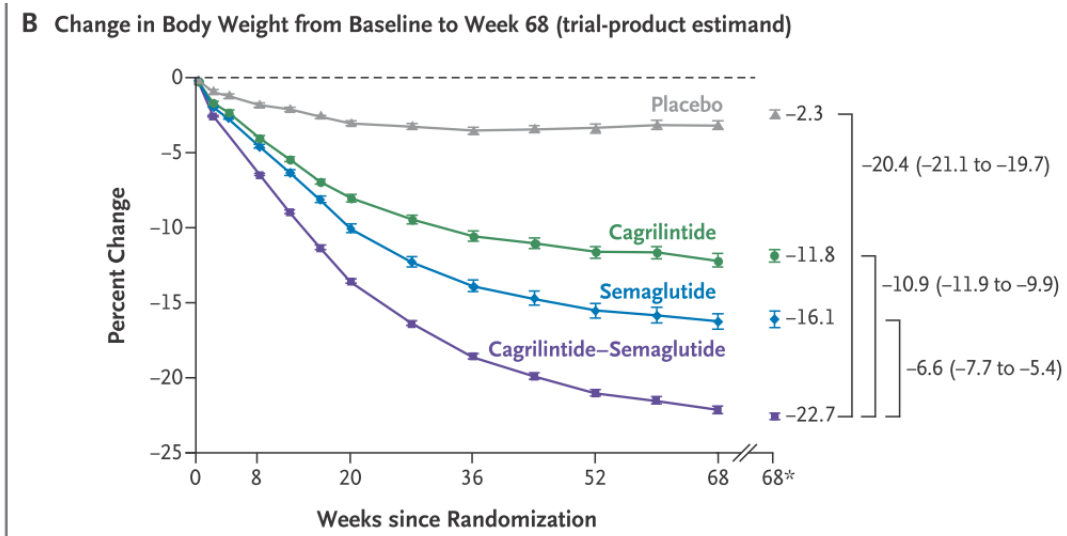
RESULTS

A total of 3417 participants underwent randomization, with 2108 assigned to receive cagrilintide–semaglutide, 302 to receive semaglutide, 302 to receive cagrilintide, and 705 to receive placebo. The estimated mean percent change in body weight from baseline to week 68 was –20.4% with cagrilintide–semaglutide as compared with –3.0% with placebo (estimated difference, –17.3 percentage points; 95% confidence interval, –18.1 to –16.6; P<0.001). Participants receiving cagrilintide–semaglutide were more likely than those receiving placebo to reach weight-loss targets of 5% or more, 20% or more, 25% or more, and 30% or more (P<0.001 for all comparisons). Gastrointestinal adverse events (affecting 79.6% in the cagrilintide–semaglutide group and 39.9% in the placebo group), including nausea, vomiting, diarrhea, constipation, or abdominal pain, were mainly transient and mild-to-moderate in severity.

CONCLUSIONS

Cagrilintide–semaglutide provided significant and clinically relevant body-weight reductions in adults with overweight or obesity, as compared with placebo. (Funded by Novo Nordisk; REDEFINE 1 ClinicalTrials.gov number, NCT05567796.)





No. at Risk

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

Table 3. Adverse Events.*

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

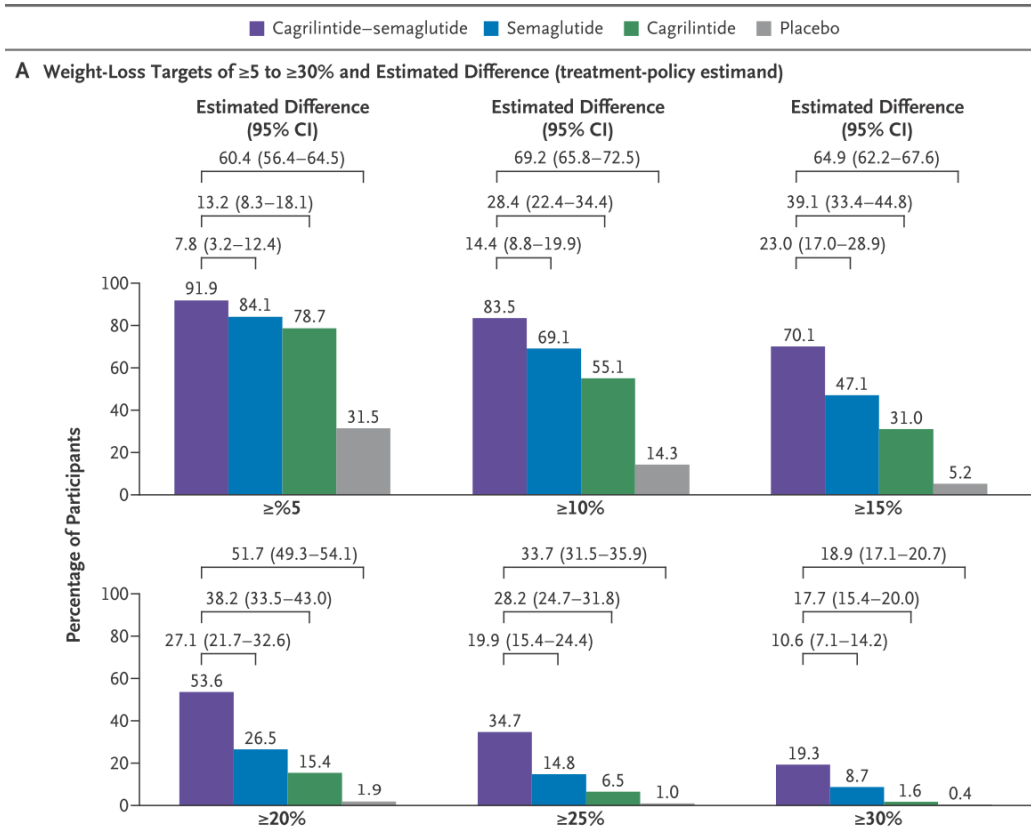
Garvey WT, et al. N Engl J Med. 2025 Jun 22. Epub ahead of print. PMID: 40544433.

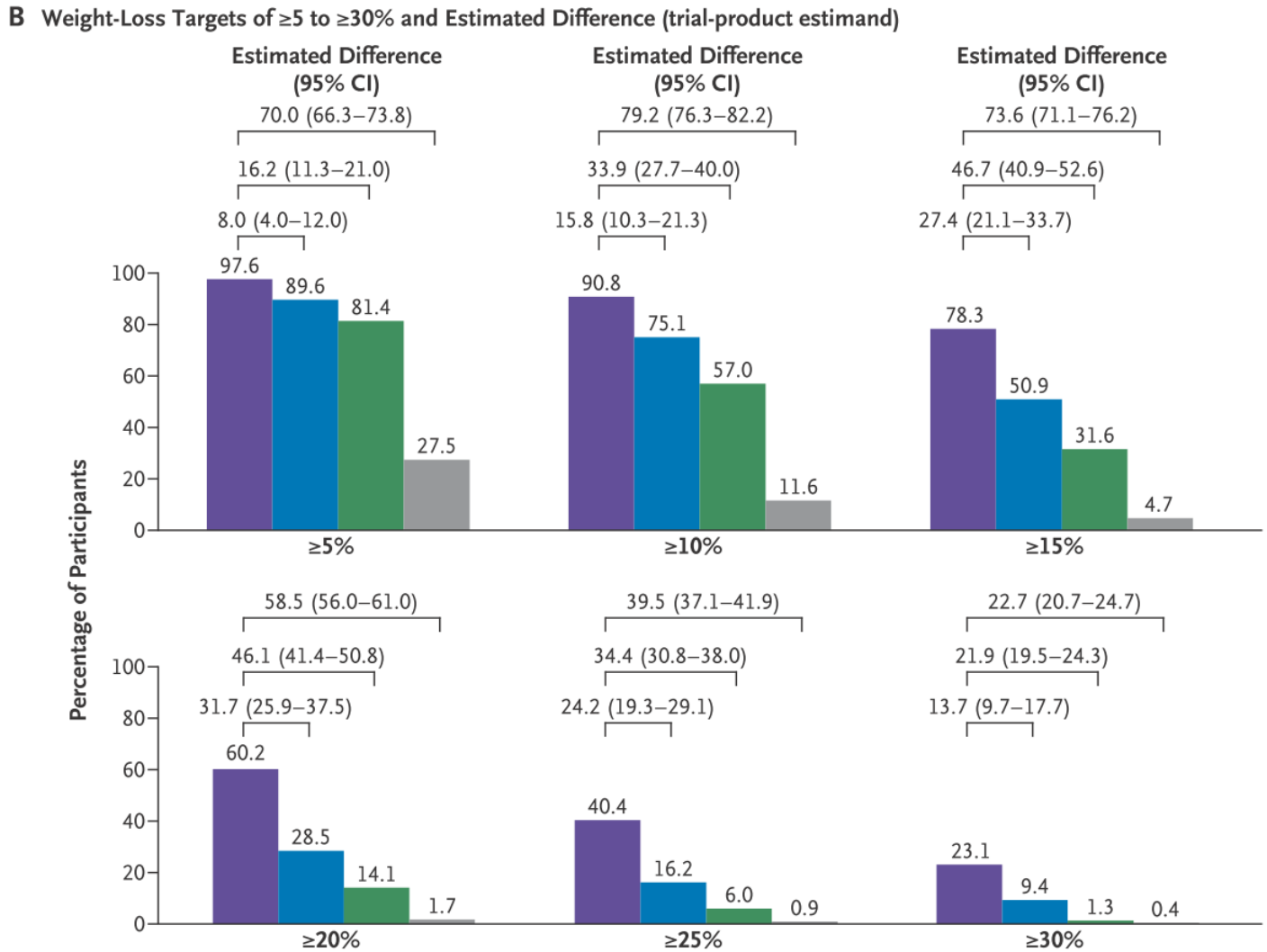
REDEFINE 1 (Obesity only)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity





Garvey WT, et al. N Engl J Med. 2025 Jun 22. Epub ahead of print. PMID: 40544433.

REDEFINE 2 (T2DM + BMI ≥ 27)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cagrilintide–Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes

BACKGROUND

Cagrilintide and semaglutide have each been shown to induce weight loss as monotherapies. Data are needed on the coadministration of cagrilintide and semaglutide (called CagriSema) for weight management in adults with type 2 diabetes, including those in a subgroup who are undergoing continuous glucose monitoring.

METHODS

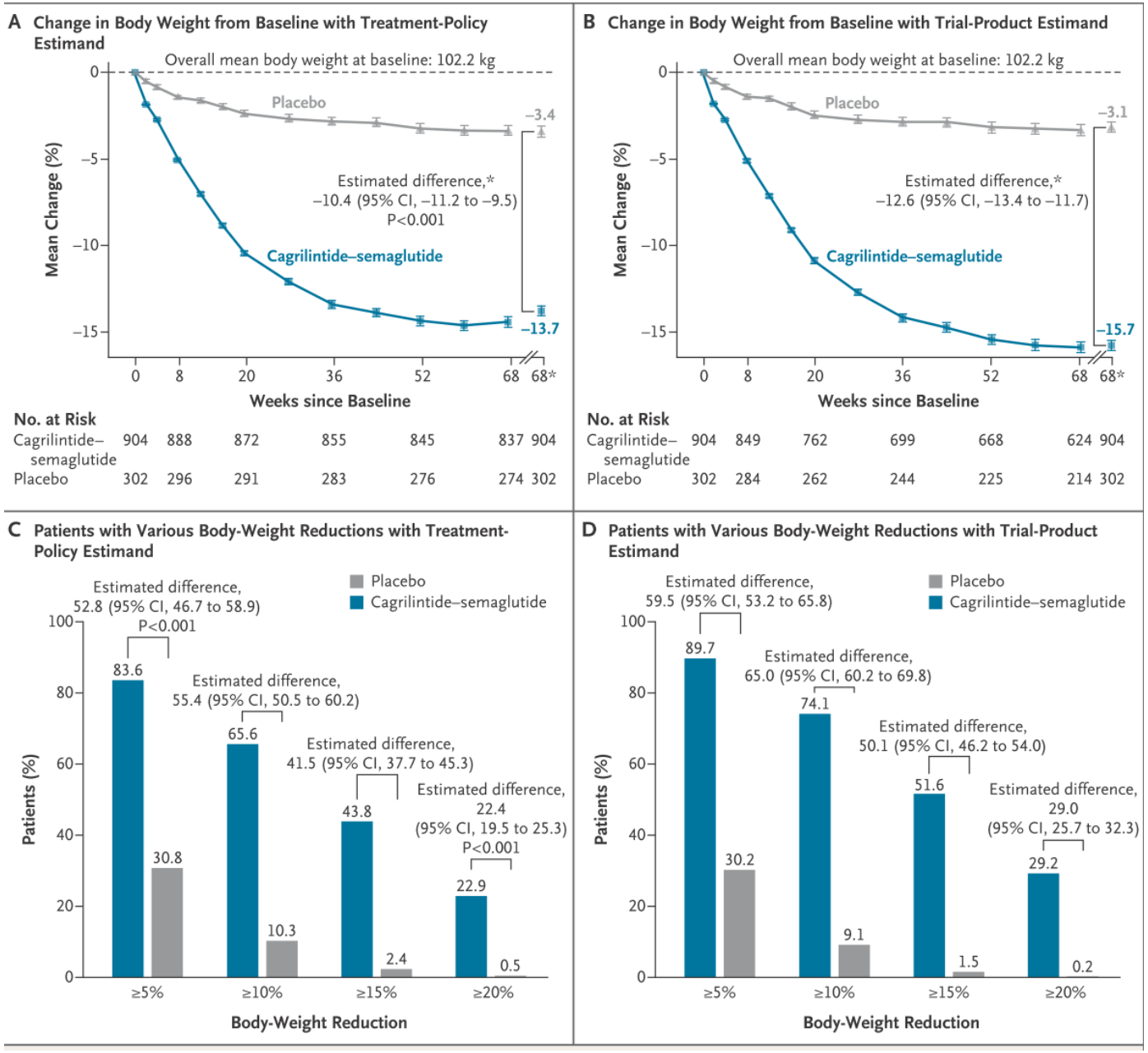
In this phase 3a, double-blind, randomized, placebo-controlled trial conducted in 12 countries, we assigned adults with a body-mass index of 27 or more, a glycated hemoglobin level of 7 to 10%, and type 2 diabetes in a 3:1 ratio to receive once-weekly cagrilintide–semaglutide (2.4 mg each) or placebo, along with lifestyle intervention, for 68 weeks. The two primary end points were the percent change in body weight and the percentage of patients with a weight reduction of at least 5%. Additional end points were changes in glycemic measures and safety assessments. Effect estimates were calculated with the use of the treatment-policy estimand (consistent with the intention-to-treat principle).

RESULTS

A total of 1206 patients underwent randomization to either the cagrilintide–semaglutide group (904 patients) or the placebo group (302 patients). The estimated mean change in body weight from baseline to week 68 was –13.7% in the cagrilintide–semaglutide group and –3.4% in the placebo group (estimated difference, –10.4 percentage points; 95% confidence interval, –11.2 to –9.5; P<0.001). More patients in the cagrilintide–semaglutide group than in the placebo group had a weight reduction of 5% or more (P<0.001); the same was true of reductions of at least 10%, 15%, and 20% (P<0.001 for the last comparison). The percentage of patients who had a glycated hemoglobin level of 6.5% or less was 73.5% in the cagrilintide–semaglutide group and 15.9% in the placebo group. Gastrointestinal adverse events were reported by 72.5% of the patients in the cagrilintide–semaglutide group and 34.4% in the placebo group, most of which were transient and mild or moderate in severity.

CONCLUSIONS

Once-weekly cagrilintide–semaglutide (at a dose of 2.4 mg each) resulted in a significantly lower body weight than placebo in adults with obesity and type 2 diabetes. (Funded by Novo Nordisk; REDEFINE 2 ClinicalTrials.gov number, NCT05394519.)



Davies MJ, et al. N Engl J Med. 2025 Jun 22. Epub ahead of print. PMID: 40544432.

REDEFINE 2 (T2DM + BMI ≥ 27)

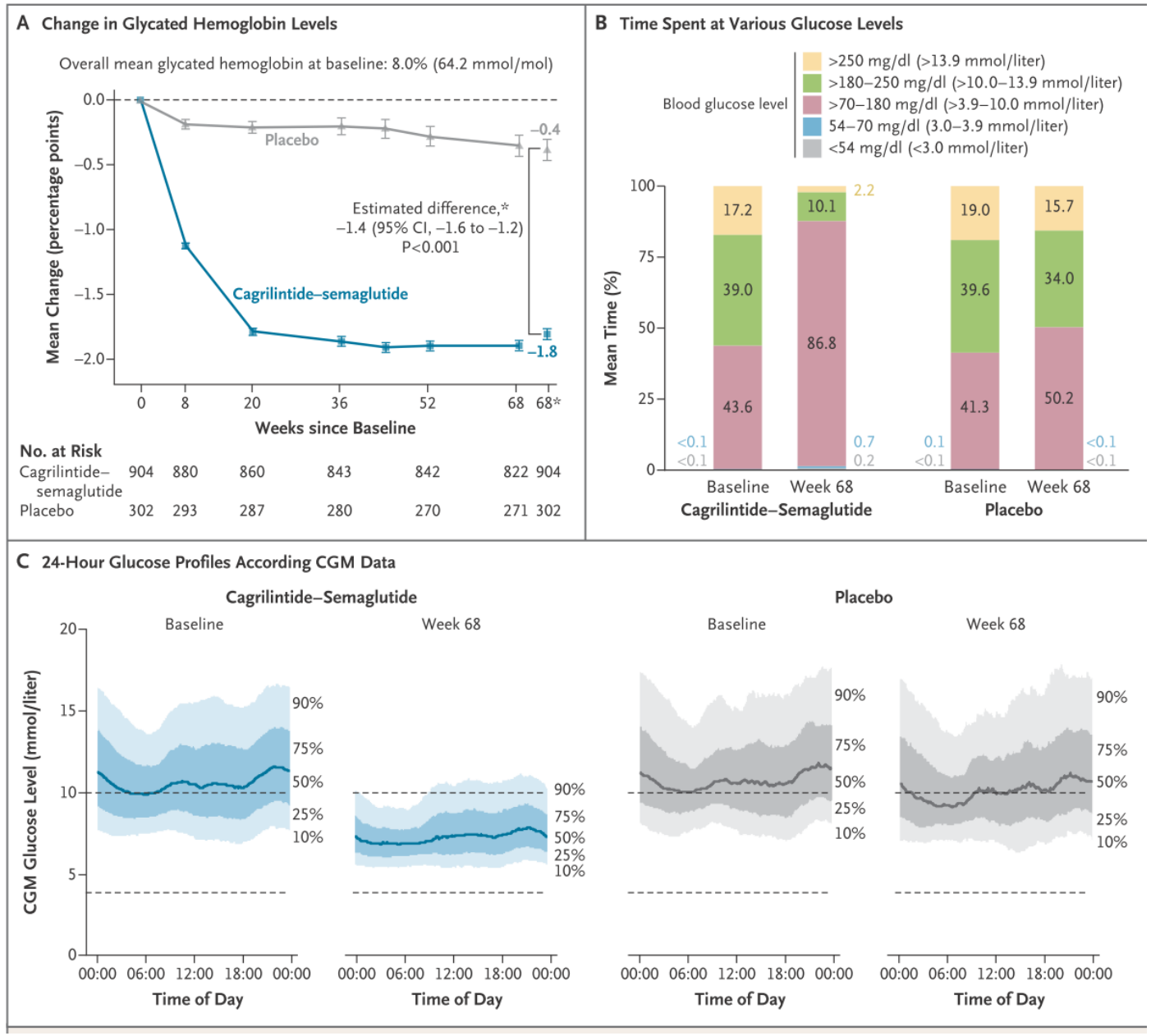
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cagrilintide–Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes

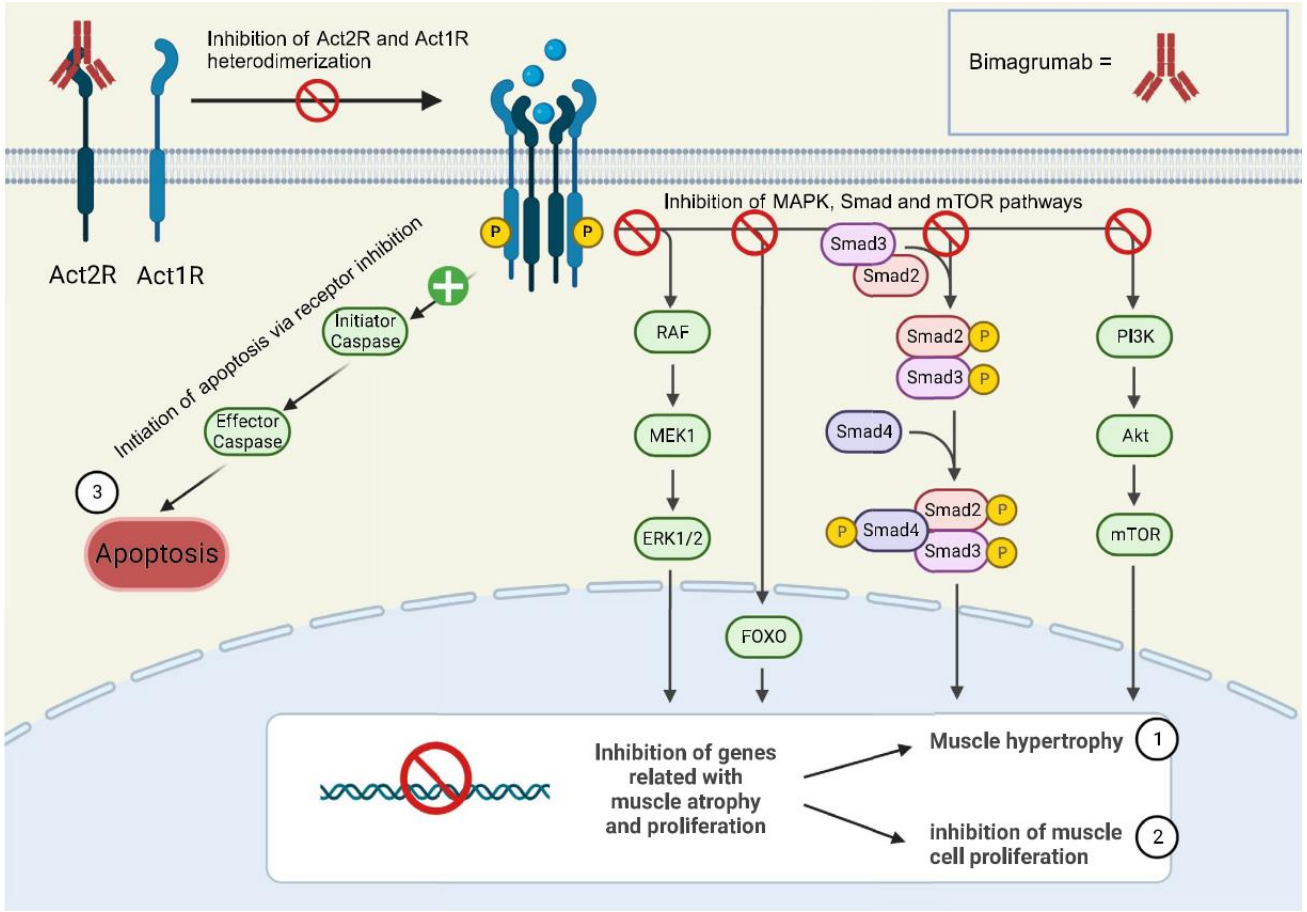
Table 3. Adverse Events.*

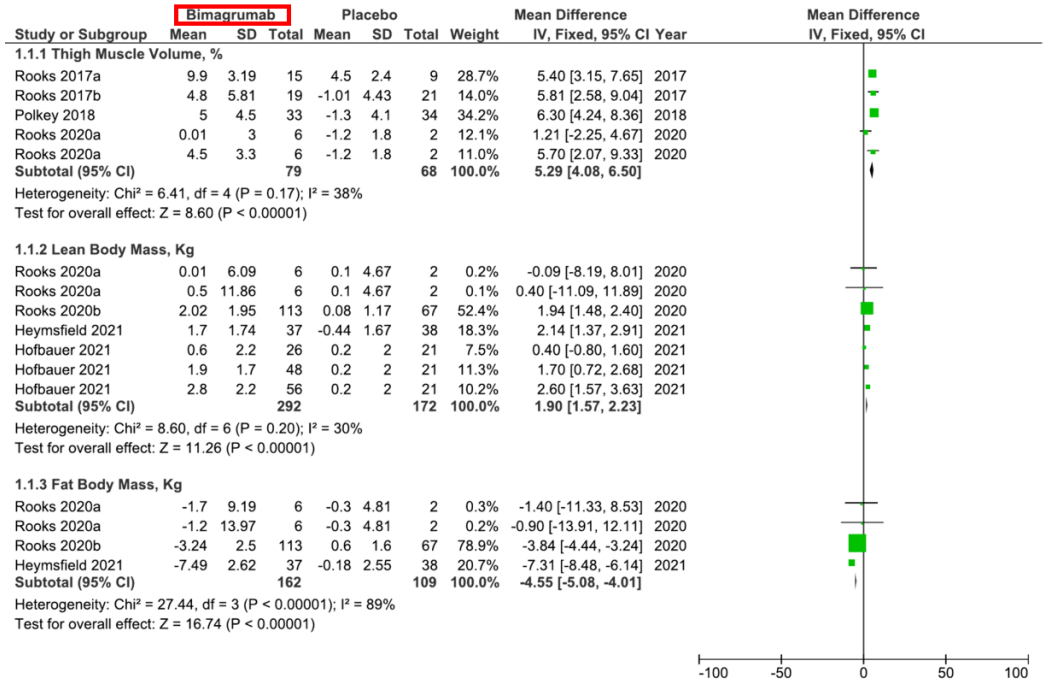
Adverse Events	Cagrilintide–Semaglutide (N=904)			Placebo (N=302)		
	Patients	Events	Event Rate†	Patients	Events	Event Rate†
	no. (%)	no.		no. (%)	no.	
Any	815 (90.2)	6088	477.4	258 (85.4)	1275	301.6
Serious	94 (10.4)	138	10.8	39 (12.9)	51	12.1
Leading to permanent discontinuation						
Any adverse event	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)	—	—



Davies MJ, et al. N Engl J Med. 2025 Jun 22. Epub ahead of print. PMID: 40544432.

Mechanism of Action of Bimagrumab





Cellular Signal Targets and Metabolic Effects of anti-Activin Type 2 Receptor Antibody Bimagrumab

Kanbay M, et al. Aging Clin Exp Res 36:185, 2024

(T2DM + BMI 28-40)

JAMA Network Open

Original Investigation | Nutrition, Obesity, and Exercise

Effect of Bimagrumab vs Placebo on Body Fat Mass Among Adults With Type 2 Diabetes and Obesity

A Phase 2 Randomized Clinical Trial

Abstract

IMPORTANCE Antibody blockade of activin type II receptor (ActRII) signaling stimulates skeletal muscle growth. Previous clinical studies suggest that ActRII inhibition with the monoclonal antibody bimagrumab also promotes excess adipose tissue loss and improves insulin resistance.

OBJECTIVE To evaluate the efficacy and safety of bimagrumab on body composition and glycemic control in adults with type 2 diabetes and overweight and obesity.

DESIGN, SETTING, AND PARTICIPANTS This double-masked, placebo-controlled, 48-week, phase 2 randomized clinical trial was conducted among adults with type 2 diabetes, body mass index between 28 and 40, and glycated hemoglobin (HbA_{1c}) levels between 6.5% and 10.0% at 9 US and UK sites. The trial was conducted from February 2017 to May 2019. Only participants who completed a full treatment regimen were included in analysis.

INTERVENTIONS Patients were randomized to intravenous infusion of bimagrumab (10 mg/kg up to 1200 mg in 5% dextrose solution) or placebo (5% dextrose solution) treatment every 4 weeks for 48 weeks; both groups received diet and exercise counseling.

MAIN OUTCOMES AND MEASURES The primary end point was least square mean change from baseline to week 48 in total body fat mass (FM); secondary and exploratory end points were lean mass (LM), waist circumference (WC), HbA_{1c} level, and body weight (BW) changes from baseline to week 48.

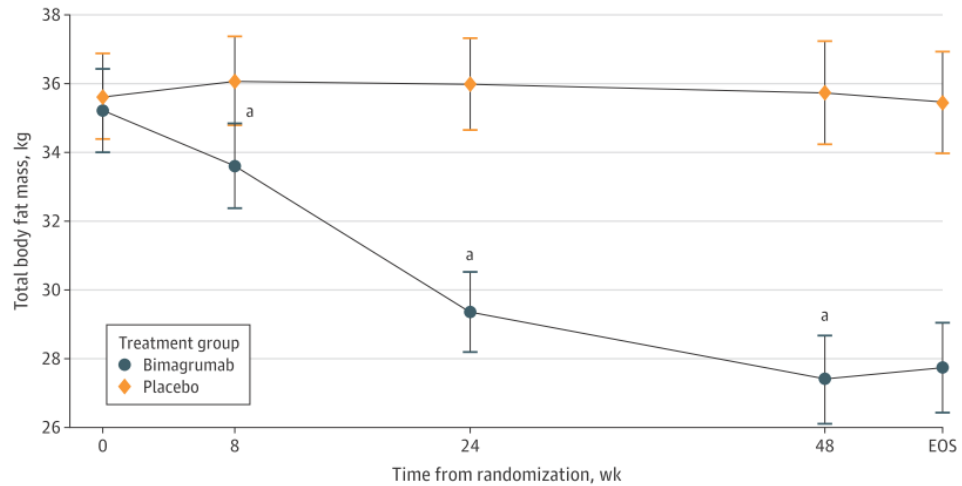
RESULTS A total of 75 patients were randomized to bimagrumab (n = 37; 23 [62.2%] women) or placebo (n = 38; 12 [31.6%] women); 58 (77.3%) completed the 48-week study. Patients at baseline had a mean (SD) age of 60.4 (7.7) years; mean (SD) BMI of 32.9 (3.4); mean (SD) BW of 93.6 (14.9) kg mean (SD) FM of 35.4 (7.5) kg; and mean (SD) HbA_{1c} level of 7.8% (1.0%). Changes at week 48 for bimagrumab vs placebo were as follows: FM, −20.5% (−7.5 kg [80% CI, −8.3 to −6.6 kg]) vs −0.5% (−0.18 kg [80% CI, −0.99 to 0.63 kg]) ($P < .001$); LM, 3.6% (1.70 kg [80% CI, 1.1 to 2.3 kg]) vs −0.8% (−0.4 kg [80% CI, −1.0 to 0.1 kg]) ($P < .001$); WC, −9.0 cm (80% CI, −10.3 to −7.7 cm) vs 0.5 cm (80% CI, −0.8 to 1.7 cm) ($P < .001$); HbA_{1c} level, −0.76 percentage points (80% CI, −1.05 to −0.48 percentage points) vs 0.04 percentage points (80% CI, −0.23 to 0.31 percentage points) ($P = .005$), and BW, −6.5% (−5.9 kg [80% CI, −7.1 to −4.7 kg]) vs −0.8% (−0.8 kg [80% CI, −1.9 to 0.3 kg]) ($P < .001$). Bimagrumab's safety and tolerability profile was consistent with prior studies.

CONCLUSIONS AND RELEVANCE In this phase 2 randomized clinical trial, ActRII blockade with bimagrumab led to significant loss of FM, gain in LM, and metabolic improvements during 48 weeks

Table 2. Major End Points

End Point	Change (80% CI) [Participants, No.][a] Bimagrumab[b]	Placebo[b]	Difference[b]	*P* value
Primary				
FM, kg	−7.49 (−8.33 to −6.64) [26]	−0.18 (−0.99 to 0.63) [29]	−7.31 (−8.48 to −6.14)	<.001
Secondary				
Lean mass, kg	1.70 (1.14 to 2.26) [26]	−0.44 (−0.97 to 0.09) [29]	2.14 (1.36 to 2.93)	<.001
Body weight, kg	−5.90 (−7.08 to −4.71) [26]	−0.79 (−1.92 to 0.33) [30]	−5.10 (−6.74 to −3.47)	<.001
BMI	−2.19 (−2.60 to −1.78) [26]	−0.28 (−0.67 to 0.11) [30]	−1.91 (−2.48 to −1.34)	<.001
Waist circumference, cm	−9.00 (−10.3 to −7.68) [26]	0.45 (−0.79 to 1.69) [30]	−9.46 (−11.3 to −7.64)	<.001
Waist-to-hip ratio	−0.05 (−0.06 to −0.04) [26]	0.01 (0.00 to 0.02) [30]	−0.06 (−0.08 to −0.04)	<.001
HbA_{1c}, %	−0.76 (−1.05 to −0.48) [26]	0.04 (−0.23 to 0.31) [30]	−0.80 (−1.20 to −0.41)	.005
HOMA2, week 36	−0.09 (−0.44 to 0.25) [25]	0.57 (0.24 to 0.90) [27]	−0.66 (−1.14 to −0.18)	.08
QUICKI, week 36	0.01 (0.01 to 0.01) [26]	0.00 (0.00 to 0.00) [30]	0.01 (0.00 to 0.01)	.03
Matsuda Index	3.15 (2.39 to 3.91) [26]	1.78 (1.05 to 2.51) [28]	1.37 (0.31 to 2.43)	.10
Exploratory				
Hepatic fat fraction, %				
Week 24	−4.60 (−6.07 to −3.12) [18]	0.23 (−1.61 to 2.08) [11]	−4.83 (−7.20 to −2.46)	.006
Week 48	−7.00 (−8.58 to −5.43) [5]	−2.33 (−4.16 to −0.51) [5]	−4.67 (−7.09 to −2.25)	.01
Abdominal SAT, L				
Week 24	−0.97 (−1.37 to −0.56) [18]	−0.14 (−0.65 to 0.37) [11]	−0.83 (−1.48 to −0.18)	.05
Week 48	−1.71 (−2.40 to −1.03) [5]	−0.52 (−1.30 to 0.26) [4]	−1.19 (−2.23 to −0.15)	.07
Abdominal VAT, L				
Week 24	−1.49 (−1.69 to −1.29) [18]	0.22 (−0.03 to 0.48) [11]	−1.71 (−2.04 to −1.39)	<.001
Week 48	−1.52 (−2.42 to −0.62) [5]	−0.01 (−1.05 to 1.03) [4]	−1.51 (−2.87 to −0.14)	.08

Figure 2. Effect of Bimagrumab on Total Body Fat Mass



Heymsfield SB, et al. JAMA Netw Open 4:e2033457, 2021

American Diabetes Association®

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Embargoed until June 23, 2025 at 8:00am CT

New GLP-1 Therapies Enhance Quality of Weight Loss by Improving Muscle Preservation

Research indicates potential for new wave of breakthroughs in maintaining lean mass for patients taking GLP-1-based medications

CHICAGO, IL (June 23, 2025) — Findings from two groundbreaking studies highlight potential pharmacological and biosensor solutions for muscle mass preservation in patients undergoing obesity treatment therapy. Results from the BELIEVE study of bimagrumab and semaglutide combination therapy and a study of a novel continuous protein sensor for sarcopenia management were featured as a late-breaking symposium and late-breaking poster, respectively, at the 85th Scientific Sessions of the American Diabetes Association® (ADA) in Chicago.

Combination Therapy of Bimagrumab and Semaglutide Enhances Fat Loss and Preserves Muscle

Findings of study demonstrating the effectiveness of combining bimagrumab – a drug designed to combat muscle loss – with a common GLP-1 receptor agonist (RA), semaglutide, were presented during a late-breaking symposium.

The BELIEVE Phase 2b trial was a randomized, double-blind, placebo-controlled, multicenter study evaluating the effects of bimagrumab, alone and in combination with semaglutide, in adults with overweight or obesity. Bimagrumab is a first-in-class monoclonal antibody that

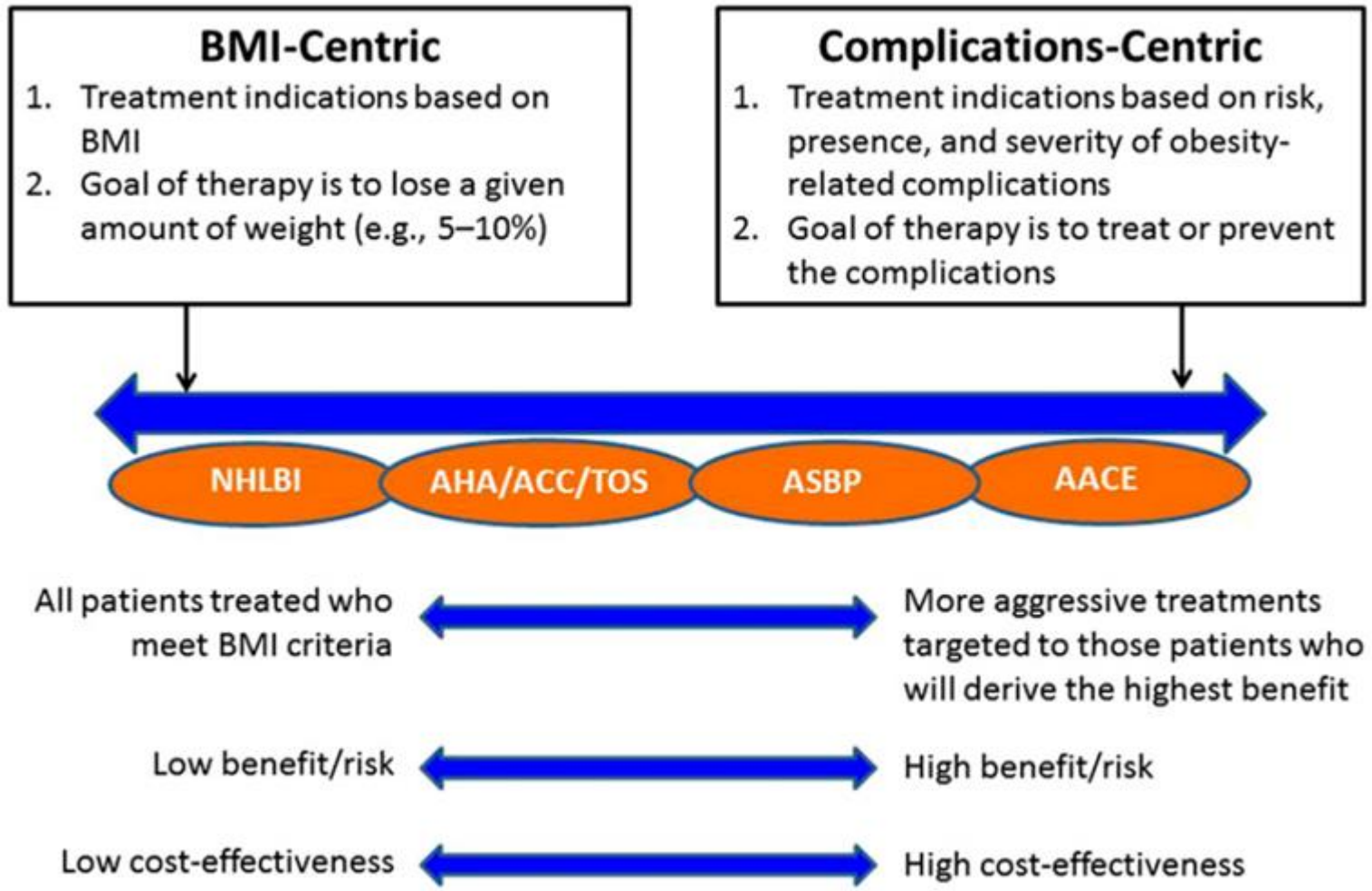
targets activin type II receptors, promoting muscle preservation and growth. 507 participants received semaglutide as a once-weekly subcutaneous injection and/or bimagrumab administered via intravenous (IV) infusion at weeks 4, 16, 28, and 40. The primary endpoint was change in body weight (BW) from baseline. Secondary endpoints included changes in waist circumference, total body fat mass, visceral adipose tissue, and lean mass.

The results demonstrated the combination of bimagrumab and semaglutide therapy led to greater reductions in weight, body fat, visceral fat, and markers of inflammation compared to either treatment alone. The combination therapy yielded 92.8% of total weight loss from fat mass compared to semaglutide alone (71.8%) and a 22.1% decrease in bodyweight (−10.8% bimagrumab alone; −15.7% semaglutide alone). Notably, with the use of bimagrumab alone, 100% of weight loss was attributed to fat mass and there was an increase of 2.5% total lean mass.

"This study represents another major step forward in the evolution of obesity treatment, building on the significant weight loss benefits of semaglutide and combining it with bimagrumab to improve patient outcomes," said Steven Heymsfield, MD, Professor at Pennington Biomedical Research Center and lead author of the study. "These insights indicate that is not only possible to achieve substantial fat loss, but also to preserve, or even enhance, lean mass in the process."

The researchers are conducting studies of bimagrumab in combination with tirzepatide to evaluate its impact on both efficacy and safety.

藥物分配(公平)問題: 誰可以用? 誰用了最好? (效益最大化)



Cefalu WT. Diabetes Care 38:1567-82, 2015

Diabetes and Obesity: Fair Allocation of Drugs

Table 2. Fair-Allocation Framework for GLP-1 and Dual GLP-1–GIP Receptor Agonists.*

Tier	Objective	Distribution Criteria
1	Minimize potential years of life lost by preventing excess and premature death	People with class III obesity (BMI, ≥40) and people with severe type 2 diabetes (glycated hemoglobin level, >8%) whose disease hasn't responded to alternative treatment Phase 1: younger patients (e.g., <50 yr of age) Phase 2: older patients
2	Prevent imminent medical complications, such as cardiovascular events	People with class II obesity (BMI, 35.0–39.9), followed by people with severe type 2 diabetes (glycated hemoglobin level, >8%) Phase 1: younger patients Phase 2: older patients
3	Prevent future medical complications, such as cardiovascular events	People with class I obesity (BMI, 30.0–34.9), followed by people with type 2 diabetes (glycated hemoglobin level, >7%) whose disease hasn't responded to alternative treatment Phase 1: younger patients Phase 2: older patients
4	Improve quality of life and social and emotional health	People with overweight (BMI, 25.0–29.9) or type 2 diabetes (glycated hemoglobin level, >7%) who aren't eligible under another tier Phase 1: younger patients Phase 2: older patients

* The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. GIP denotes glucose-dependent insulinotropic polypeptide, and GLP-1 glucagon-like peptide 1.

Emanuel EJ, et al. N Engl J Med 390: 1839-1842, 2024

觀點：（體重控制）

- 肥胖與第2型糖尿病均為「終身」「慢性疾病」：減重與"對作"
- 用藥治療需考慮
  - ✓ 治療的目的：用在誰→體重控制/血糖控制/預防(併生)疾病
  - ✓ 藥物劑量：減重劑量 vs. 控糖劑量
  - ✓ 用藥效果：個案、"專家"意見、實證→Evidence (+, 短期, Level: 期待↑)
  - ✓ 用藥策略：Debulking→Maintenance
  - ✓ 藥效持續/用藥多久問題：停藥後會如何?
    - ➢ Cure? Remission? Recurrence? active surveillance (watchful waiting)
  - ✓ 藥物分配(公平)問題：誰可以用？誰用了最好?（效益最大化）
- 背後的科學原理：Why↓BW? 作用機轉?
- 未來趨勢：戰國→平衡