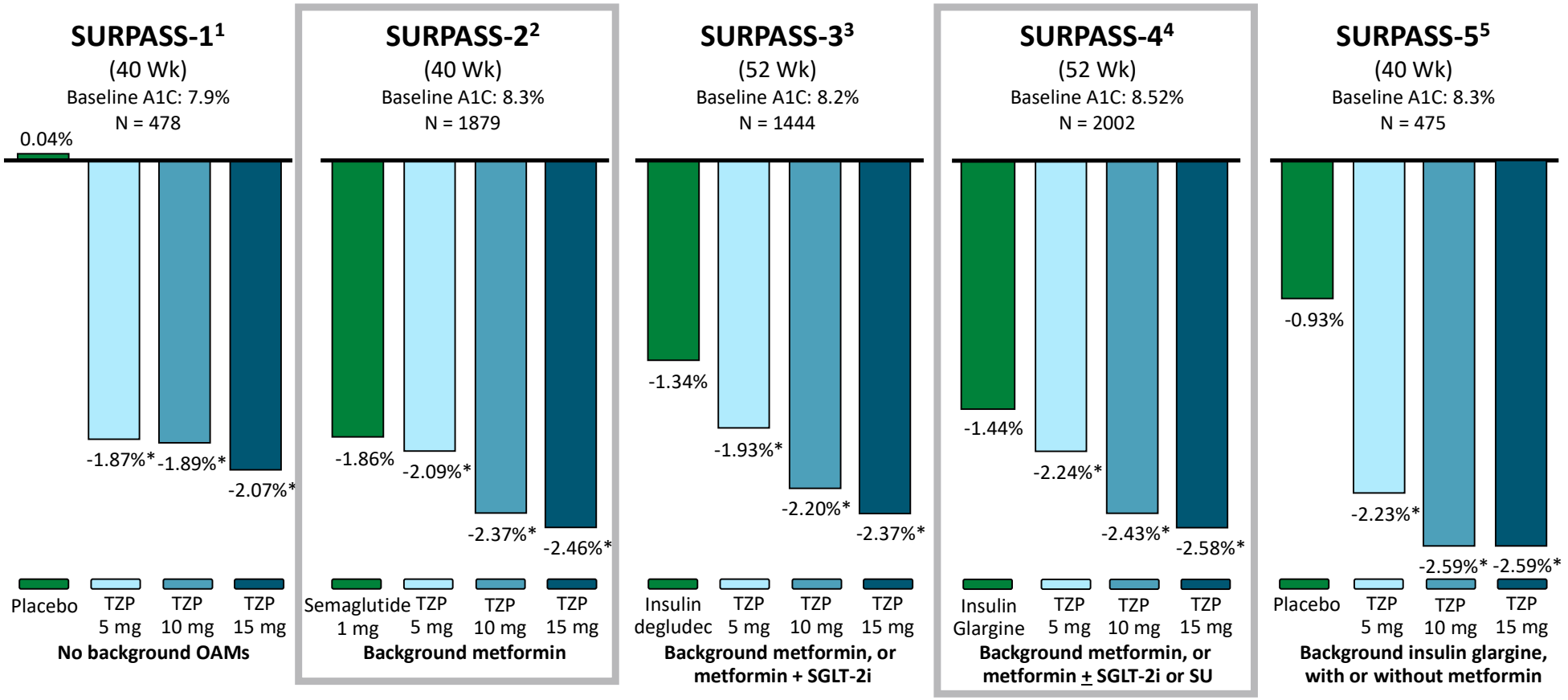
SURPASS study program (DM)

- phase III clinical program
- **eight studies** - investigated the **efficacy and safety of tirzepatide** in comparison to established antidiabetic medications **in T2D**
  - in monotherapy
  - combination with metformin
  - metformin and insulin glargine

- design of these studies was comparable
- starting with **2.5 mg once weekly** - increments of **2.5 mg every 4 weeks** until the randomized final treatment dosages of **5, 10, or 15 mg**

- *study results of the studies SURPASS-1 to SURPASS-5 have been published*
- remaining studies (SURPASS-6, SURPASS-CVOT, SURPASS-J-mono, SURPASS-J-combo; SURPASS-AP-combo - are ongoing)

SURPASS: Tirzepatide Reduces A1C in Type 2 Diabetes



1. Rosenstock. Lancet. 2021;398:143. 2. Frias. NEJM. 2021;385:503. 3. Giorgino. ADA 2021. Abstr 78-LB. 4. Del Prato. Lancet. 2021;398:1811. 5. Dahl. ADA 2021. Abstr 80-LB.

*Denotes statistical significance to comparator.

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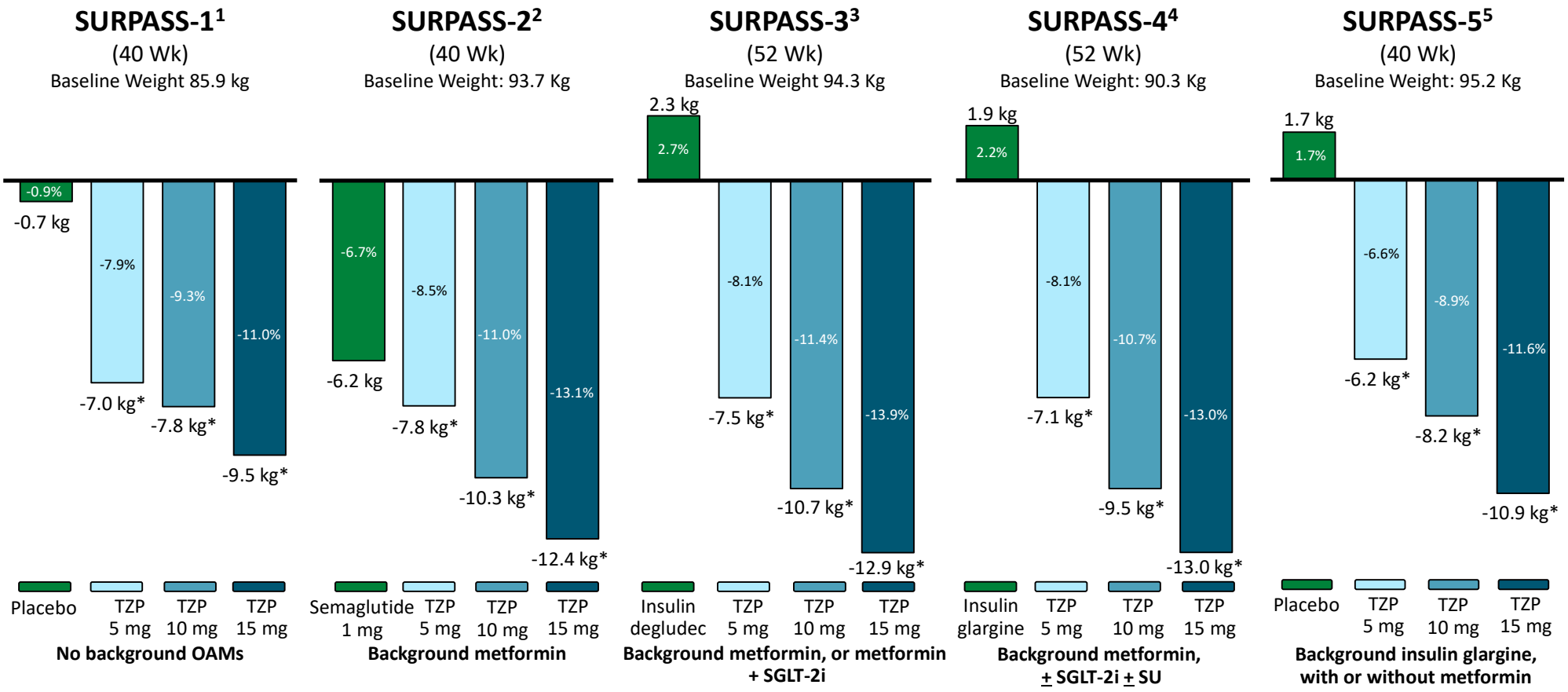
SURPASS: Weight Loss With Tirzepatide in T2D



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The NEW ENGLAND JOURNAL of MEDICINE

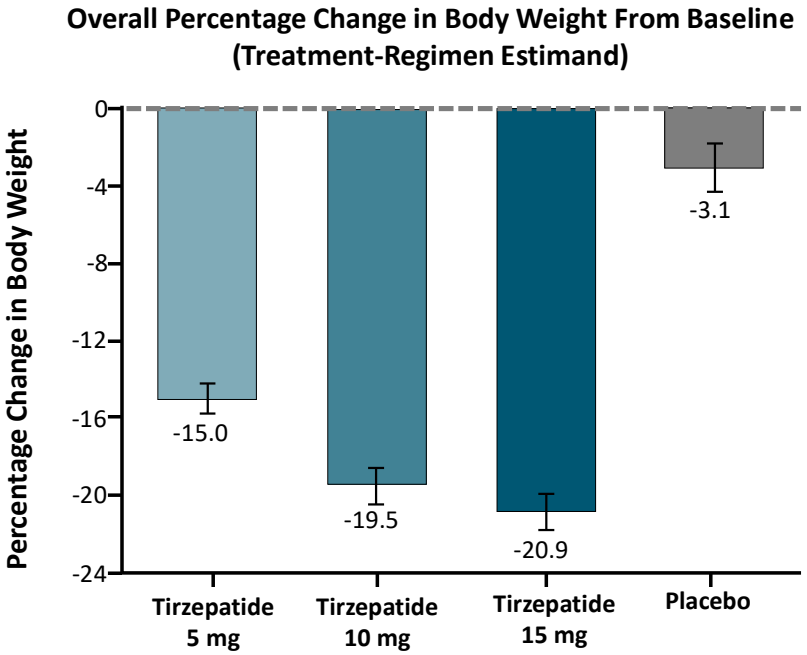
ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

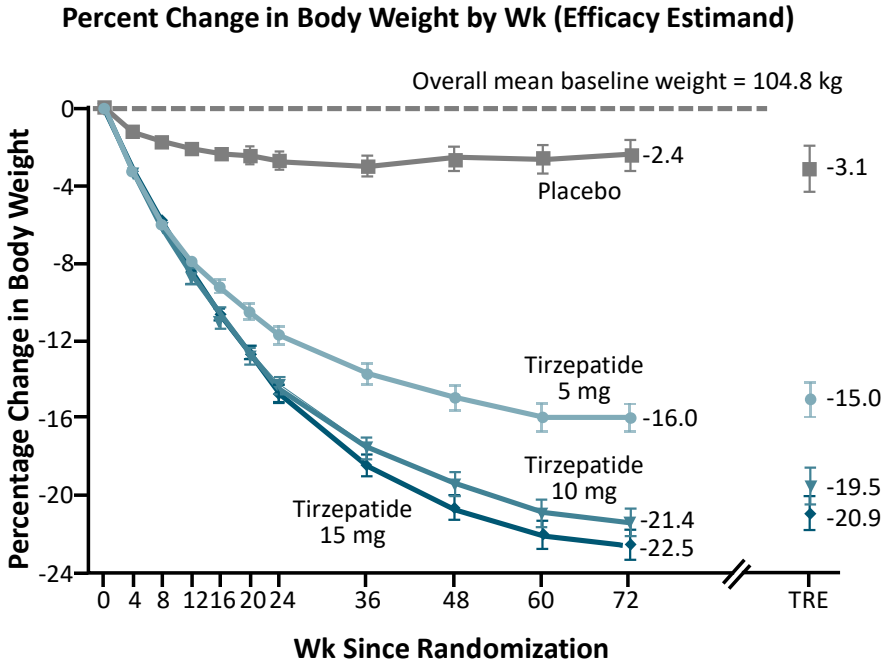
Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

SURMOUNT 1 TRIAL – primary obesity

SURMOUNT 1: Weight Loss With Tirzepatide

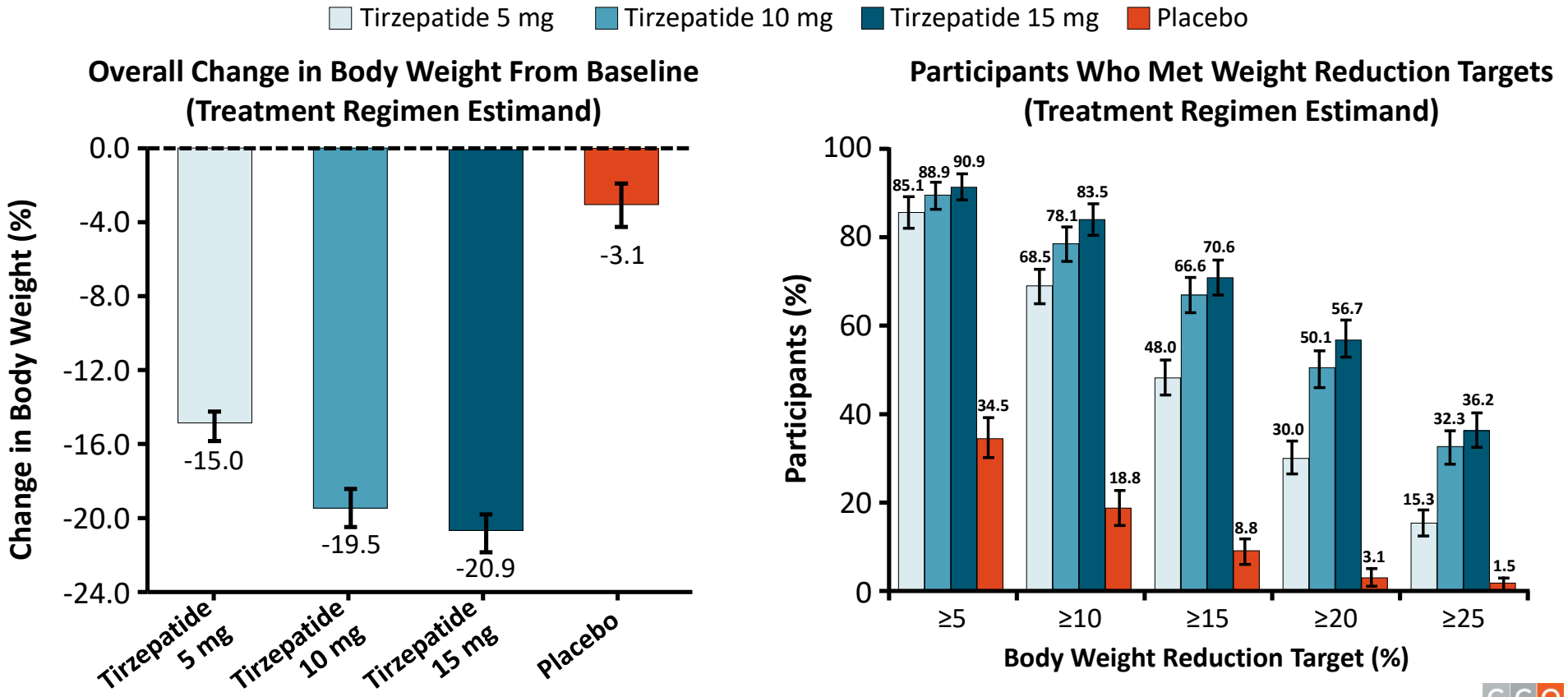




Jastreboff. NEJM. 2022;387(3):205.

Slide credit: clinicaloptions.com

Adult Effectiveness of Tirzepatide



Jastrebof. NEJM. 2022;383:205.

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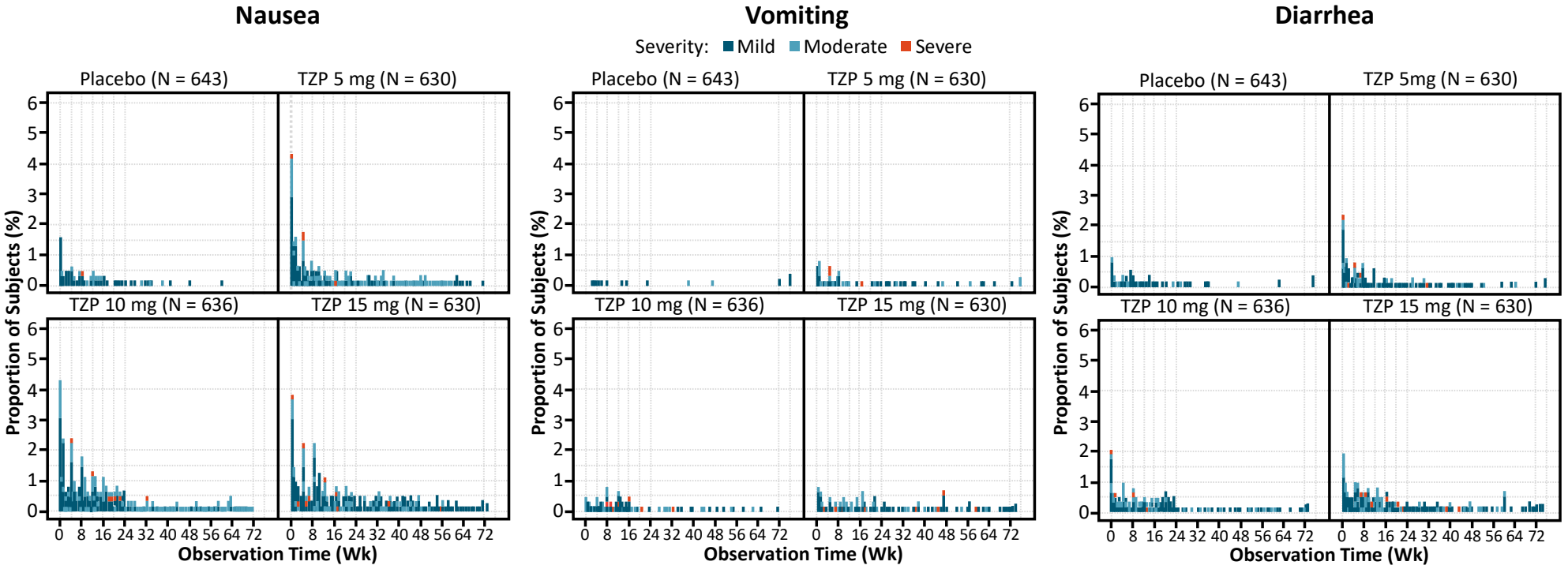
SURMOUNT 1: GI Adverse Events With Tirzepatide



Jastreboff. NEJM. 2022;387:205.

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Other upcoming medications

- **Cagrilintide** – amylin receptor agonist
- Cargri-Sema – REDEFINE 1 (2026) 3 arms 2.4 +2.4mg

- Glucagon + GLP1 = **Pemvidutide & Mazdutide**
- Glucagon + GLP1 + GIP = **Retatrutide** (phase 2 published NEJM 08/23)

- **Danuglipiron and Orfoglipiron –** orally administrated, small molecule GLP1 R agonist
- **Monthly GIP and GLP1**

- **Bimagrumab**
  - Monoclonal AB for Activin type 2 receptors
  - 20% fat loss and 3.6% increase in muscle mass

- **Setmelanotide** – MCR4R agonist

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D., for the Retatrutide Phase 2 Obesity Trial Investigators*

Triple-Hormone-Receptor Agonist Retatrutide for Obesity

- Retatrutide = **agonist** of the **GIP, GLP1, glucagon receptors**

- phase 2, BMI >30, 338 adults, 51.8% men

- *subcutaneous* Retatrutide (**1 mg, 4 mg, 8 mg or 12 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**

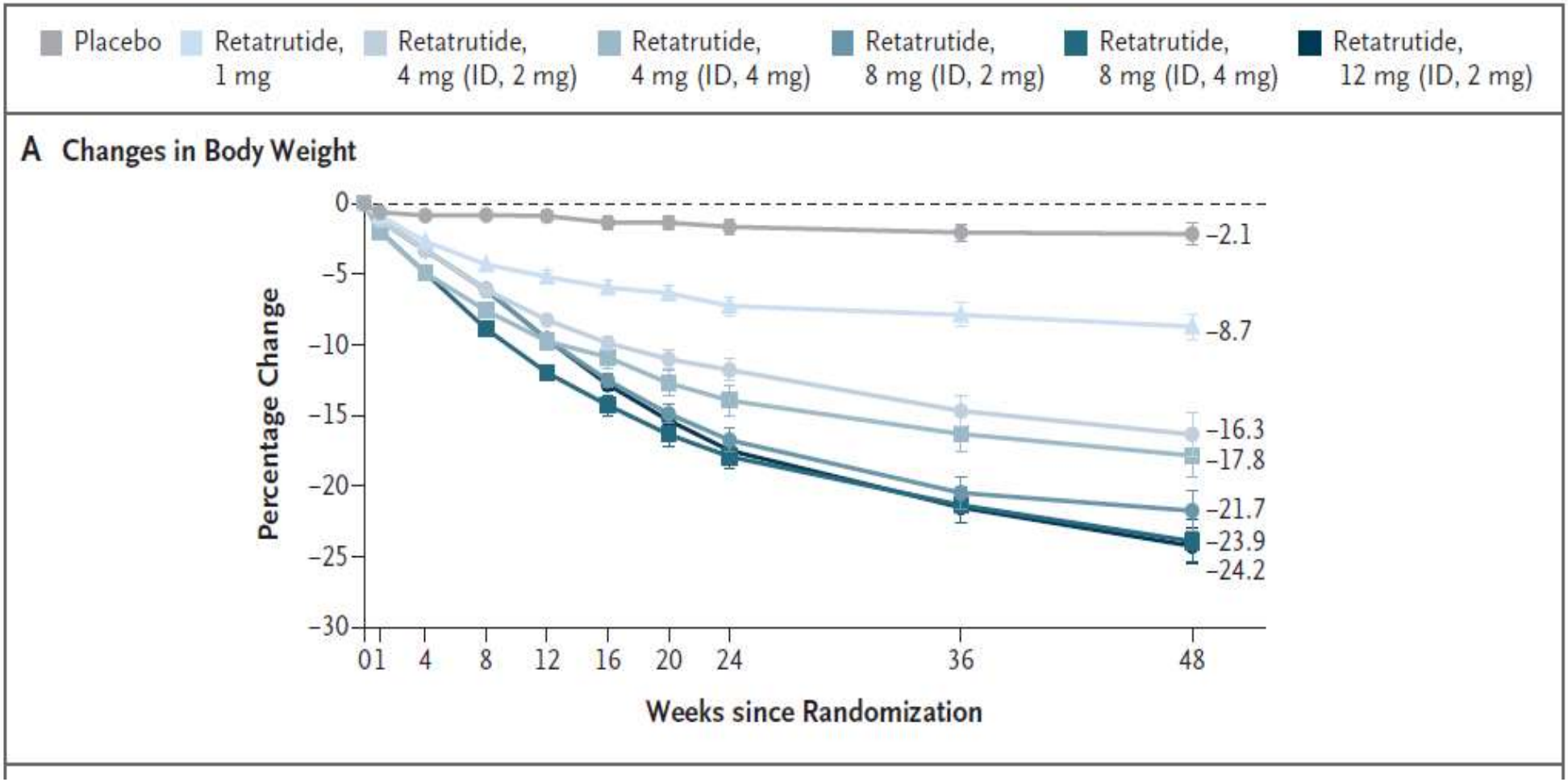
- change in body weight at **24 weeks** in the retatrutide **-17.5% in the 12-mg group**, as compared with **-1.6%** in the placebo group.
- At **48 weeks,** change in the retatrutide **-24.2% in the 12-mg group,** as compared with -2.1% in the placebo group

- At 48 weeks, a weight reduction of **5% or more, 10% or more, and 15%** or more had occurred in **100%, 93%, and 83%** of those who received **12 mg**

- The most common adverse events in the retatrutide groups were **gastrointestinal**, dose-related, were mostly mild to, *partially mitigated with a lower starting dose (2 mg vs. 4 mg).*

- **Conclusions:** In adults with obesity, retatrutide treatment for 48 weeks **resulted in substantial reductions in body weight**.

(Funded by Eli Lilly)



Retatrutide associated with improvements in cardio-metabolic measures including systolic and diastolic blood pressure, **glycated hemoglobin**, fasting glucose, insulin and lipids at weeks 24 and 48

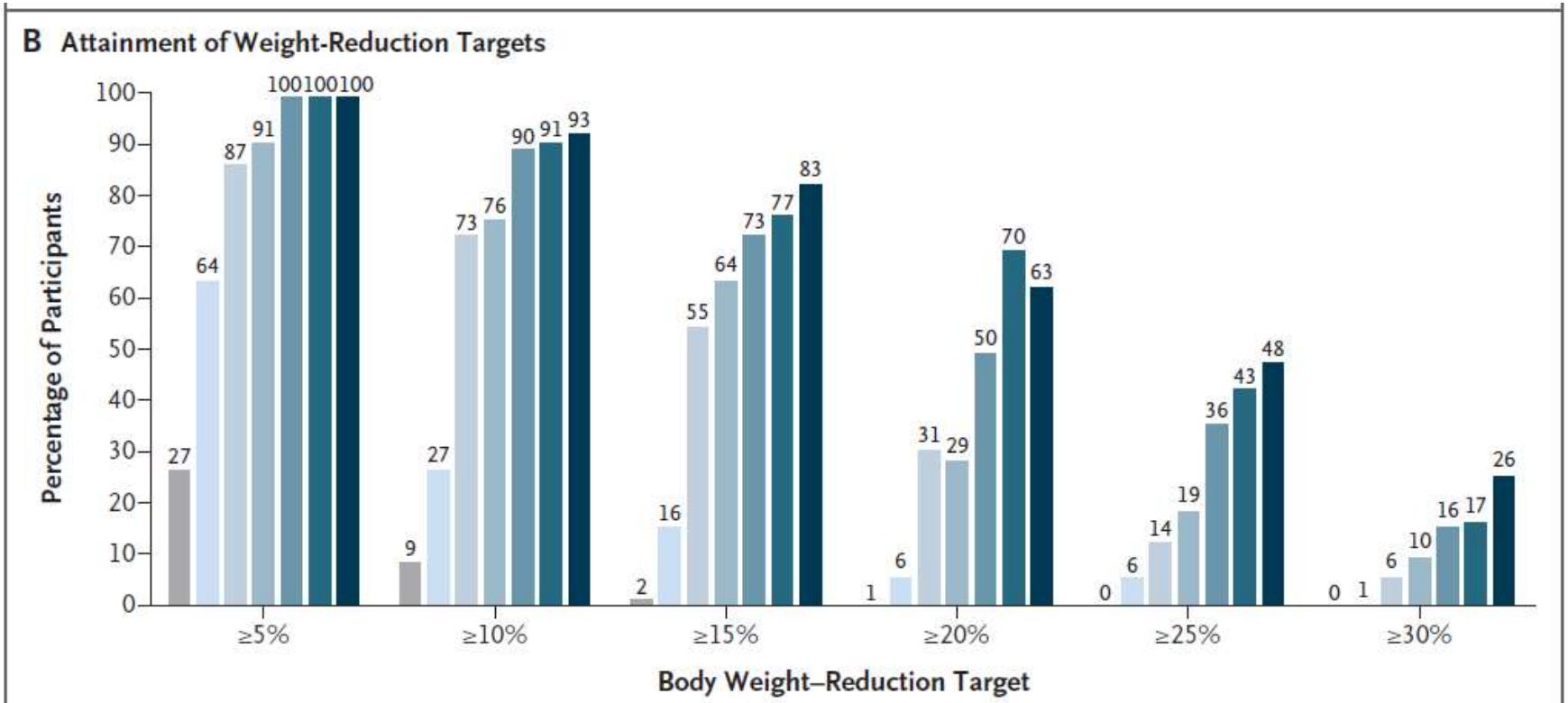
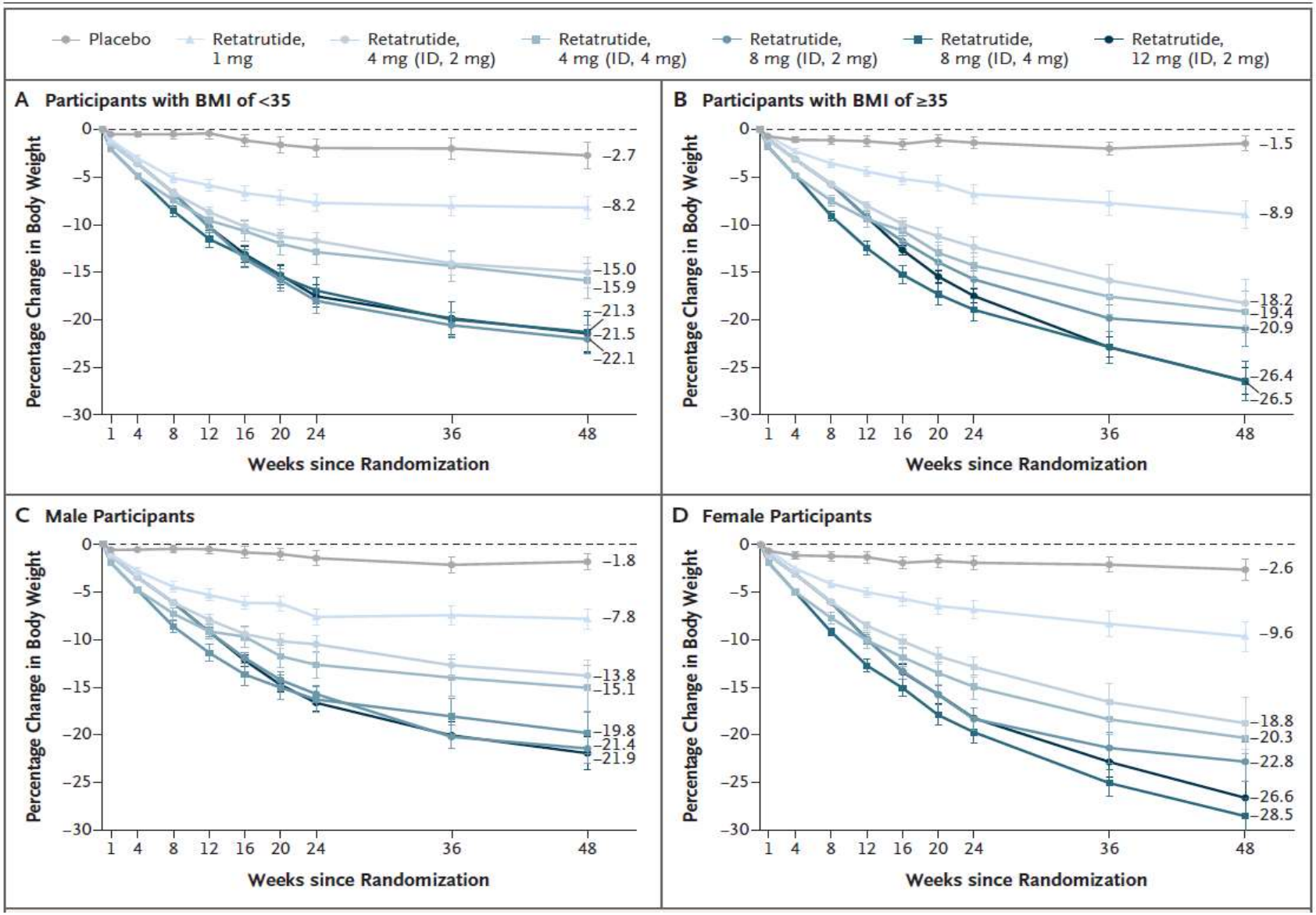


Figure 1. Changes in Body Weight with Retatrutide as Compared with Placebo.

Panel A shows the percentage change in body weight from baseline to week 48, derived from a mixed model for repeated measures (MMRM) analysis for the efficacy estimand. The values shown are least-squares means; I bars indicate standard errors. Panel B shows the percentages of participants with percentage body-weight reductions of at least 5%, 10%, 15%, 20%, 25%, and 30% from baseline to week 48. Efficacy end points were analyzed with data from all the participants who underwent randomization, excluding those who discontinued treatment because of inadvertent enrollment. ID denotes initial dose.


Placebo
Retatrutide, 1 mg
Retatrutide, 4 mg (ID, 2 mg)
Retatrutide, 4 mg (ID, 4 mg)
Retatrutide, 8 mg (ID, 2 mg)
Retatrutide, 8 mg (ID, 4 mg)
Retatrutide, 12 mg (ID, 2 mg)
A Participants with BMI of <35
B Participants with BMI of ≥35
C Male Participants
D Female Participants
Percentage Change in Body Weight
Weeks since Randomization
0
−5
−10
−15
−20
−25
−30
1 4 8 12 16 20 24 36 48
−2.7
−8.2
−15.0
−15.9
−21.3
−21.5
−22.1
−1.5
−8.9
−18.2
−19.4
−20.9
−26.4
−26.5
−1.8
−7.8
−13.8
−15.1
−19.8
−21.4
−21.9
−2.6
−9.6
−18.8
−20.3
−22.8
−26.6
−28.5

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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

Steven B. Heymsfield, MD; Laura A. Coleman, PhD, RD; Ram Miller, MD; Daniel S. Rooks, PhD; Didier Laurent, PhD; Olivier Petricoul, PhD; Jens Praestgaard, PhD; Therese Swan, PharmD; Thomas Wade, MD; Robert G. Perry, MD; Bret H. Goodpaster, PhD; Ronenn Roubenoff, MD, MHS

Bimagrumab blocks activin type II receptors associated with growth of skeletal muscle

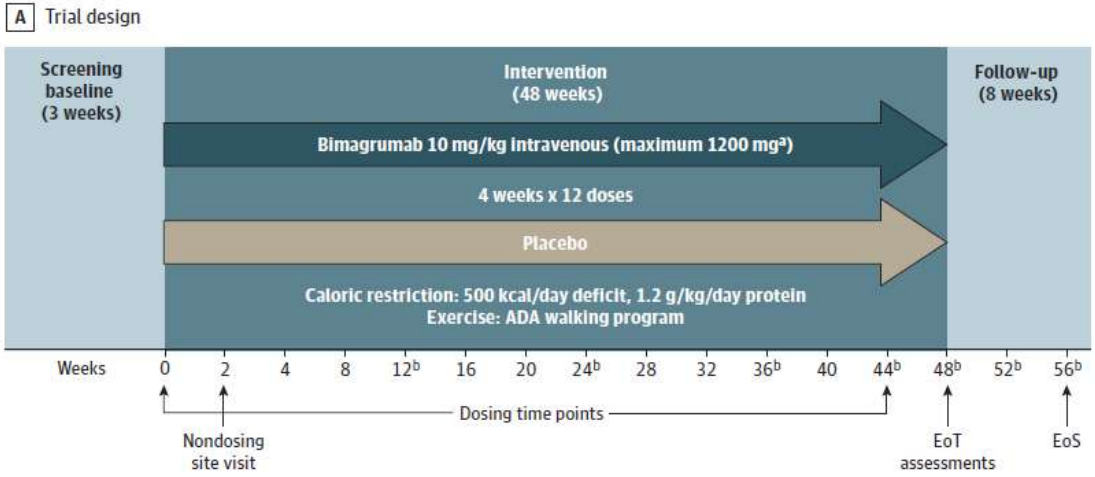


Figure 2. Effect of Bimagrumab on Total Body Fat Mass

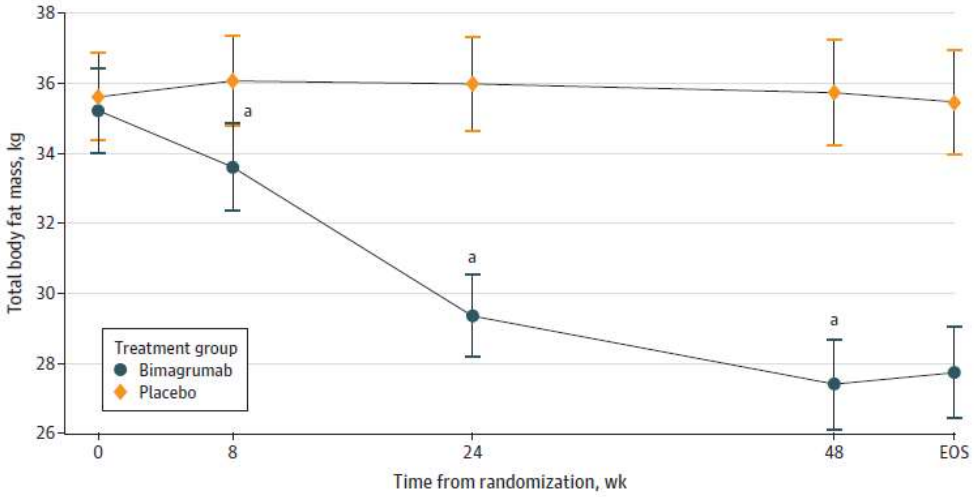


Table 3. Adverse Events[a]

	Patients, No. (%)	
Adverse event	Bimagrumab group	Placebo group
Death	0	0
Serious adverse events	3 (8)	3 (8)
Any adverse event	31 (84)	31 (82)
Adverse event leading to study discontinuation	5 (14)	0
Most frequent adverse events[b]		
Diarrhea	15 (41)	4 (11)
Muscle spasms	15 (41)	1 (3)
Upper respiratory tract infection	6 (16)	5 (13)
Lipase level increased	4 (11)	2 (5)
Headache	0	5 (13)
Hypertension	3 (8)	1 (3)
Nausea	4 (11)	0
Rash	2 (5)	2 (5)

Table 2. Major End Points

End Point	Change (80% CI) [Participants, No.][a]			*P* value
	Bimagrumab[b]	Placebo[b]	Difference[b]	
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

CNS Regulation of Energy Balance

- Energy balance is controlled by regions of the CNS - hypothalamus and caudal brainstem

- **hypothalamus** = 'command center' for energy balance regulation
- discrete nuclei that are fundamental for energy homeostasis
- ARC contains two major neuronal populations that control caloric intake and expenditure

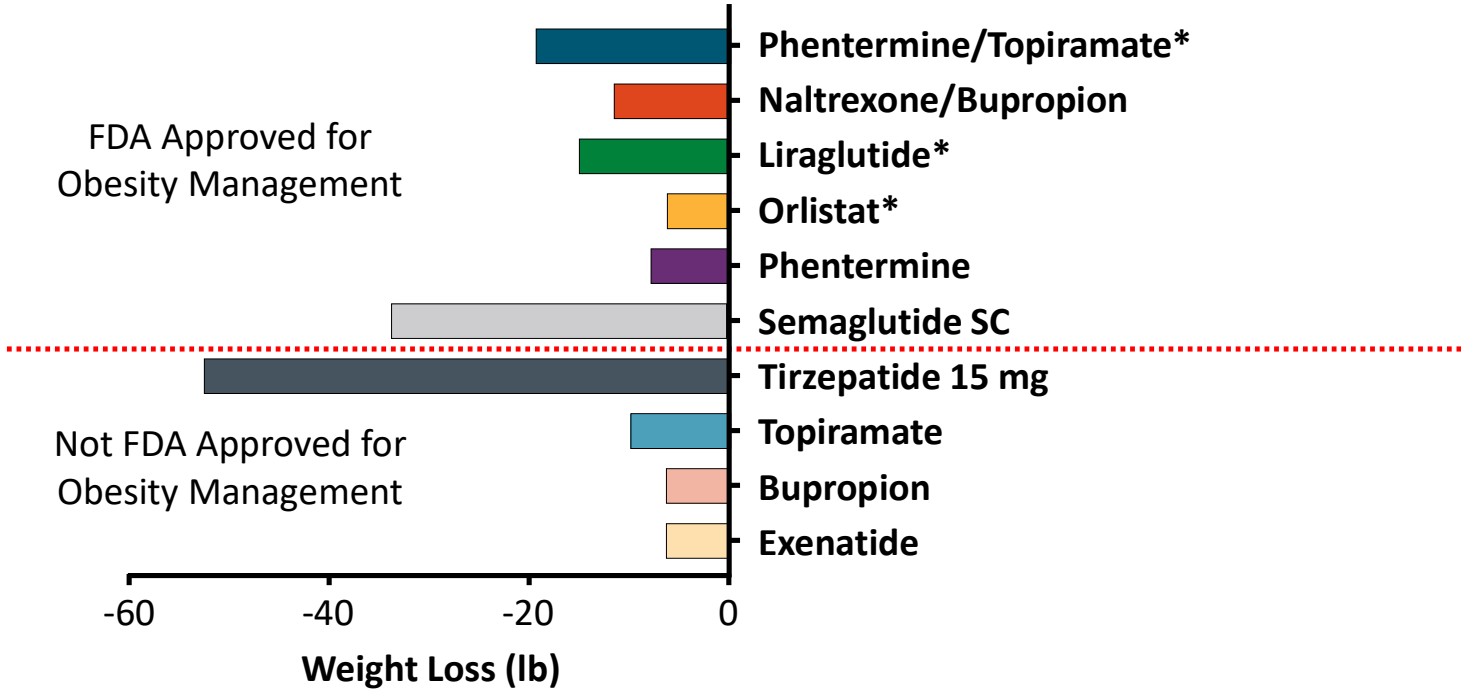
- **brainstem** - important role in the control of food intake - responding to **short-term satiety signals**
- dorsal vagal complex (area postrema, nucleus tractus solitarius, dorsal nucleus of the vagus) controls meal size and frequency

- Similarly to the hypothalamus, these nuclei are located in close **proximity to the ventricular system** and thus have direct access to circulating hormones and nutrients

brain senses, monitors, and integrates dietary nutrient, hormonal (gut peptides GLP-1, PYY, etc), and neural (vagal afferent) signals from the gastrointestinal tract

- caloric intake and energy balance - modulated by brain regions associated with motivational and reward-related feeding, including the ventral tegmental area, nucleus accumbens, amygdala, others

Average Weight Loss With Pharmacotherapy



*Approved in pediatrics.

Adapted from Jastrebof. NEJM. 2022;383:205. Wilding. NEJM. 2021;384:989. Butch ABOM Course 2016.

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