New and Emerging Pharmaceutical Options

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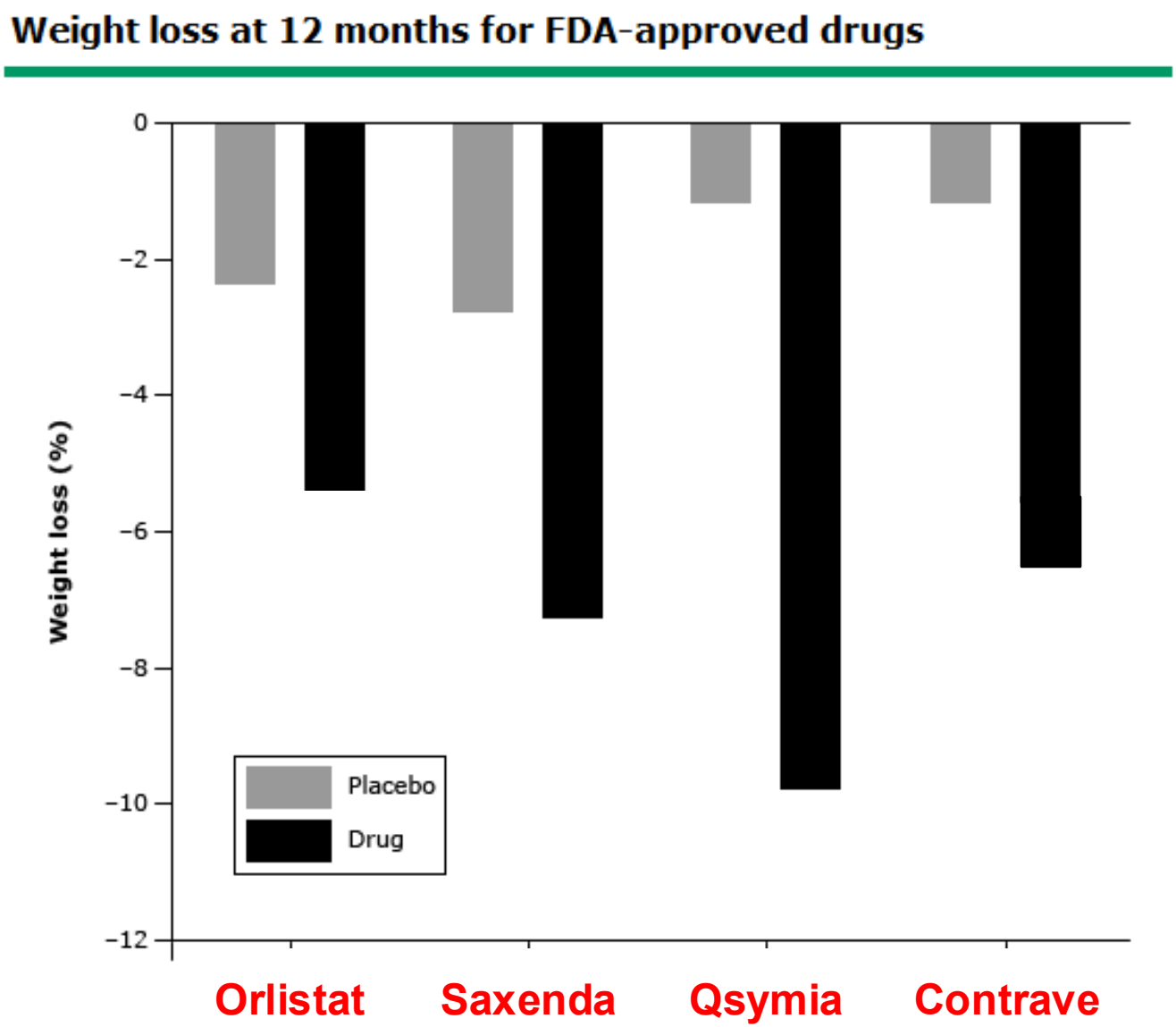
University of Washington
VA Puget Sound Health Care System

Scientific Advisory Boards

- Lumen Bioscience
- Morphic Medical
- AbbVie
- Endogenex

Older Obesity Medicines



Placebo-subtracted weight loss: ~3-8%

Khera, R, et al.. *JAMA* 315.22::2424 (2016)

Semaglutide

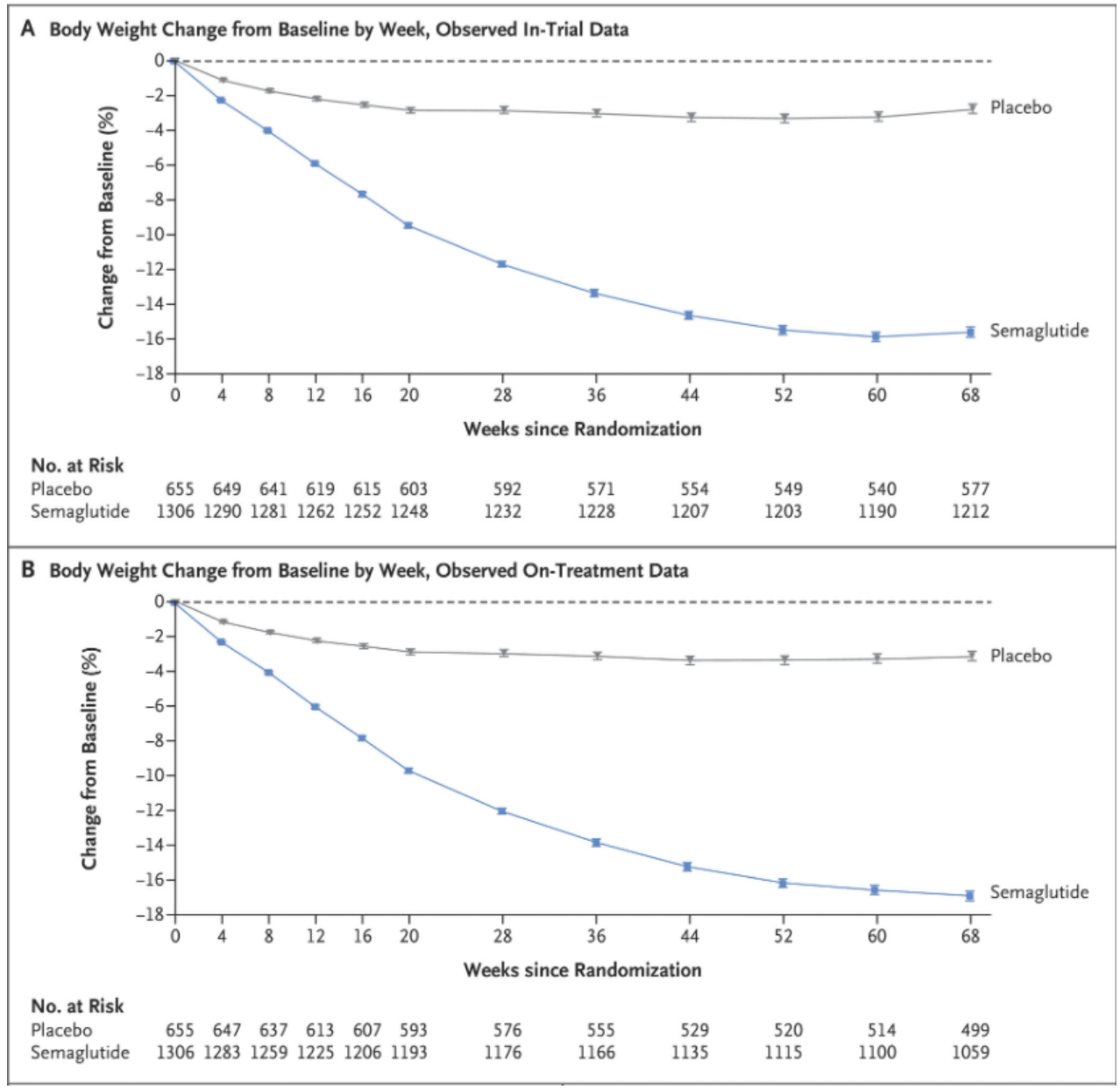
a GLP-1 receptor agonist

GLP-1 receptor agonists were developed in part based on studies examining how metabolic-bariatric surgery works

STEP 1: Semaglutide *vs*. Placebo - *No Diabetes*

n=1,961

Body Weight Change (%)

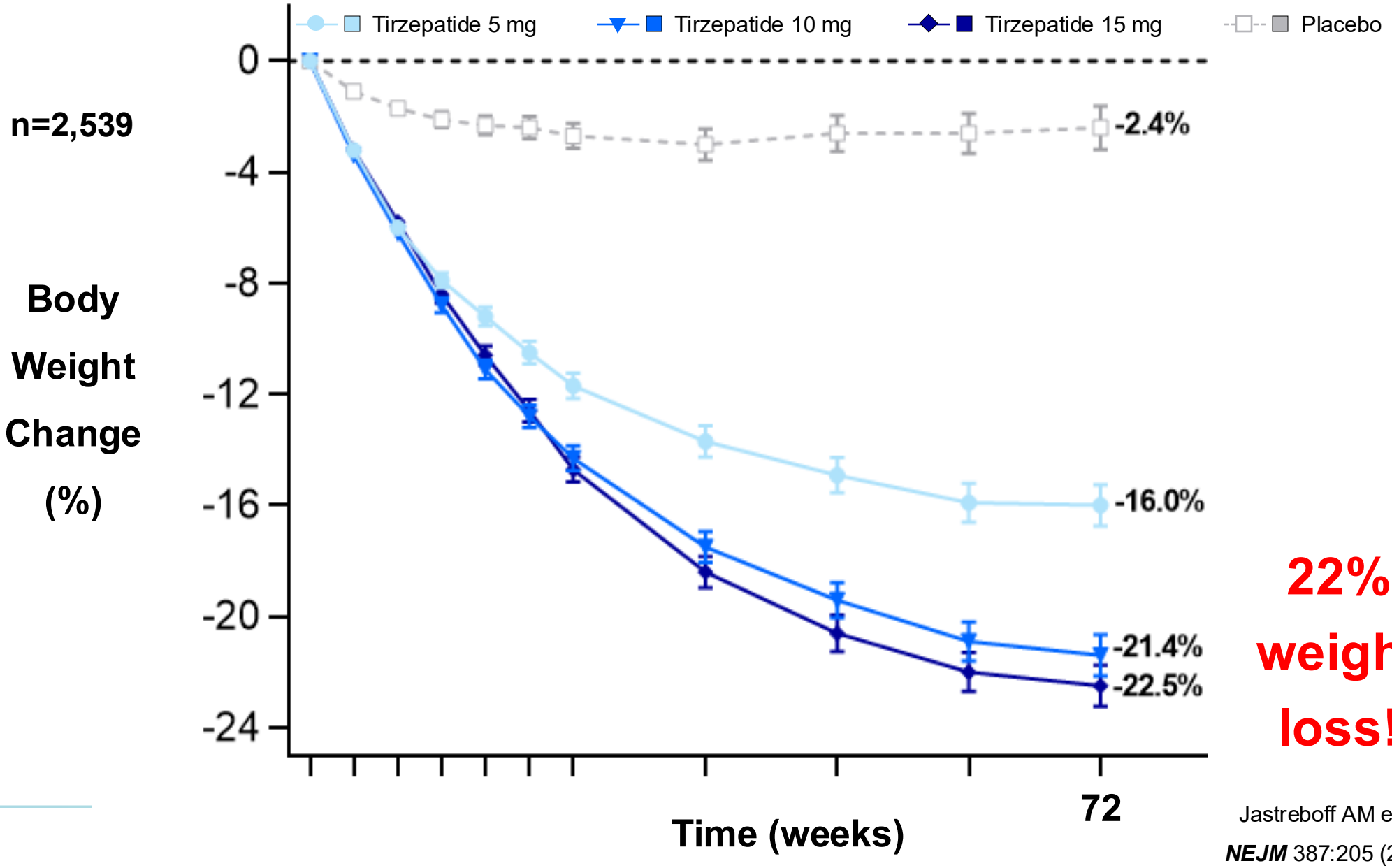


15% weight loss

Wilding, et al.

NEJM 384:989 (2021)

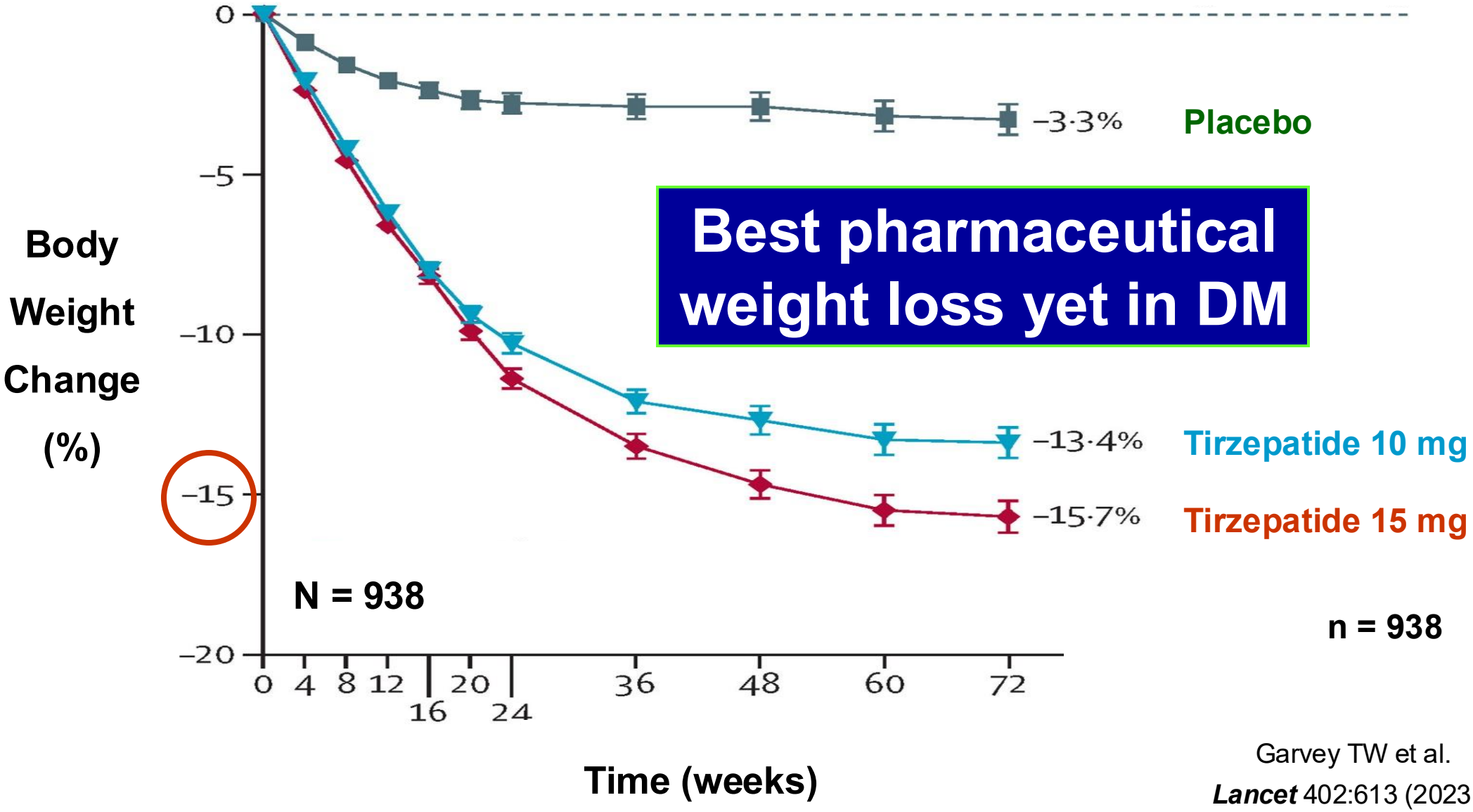
SURMOUNT-1: Tirzepatide *vs.* Placebo – *No Diabetes*



22% weight loss!

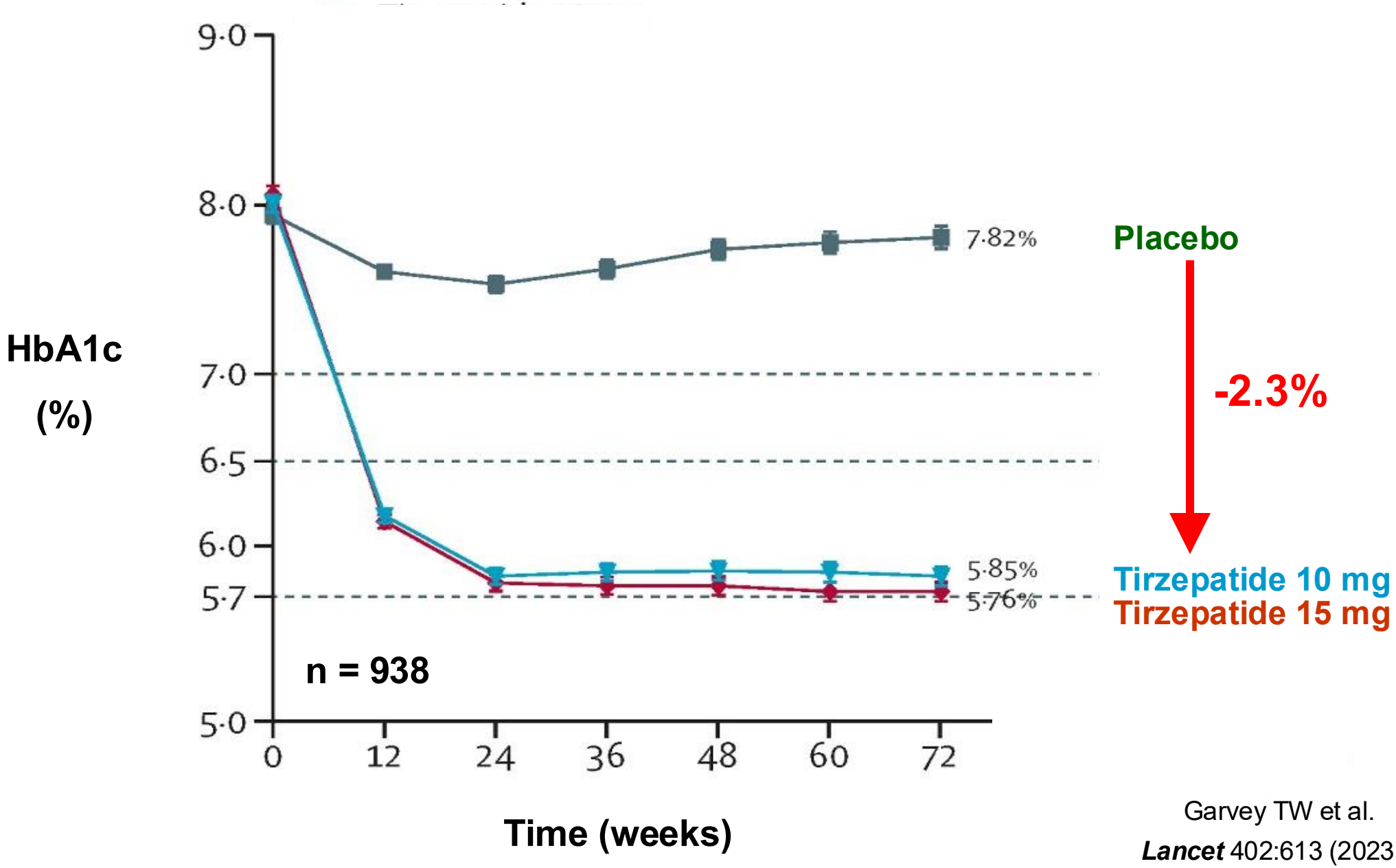
Jastreboff AM et al.
NEJM 387:205 (2022)

SURMOUNT 2: Tirzepatide *vs.* Placebo *With Diabetes*



Garvey TW et al.
Lancet 402:613 (2023)

SURMOUNT 2: Tirzepatide *vs*. Placebo ***With Diabetes***



Garvey TW et al.
Lancet 402:613 (2023)

What about effects of incretin meds on harder outcomes?

Benefits on Hard Outcomes with Incretin Meds in RCTs

- **Weight loss & diabetes improvement**
  - Improved lipids & bp
- **↓ Major adverse kidney events**
  - Perkovic V, ***NEJM*** 2024 (FLOW)
- **↓ Major adverse liver events**
  - Kanwal F, ***JAMA IM*** 2024
- **↓ Sleep apnea** (↓ AHI by 50%)
  - Malhotra A, ***NEJM*** 2024 (SURMOUNT-OSA)
- **Osteoarthritis improvement**
  - Bliddal H, ***NEJM*** 2024
- **↓ CHF**
  - STEP-HFpEF & SUMMIT
- **↓ Major adverse cardiovascular events**
  - SELECT, SUSTAIN 6, SURPASS-CVOT

Promising additional findings from observational studies

Other Possible Benefits with Incretin Meds

- ↓ Cancer
- ↓ Alcohol & substance abuse
- ↓ Suicide & self harm
- ↓ Dementia

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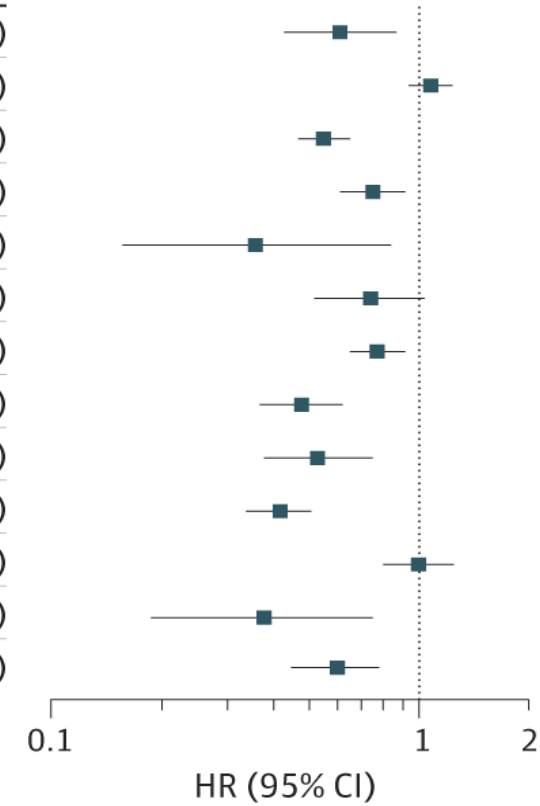
Incretin Med Use Associated with Reduced Cancer Risk

In 10 out of 13 Obesity-Associated Malignancies

n = 1.7 million

Outcome (N = 1 651 452)	Group prescribed GLP-IRAs but not insulin, No (%) (n = 48 983)	Group prescribed insulin but not GLP-IRAs, No (%) (n = 1 044 745)	HR (95% CI)
Esophageal cancer (n = 48 437)	49 (0.10)	77 (0.16)	0.60 (0.42-0.86)
Breast cancer (n = 13 768)	427 (3.08)	379 (2.94)	1.07 (0.93-1.23)
Colorectal cancer (n = 48 443)	223 (0.46)	391 (0.81)	0.54 (0.46-0.64)
Endometrial cancer (n = 25 750)	160 (0.62)	210 (0.82)	0.74 (0.60-0.91)
Gallbladder cancer (n = 48 587)	<10 (<0.02)	19 (0.04)	0.35 (0.15-0.83)
Stomach cancer (n = 48 449)	56 (0.12)	75 (0.16)	0.73 (0.51-1.03)
Kidney cancer (n = 48 322)	223 (0.46)	284 (0.59)	0.76 (0.64-0.91)
Hepatocellular carcinoma (n = 48 397)	79 (0.16)	167 (0.35)	0.47 (0.36-0.61)
Ovarian cancer (n = 25 739)	51 (0.20)	94 (0.37)	0.52 (0.37-0.74)
Pancreatic cancer (n = 48 490)	123 (0.25)	290 (0.60)	0.41 (0.33-0.50)
Thyroid cancer (n = 48 527)	154 (0.32)	149 (0.31)	0.99 (0.79-1.24)
Meningioma (n = 48 518)	11 (0.02)	29 (0.06)	0.37 (0.18-0.74)
Multiple myeloma (n = 48 527)	80 (0.17)	131 (0.27)	0.59 (0.44-0.77)



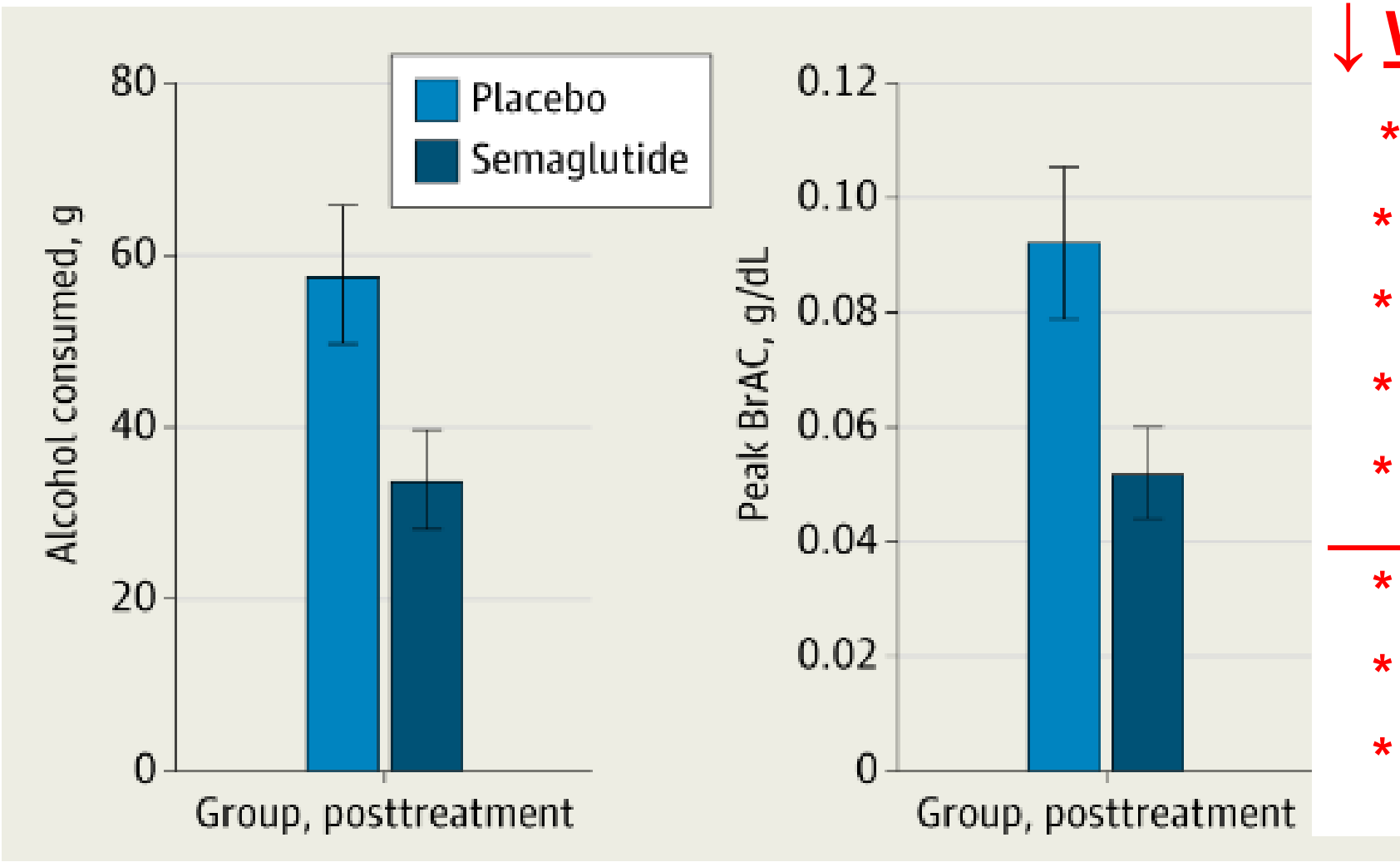
Wang L et al.
JAMA Network Open (2024)

Other Possible Benefits with Incretin Meds

- ↓ **Cancer**
  - 10 out of 13 obesity-related cancers
- ↓ **Alcohol & substance abuse**
- ↓ **Suicide & self harm**
- ↓ **Dementia**

Semaglutide Decreases Alcohol Use in an RCT

Inpatient RCT



↓ With Sema:

* EtOH drunk
* [EtOH]
* Cravings
* Heavy drinking
* Smoking

---

* Other drugs
* Gambling
* Shopping

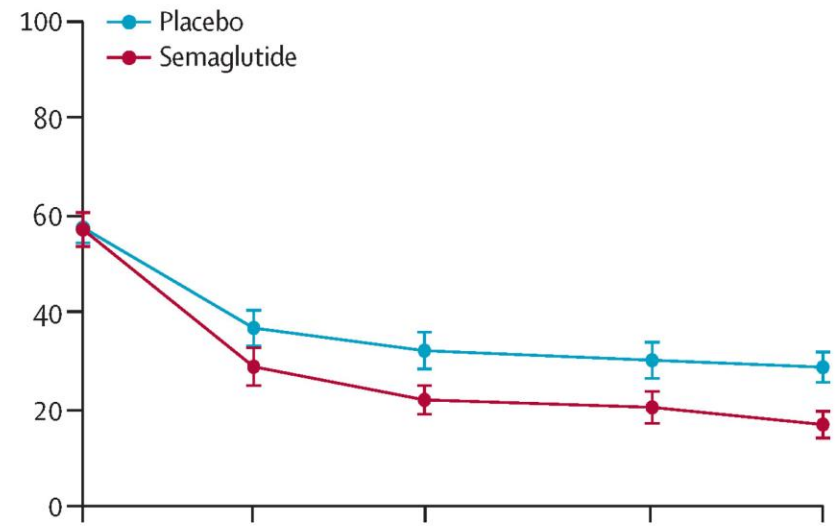
Tirzepatide Also Appears to Decrease Alcohol Use

Hendershot CS, et al
JAMA Psych 2/12/2025

Semaglutide Reduces Drinking Among People with Alcohol Use Disorder

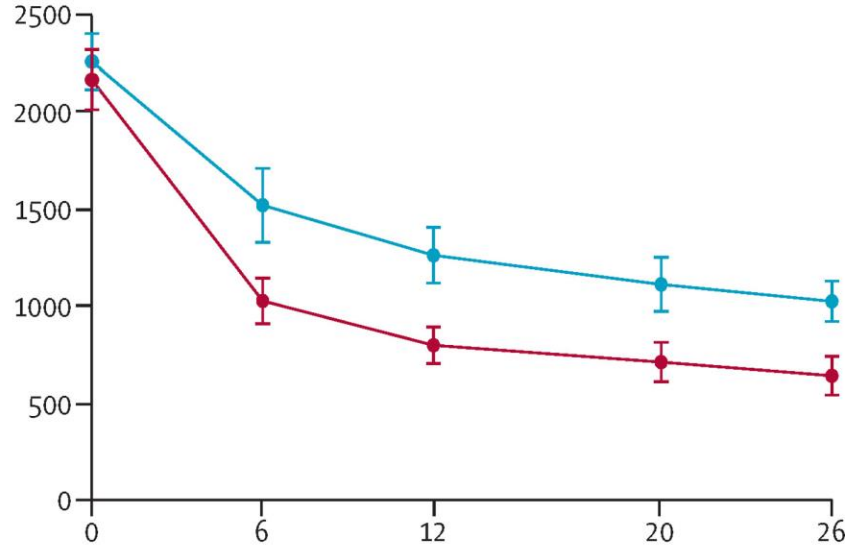
Outpatient RCT

% Heavy Drinking Days



N = 108

Alcohol Consumed (gm/month)



Weeks

↓ with Semaglutide

- **Heavy drinking days**
- **Total EtOH drunk**
- **# Drinks/day**
- **EtOH cravings**
- **EtOH exposure biomarkers**

NNT = 4

Klausen MK, et al.

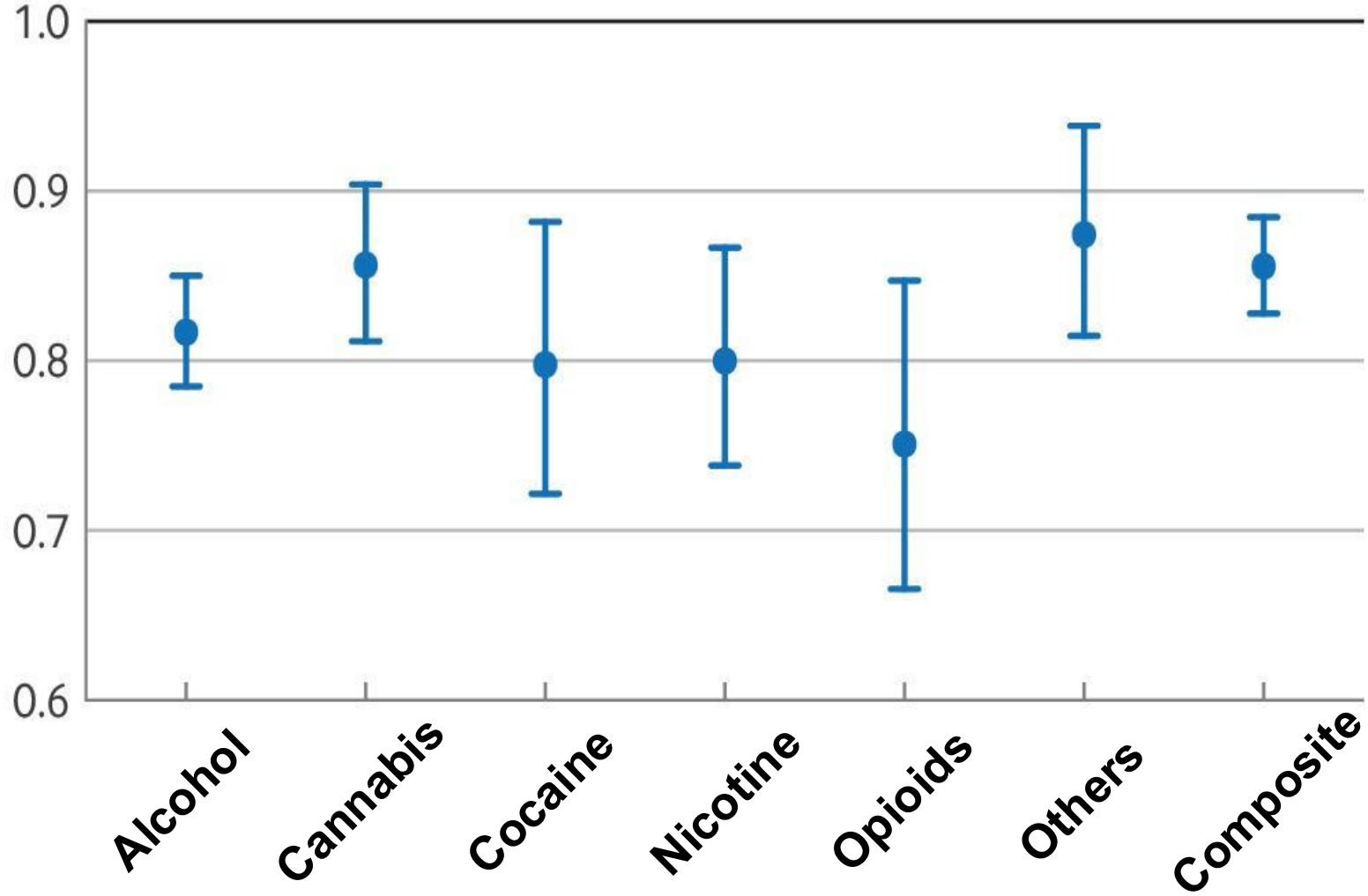
The Lancet 407:1687

(May 2026)

Lower Incidence of Substance Abuse Disorders with Incretin Med Use

n = 606,434

F/U = 3 yrs

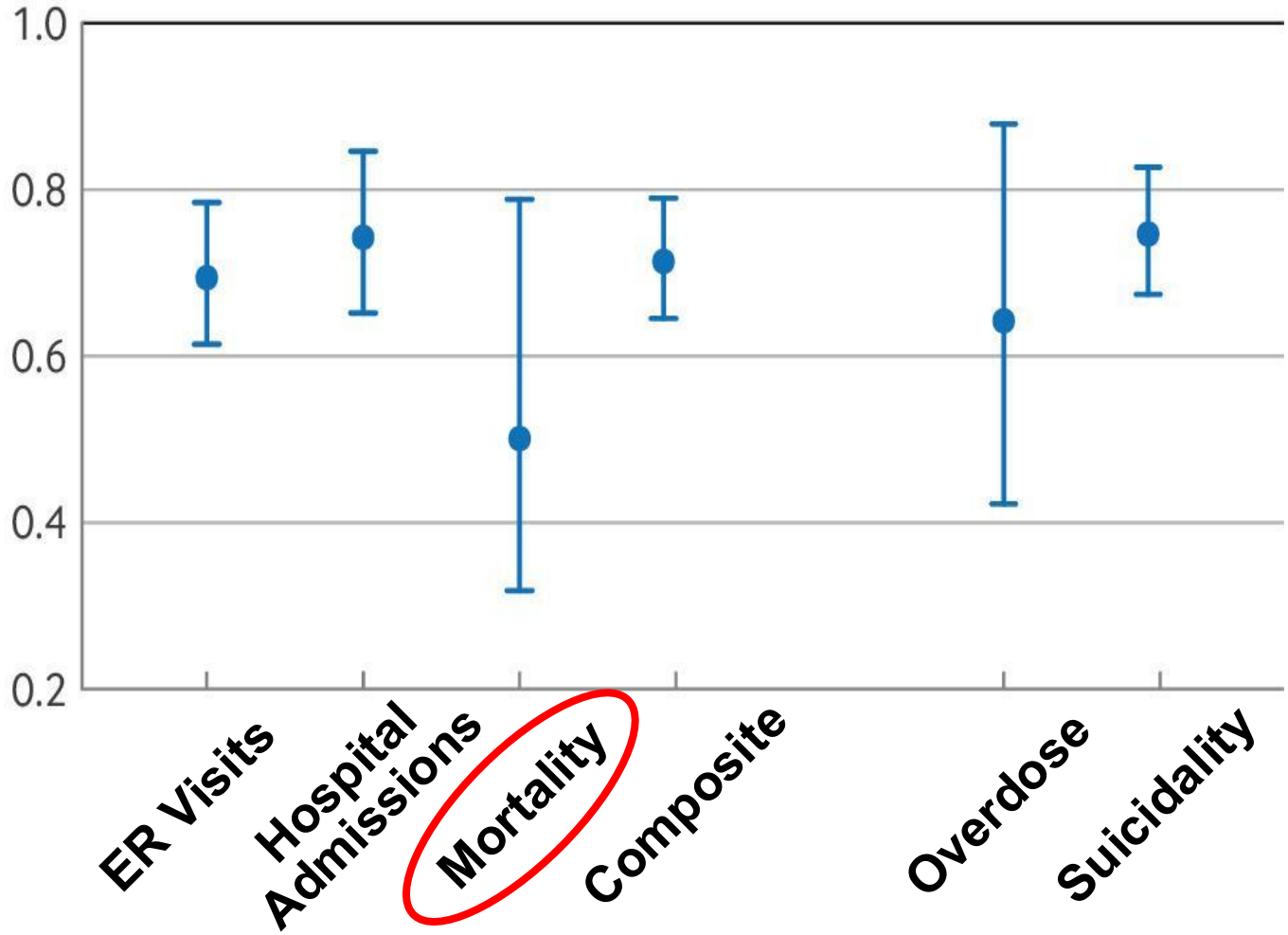


Cai M, et al.
BMJ (Epub 2026)

Lower Incidence of Adverse Outcomes Among People with Substance Abuse Disorders Using Incretin Meds

n = 606,434

F/U = 3 yrs



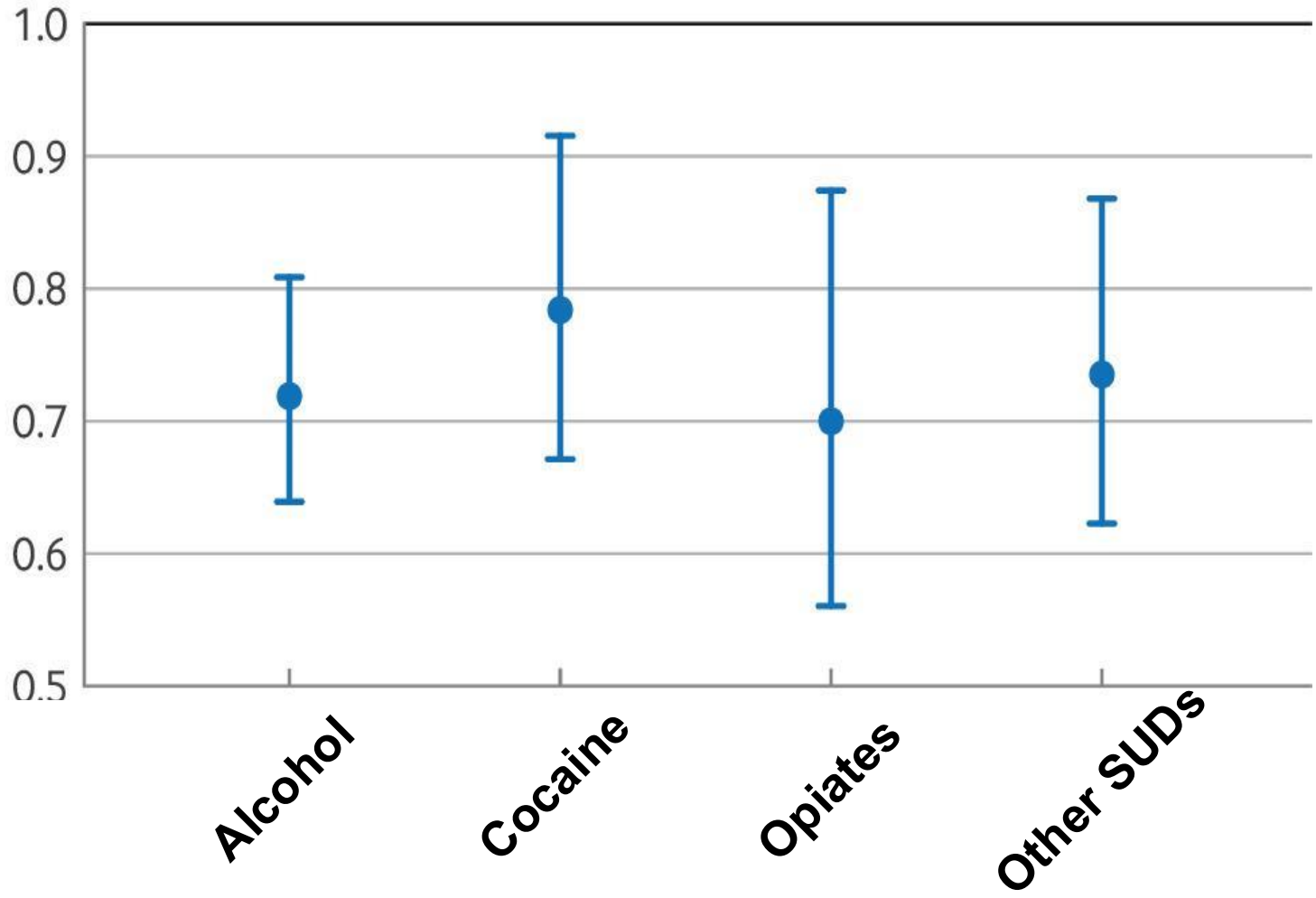
Cai M, et al.
BMJ (Epub 2026)

Lower Incidence of Adverse Outcomes Among People with Several Types of Substance Abuse Disorders

n = 606,434

F/U = 3 yrs

Hazard Ratio For Composite AE (95% CI)



Cai M, et al.
BMJ (Epub 2026)

Other Possible Benefits with Incretin Meds

- ↓ **Cancer**
  - 10 out of 13 obesity-related cancers
- ↓ **Alcohol & substance abuse**
- ↓ **Suicide & self harm**
- ↓ **Dementia**

Other Possible Benefits with Incretin Meds

- ↓ **Cancer**
  - 10 out of 13 obesity-related cancers
- ↓ **Alcohol & substance abuse**
- ↓ **Suicide & self harm**
- ↓ **Dementia**

Some of the main drawbacks of metabolic surgery are *strengths* with new obesity meds

Adverse Effects of Metabolic Surgery

- Alcohol & substance abuse
- Suicide & self harm
- Fractures

Naslund E, et al
Brit J Surg
2024

Some concerns about and major limitations of new obesity management meds

These are “Forever Drugs”

NY Times

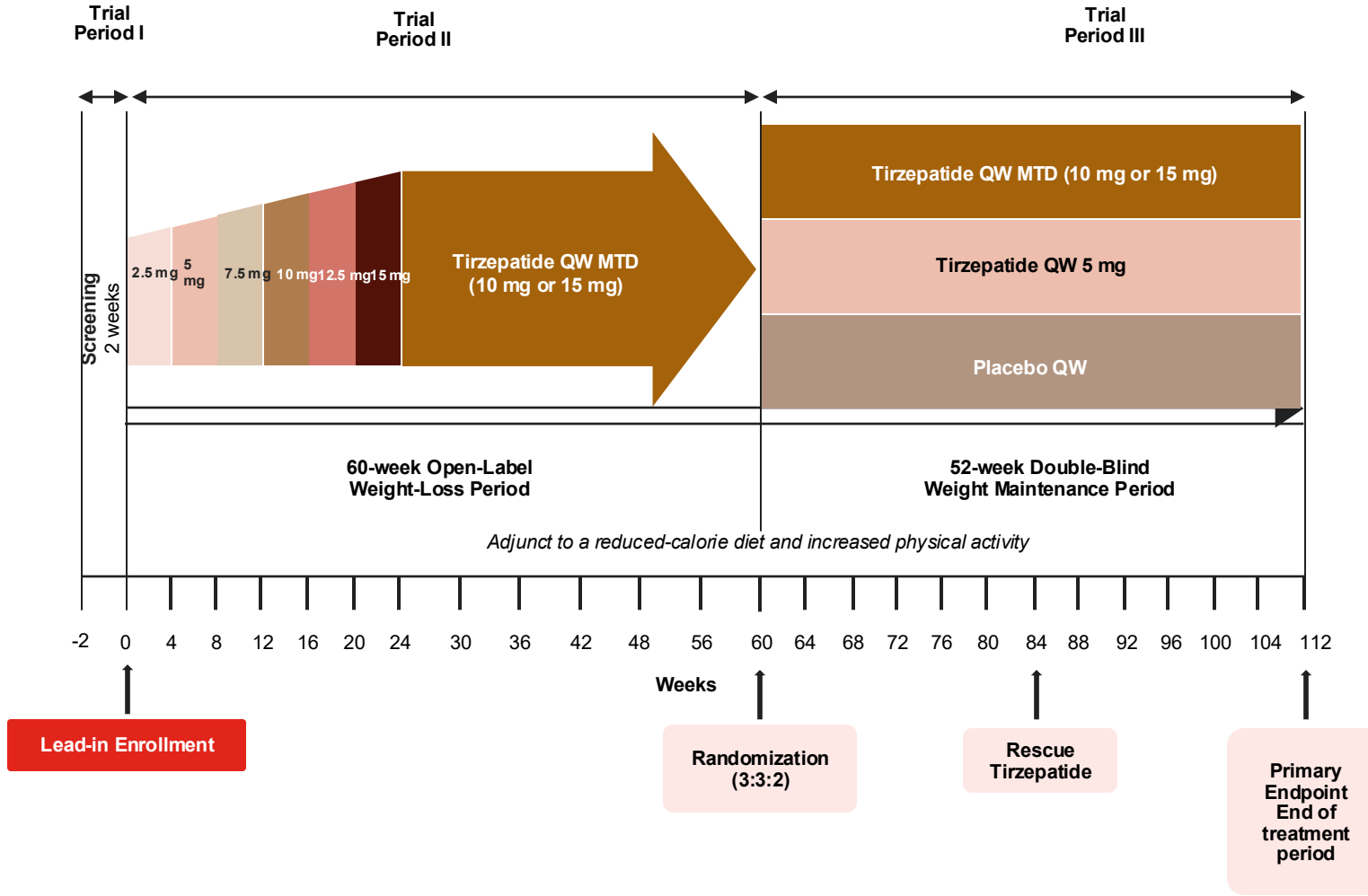
Washington Post

FDA

Strategies for long-term management with incretin mimetic meds

SURMOUNT-MAINTAIN Trial Design

Phase 3b, Multicenter, Randomized, Parallel-arm, Double-blinded, Placebo-controlled, 112-week RCT



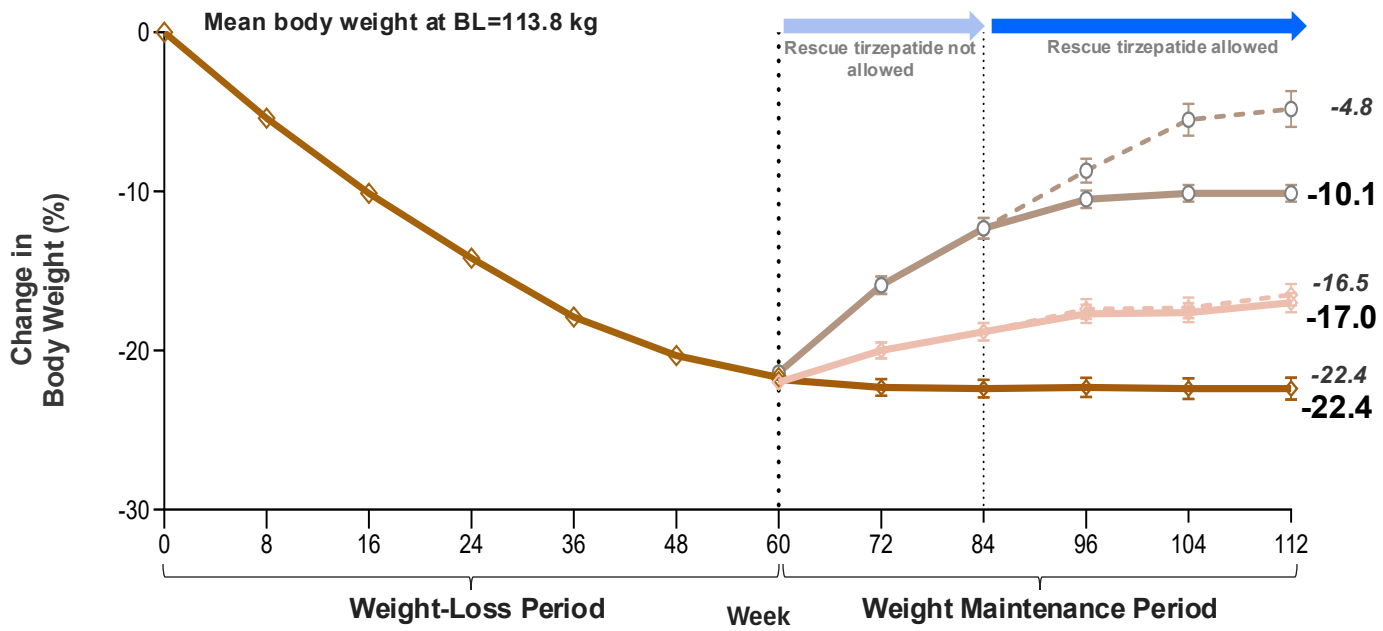
BMI=body mass index; CVD=cardiovascular disease; GLP-1RA=glucagon-like peptide-1 receptor agonist; MEN-2=multiple endocrine neoplasia syndrome type 2; MTC=medullary thyroid carcinoma; MTD=maximum tolerated dose; OSA=obstructive sleep apnea; QW=once weekly.

Horn DB, et al. *LANCET*. Published online 2026. doi:10.1016/s0140-6736(26)00656-2.

Percent Change in BW From Week 0 (Baseline) to Week 112

SURMOUNT-MAINTAIN | Primary Endpoint | mITT population (N=370)[a]

Efficacy Estimand



Treatment Group: Cumulative Number of Participants who Received Rescue Tirzepatide

Tirzepatide MTD (10 or 15 mg):	2	5	11
Tirzepatide 5 mg:	19	30	35
Placebo:	41	56	60

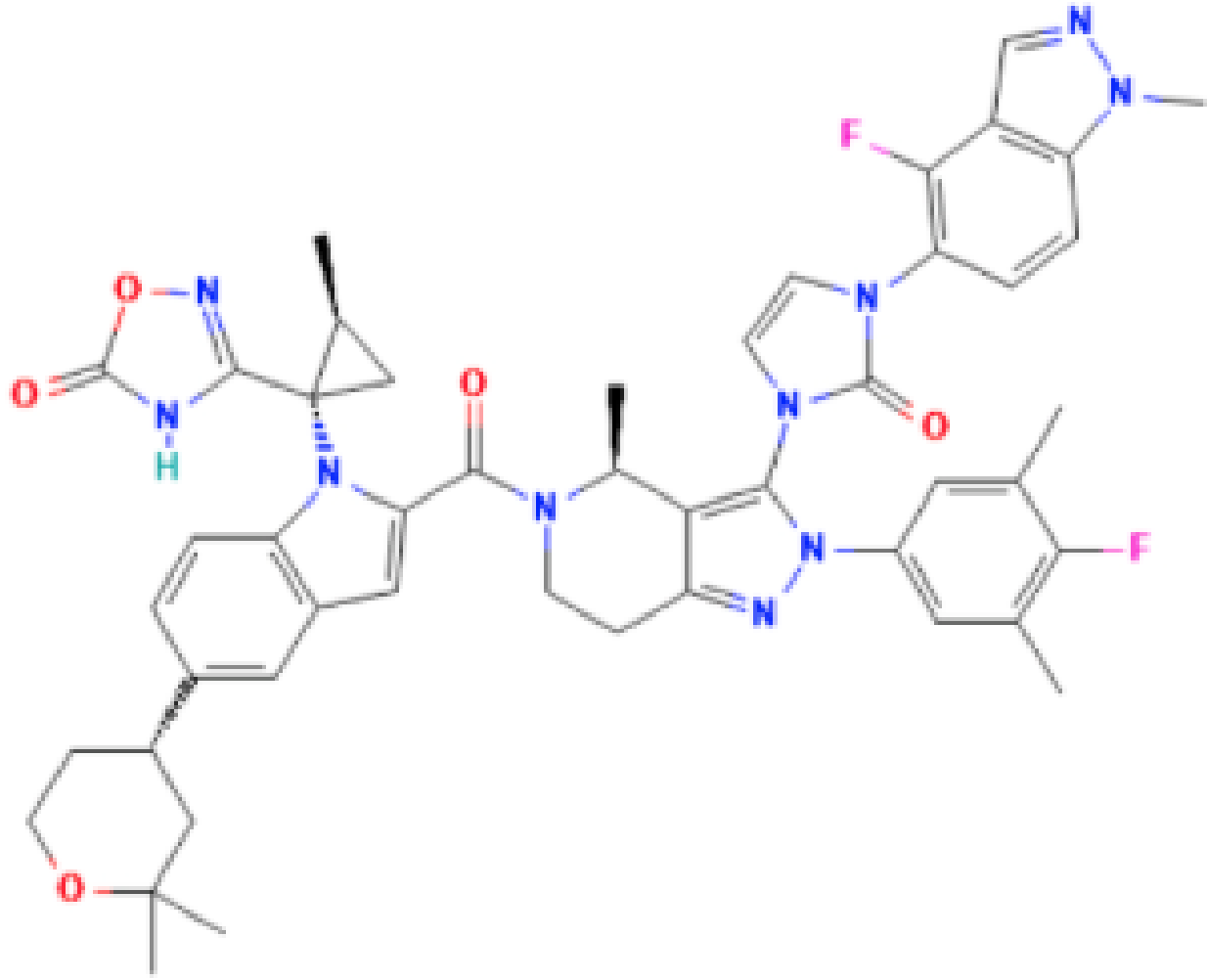
Continued TZP MTD (10 mg or 15 mg)
Reduced to TZP 5 mg
Switched to PBO
With WOCF imputation
Without WOCF imputation

Data are descriptive mean (standard error) in weight-loss period. Solid lines in the weight maintenance period indicate MBEs with WOCF imputation, whereas dotted lines indicate MBEs without WOCF imputation. The primary endpoint was tested under type 1 error procedure using an overall two-sided nominal significance level of 0·05 and controlled for multiplicity. [a]Includes all randomly assigned participants who received at least one dose of study drug during the double-blind weight-maintenance period, excluding inadvertently enrolled participants.

BL=baseline; BW=body weight; MBE=model-based estimates; mITT=modified intent-to-treat population; MTD=maximum tolerated dose; PBO=placebo; WOCF=worst observation carried forward; TZP=tirzepatide.

Horn DB, et al. *LANCET*. Published online 2026. doi:10.1016/s0140-6736(26)00656-2.

Orforglipron is an Oral Small-Molecule GLP-1 RA

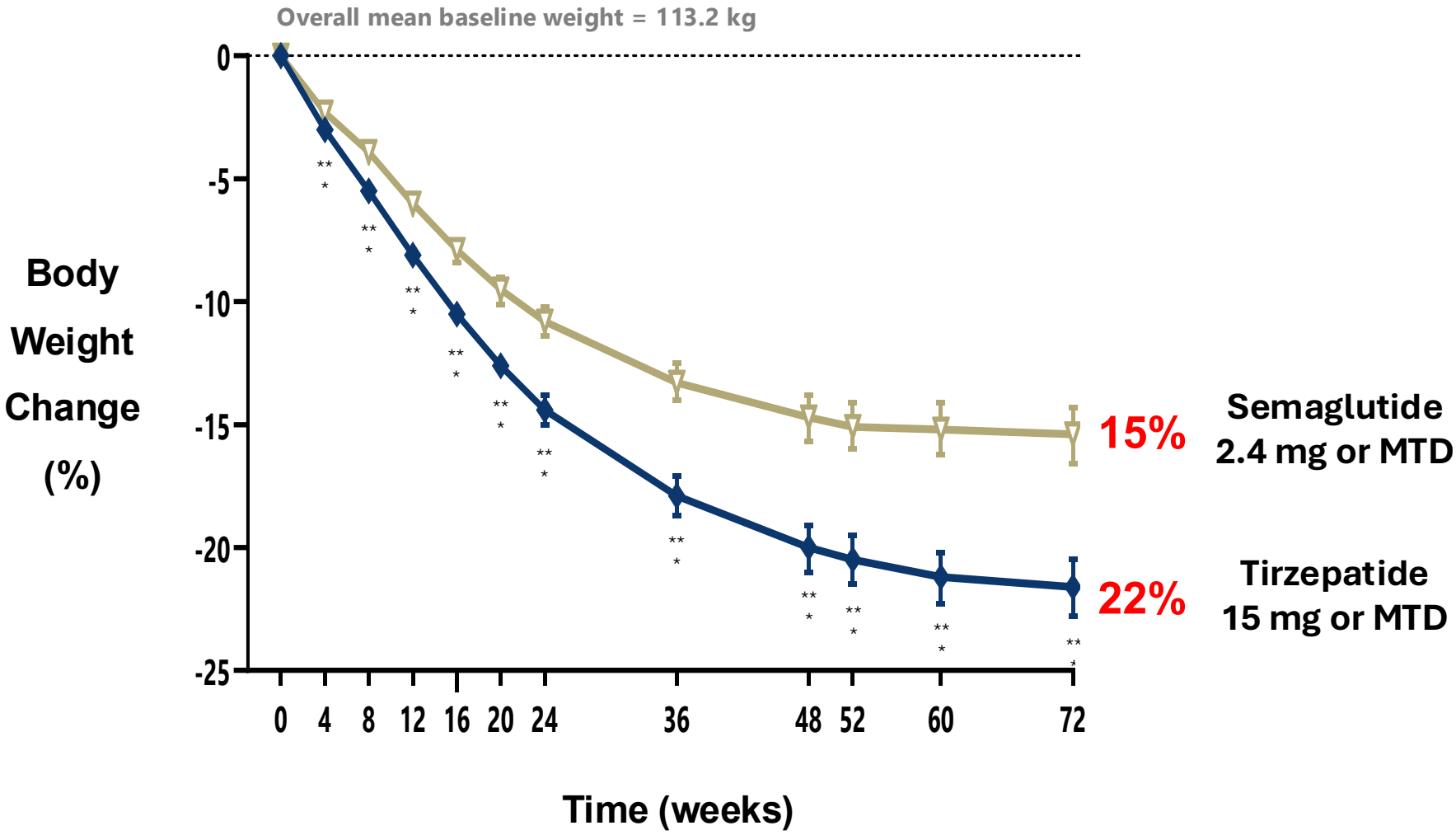


Saldívar-Cerón et al (2025)

ATTAIN-MAINTAIN

Randomized Clinical Trial

SURMOUNT-5: Tirzepatide *vs*. Semaglutide

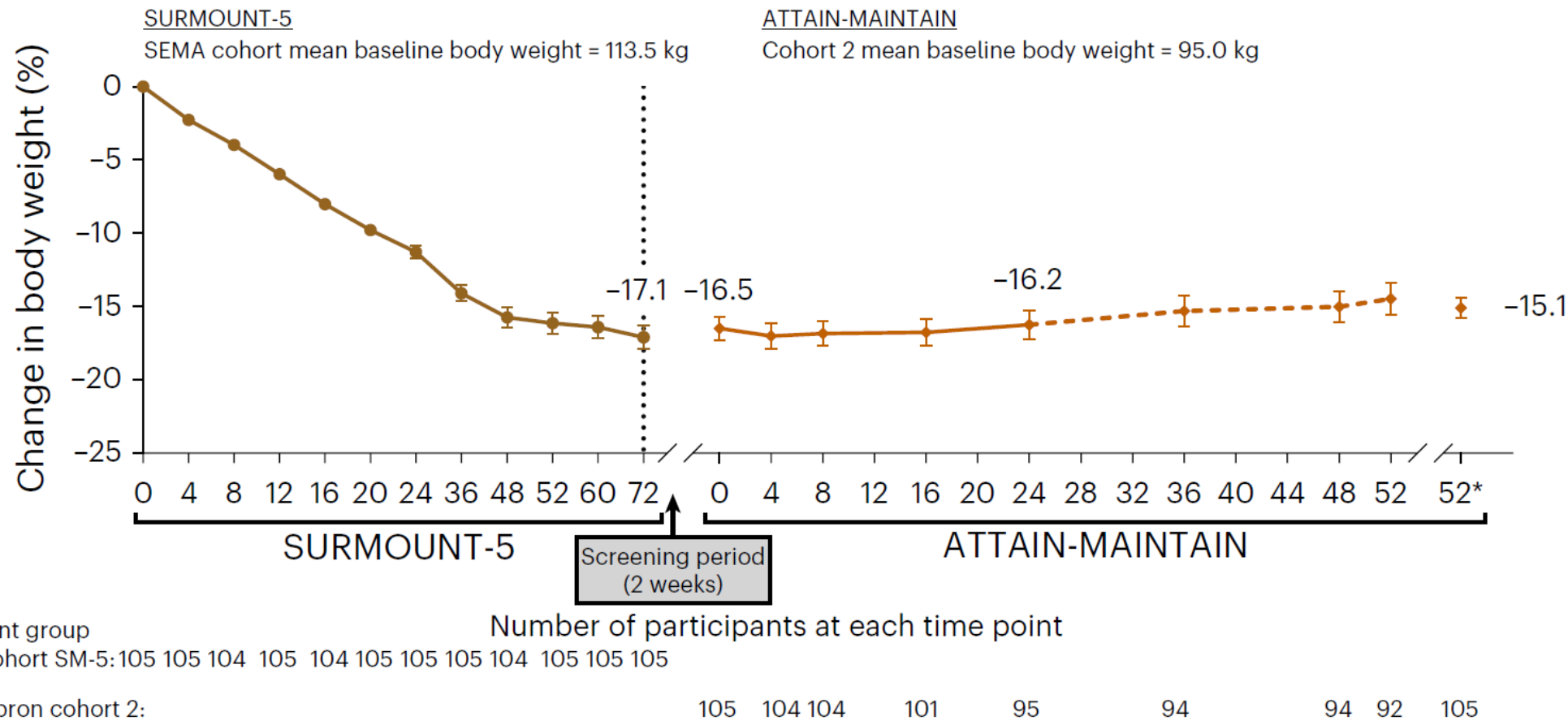


Aronne LJ, et al.

NEJM (May 2025)

ATTAIN-MAINTAIN demonstrates orforglipron's potential as a globally scalable option for minimizing weight changes after injectable therapy

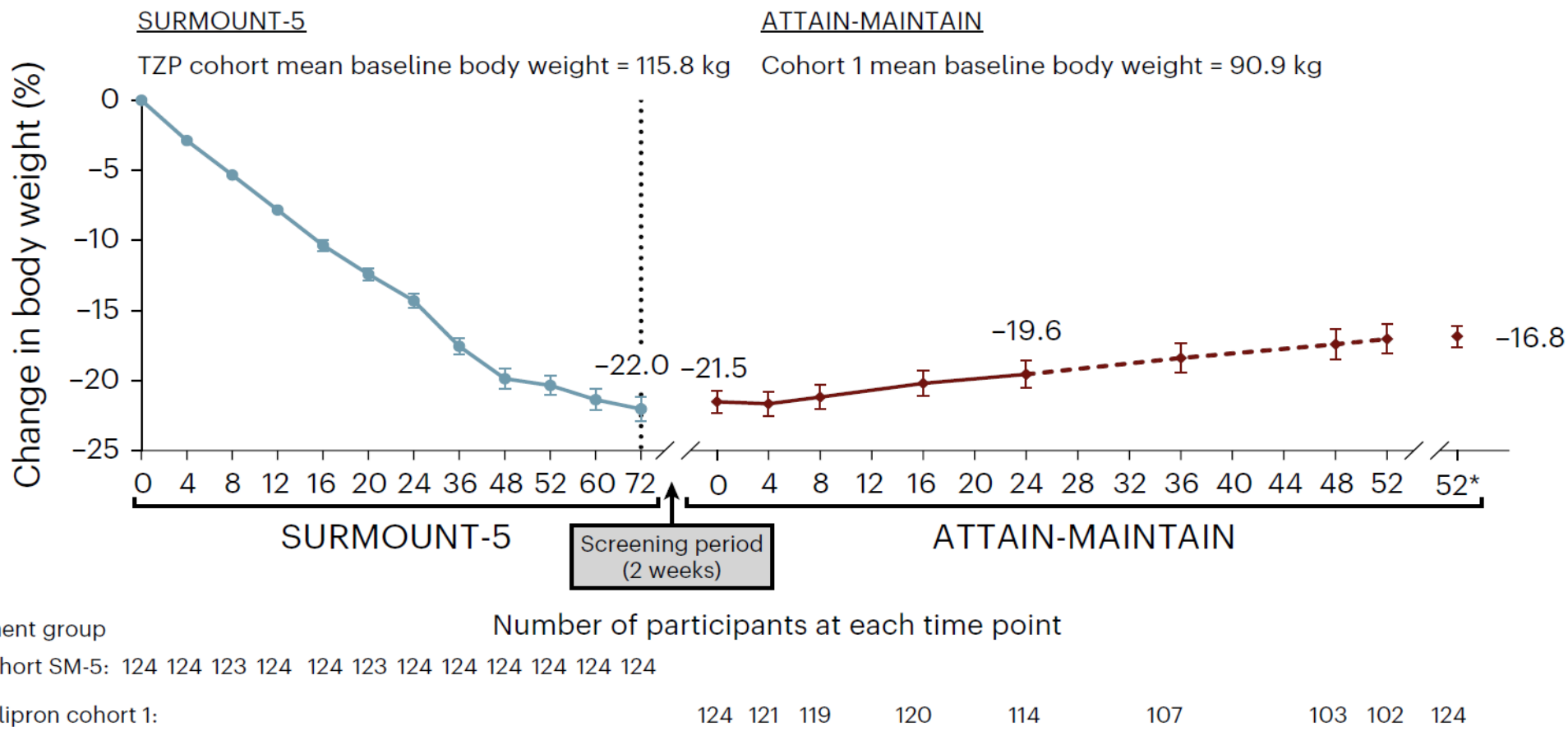
Weight change from SURMOUNT-5 to ATTAIN-MAINTAIN in cohort 2 (Semaglutide → Orforglipron)



Aronne, Louis J., et al. "Orforglipron for maintenance of body weight reduction: the double-blind, randomized phase 3b ATTAIN-MAINTAIN trial." *Nature Medicine* (2026): 1-9.

ATTAIN-MAINTAIN demonstrates orforglipron's potential as a globally scalable option for minimizing weight changes after injectable therapy

Weight change from SURMOUNT-5 to ATTAIN-MAINTAIN in cohort 1 (Tirzepatide → Orforglipron)

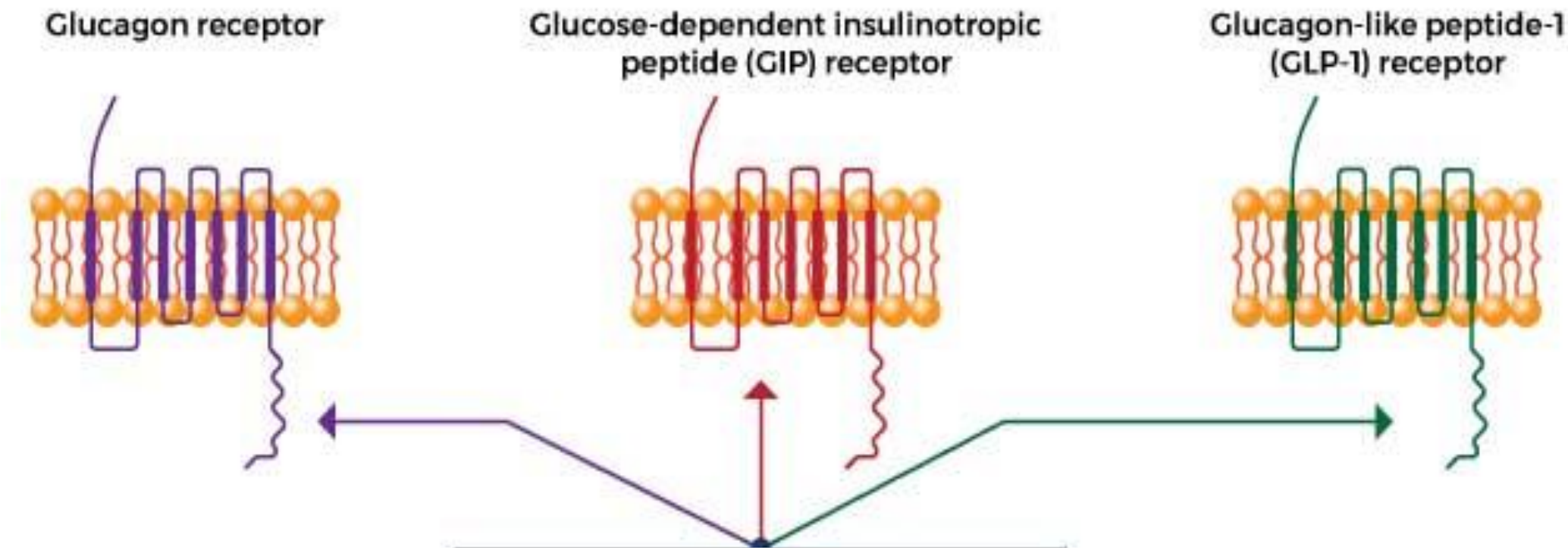


Aronne, Louis J., et al. "Orforglipron for maintenance of body weight reduction: the double-blind, randomized phase 3b ATTAIN-MAINTAIN trial." *Nature Medicine* (2026): 1-9.

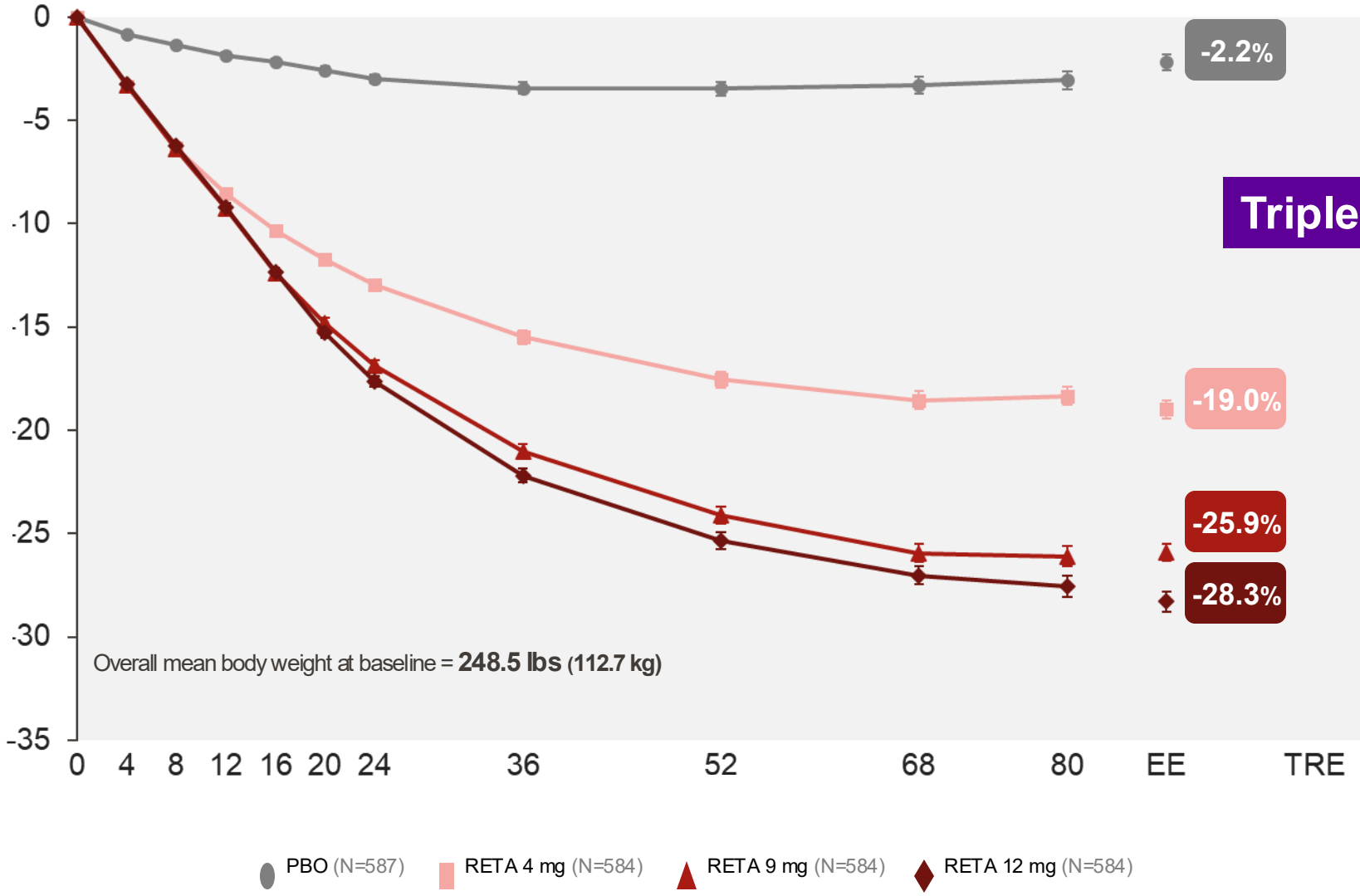
New Obesity Meds Under Development

Retatrutide

Triple G-Hormone Receptor Agonist



TRIUMPH-1: Retatrutide *vs.* Placebo – *No Diabetes*



Triple Agonist

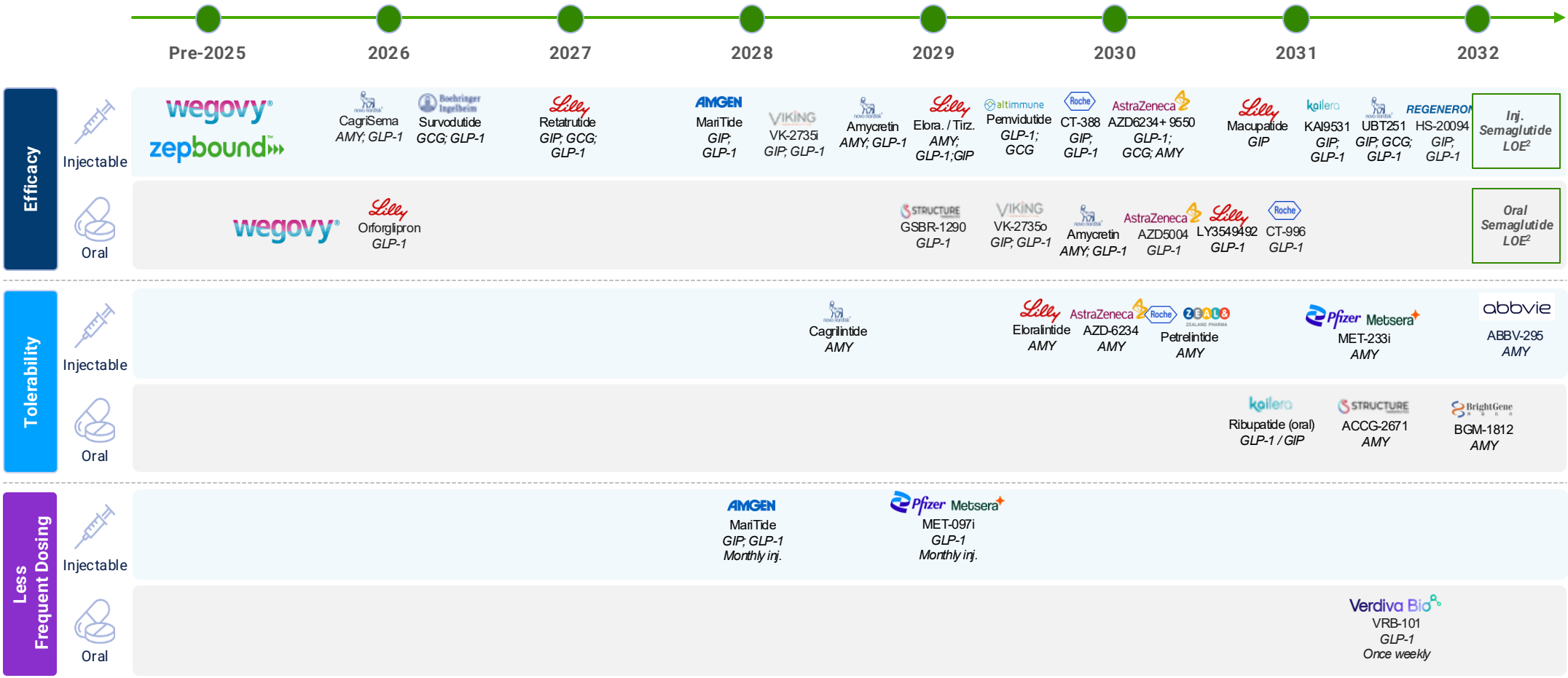
28% weight loss

Jastreboff AM et al. (unpublished)

Some Weight-Loss Drugs in Early Trials

- **New oral GLP-1 agonists**: AI design
  - Orforglipron - *NEJM* 389:877, oral sema, elecoglipron
- **GLP-1 + Amylin agonist**
  - CagriSema, amycretin, eloralintide, petrelintide
- **GLP-1 agonist + GIP *antagonist***
  - MariTide (AMG-133, *monthly* injections)
- **GLP-1 agonist + Glucagon agonist**
  - Mazdutide, pemvidutide, survodutide, G49
- **GLP-1 agonist + Glucagon *antagonist***
- **Activin-myostatin antagonists**
  - Bimagrumab, ALK4i, ALK7i, INHBEi, nimacimab, UCN2

Emerging Obesity Management Medications Through 2032



AMY = amylin receptor agonist; GCG = glucagon receptor agonist; GIP = glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1 = glucagon-like- peptide-1 receptor agonist

Investigational product launch timelines are estimates only based on publicly available information[1]

1. Source: clinicaltrials.gov, company publications
2. US Semaglutide Loss of Exclusivity (LOE) is 2032. EU LOE is 2031. China, Canada, India, and Brazil LOE is 2026.

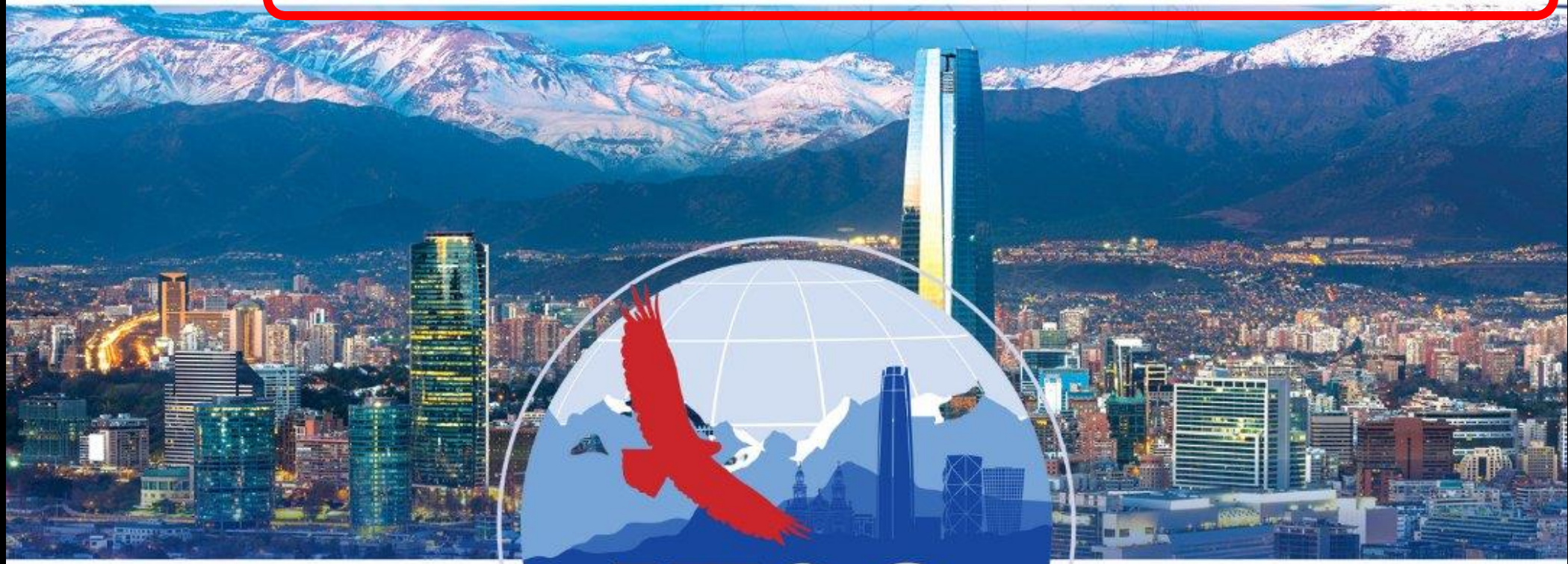
Metabolic/bariatric surgery is still more effective than any medicine!

Obesity meds augment the benefits of metabolic surgery & metabolic endoscopy

XXVIII IFSO World Congress

9-12 September 2025 | Santiago, Chile

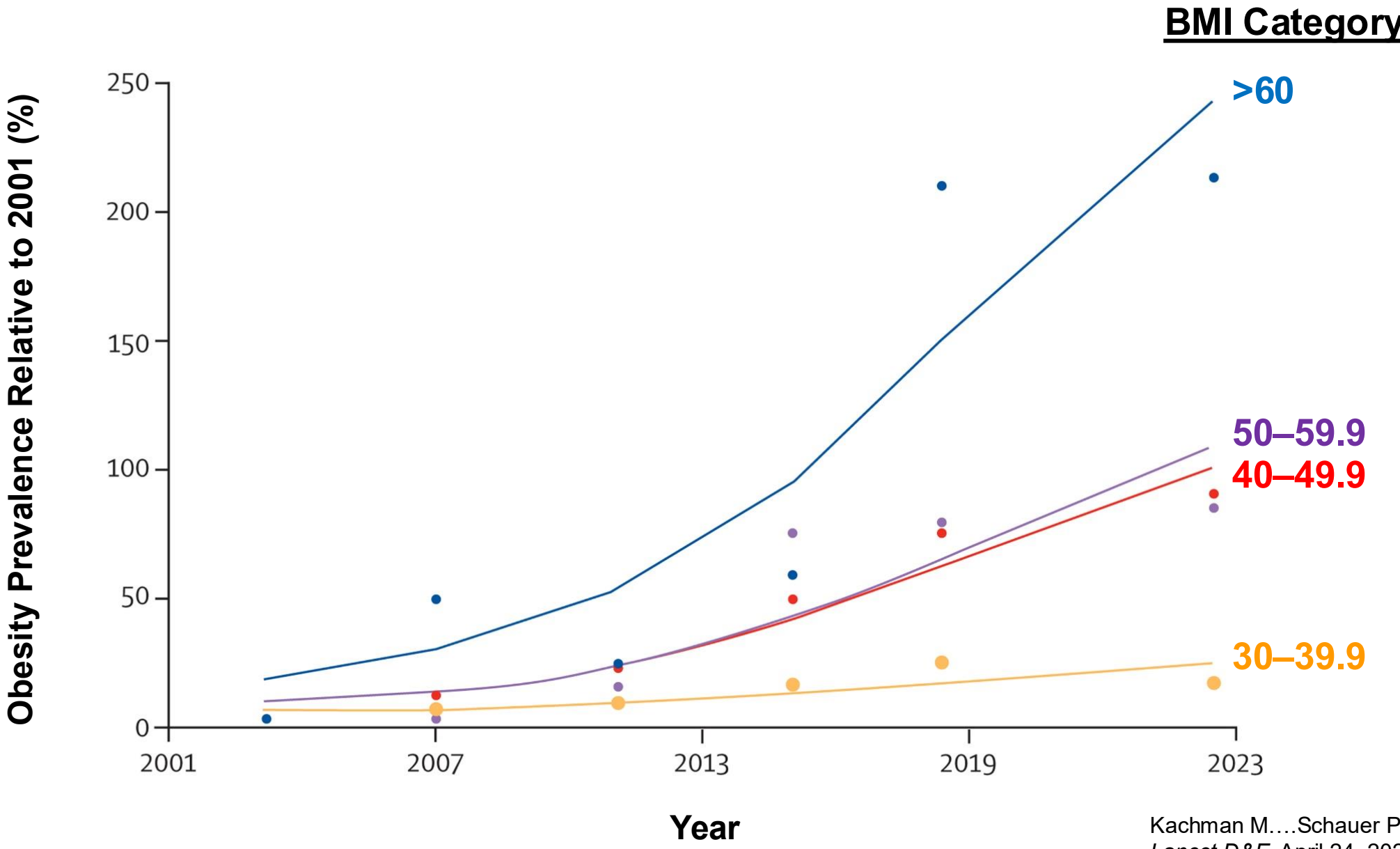
"Combined Therapies: The Dawn of a New Era"




XXX IFSO WORLD CONGRESS
"Advancing Multimodal Obesity Care"
24-27 August 2027
ifso2027.org
IFSO
PARIS 2027
See you in
PARIS

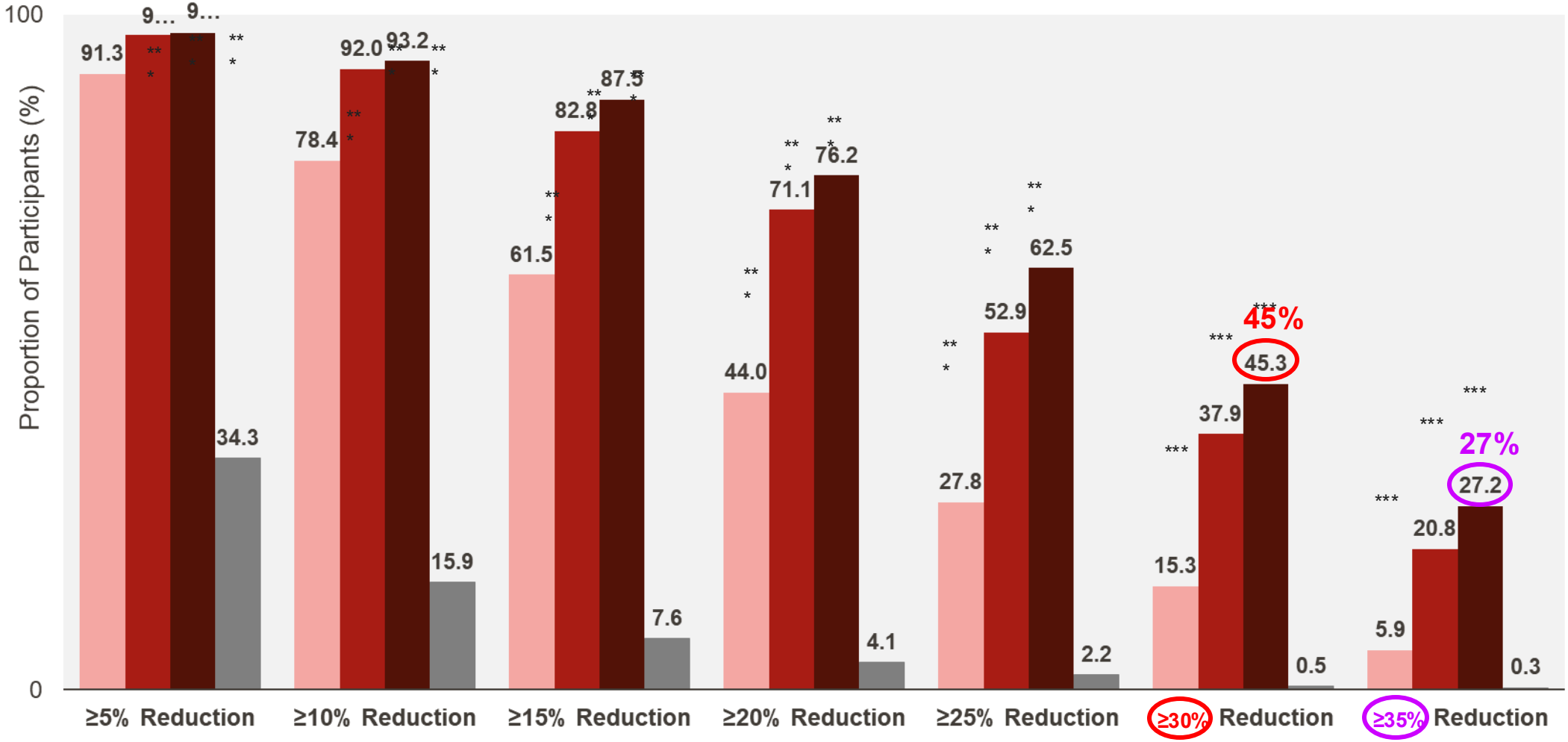
Thank you

~250% Increase of Extreme Obesity Prevalance in 20 Years



Kachman M.…Schauer PR
Lancet D&E, April 24, 2025

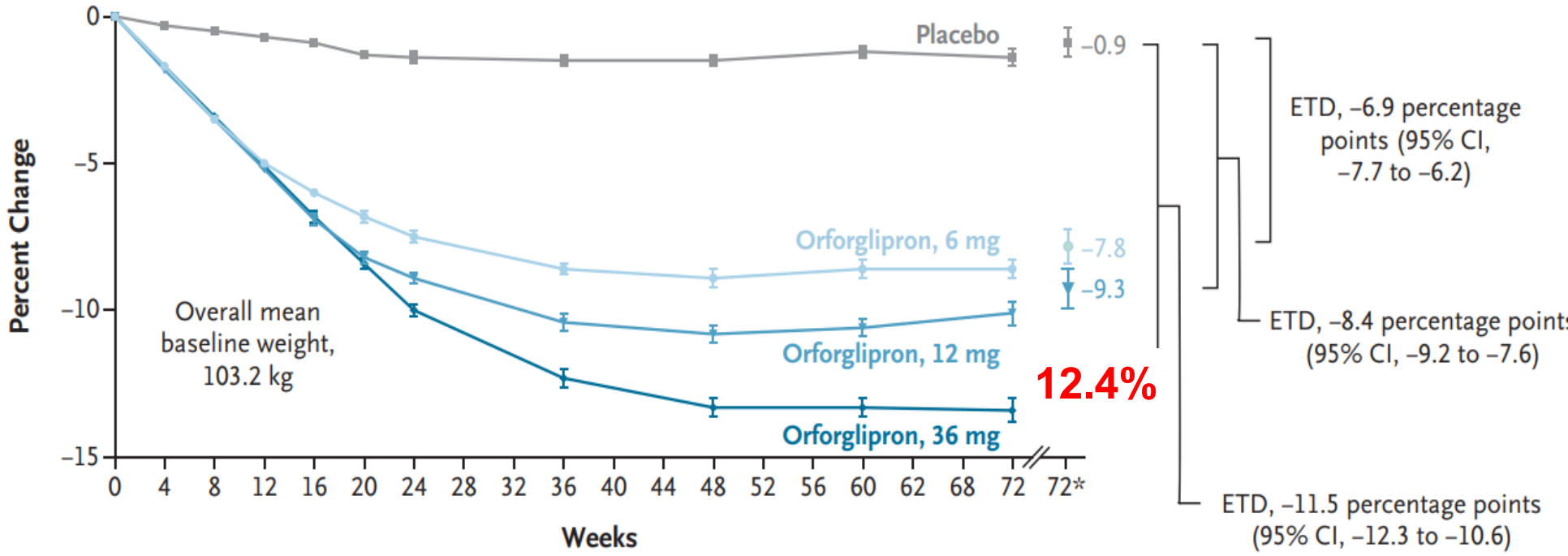
TRIUMPH-1: Percent of Participants Reaching Weight Reduction Thresholds with Retatrutide at Week 80



Jastreboff AM et al. (unpublished)

Change in Body Weight from Baseline to Week 72 (efficacy estimand)

ATTAIN-1



No. of Patients

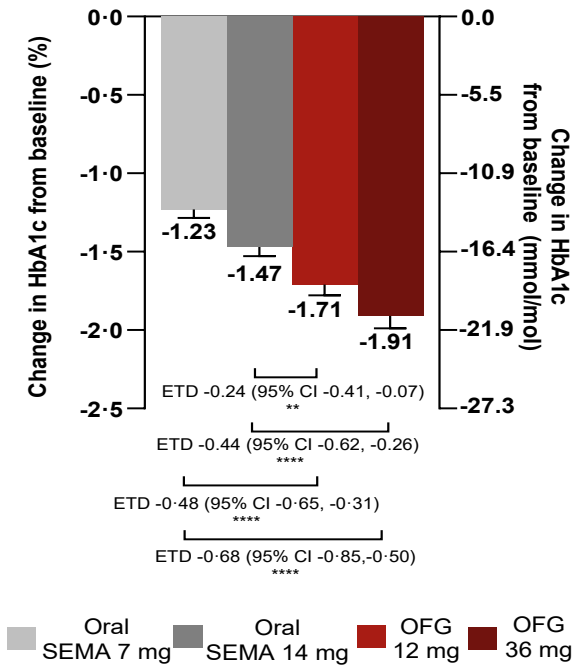
Placebo	949	937	923	910	875	847	817	766	716	688	654	949
Orforglipron, 6 mg	723	713	702	690	675	664	652	630	601	578	559	723
Orforglipron, 12 mg	725	719	695	687	672	652	648	624	602	582	559	725
Orforglipron, 36 mg	730	715	704	689	670	662	644	617	583	573	549	730

Wharton, Sean, et al. "Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment." *N Engl J Med* 393.18 (2025): 1796-1806.

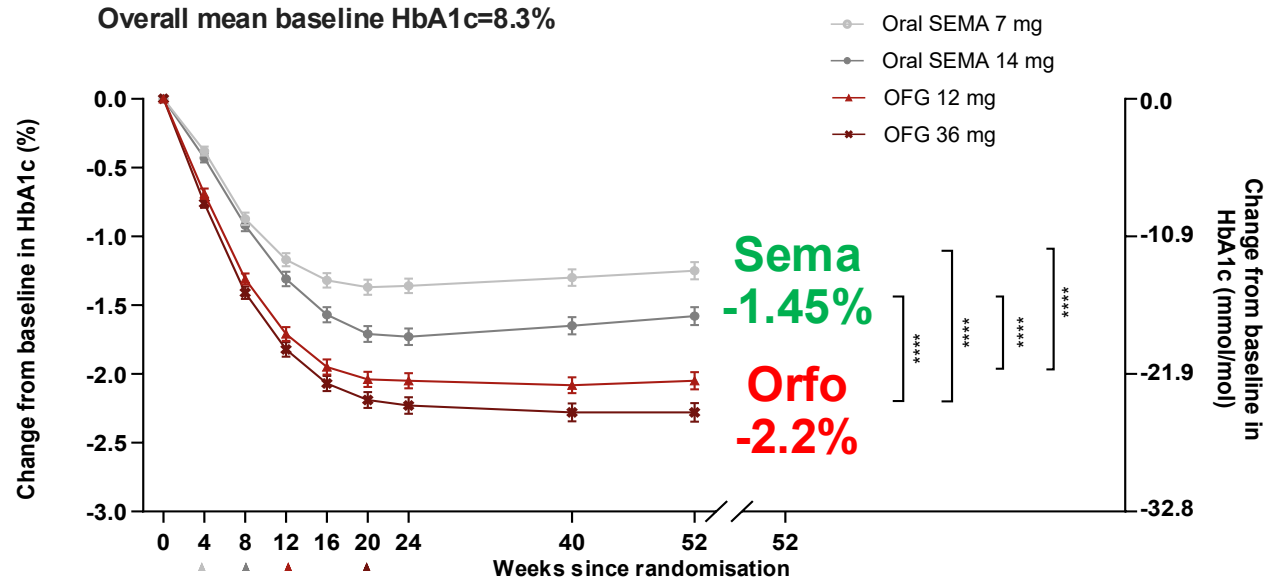
ACHIEVE-3 RCT

Change From Baseline in HbA1c at 1 Year

Treatment Regimen Estimand



Efficacy Estimand



HbA1c at end of treatment	Oral SEMA 7 mg	Oral SEMA 14 mg	OFG 12 mg	OFG 36 mg
	7.2%	6.8%	6.4%	6.1%

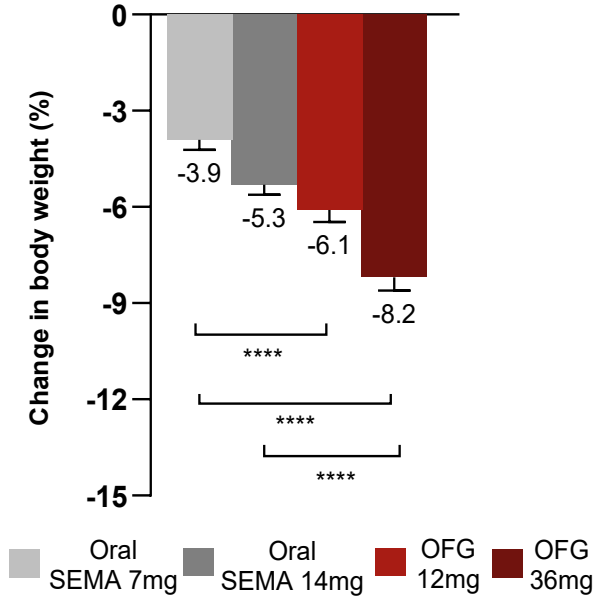
Rosenstock J, et al.

Lancet (Epub ahead of print, 2026)

ACHIEVE-3 RCT

Weight Loss at 1 Year

Treatment Regimen Estimand



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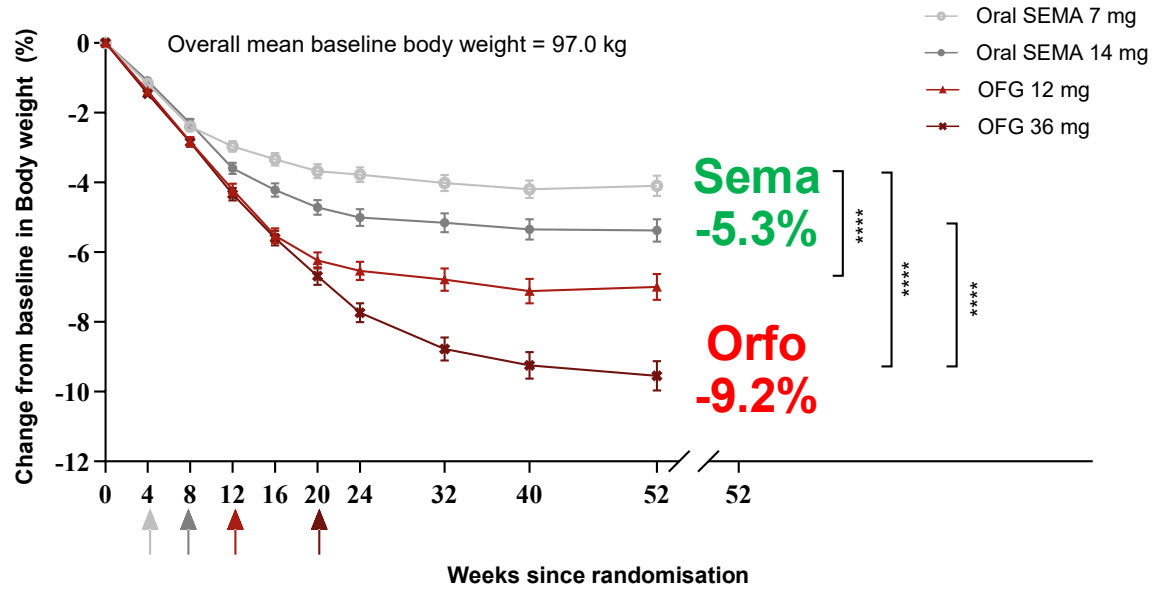
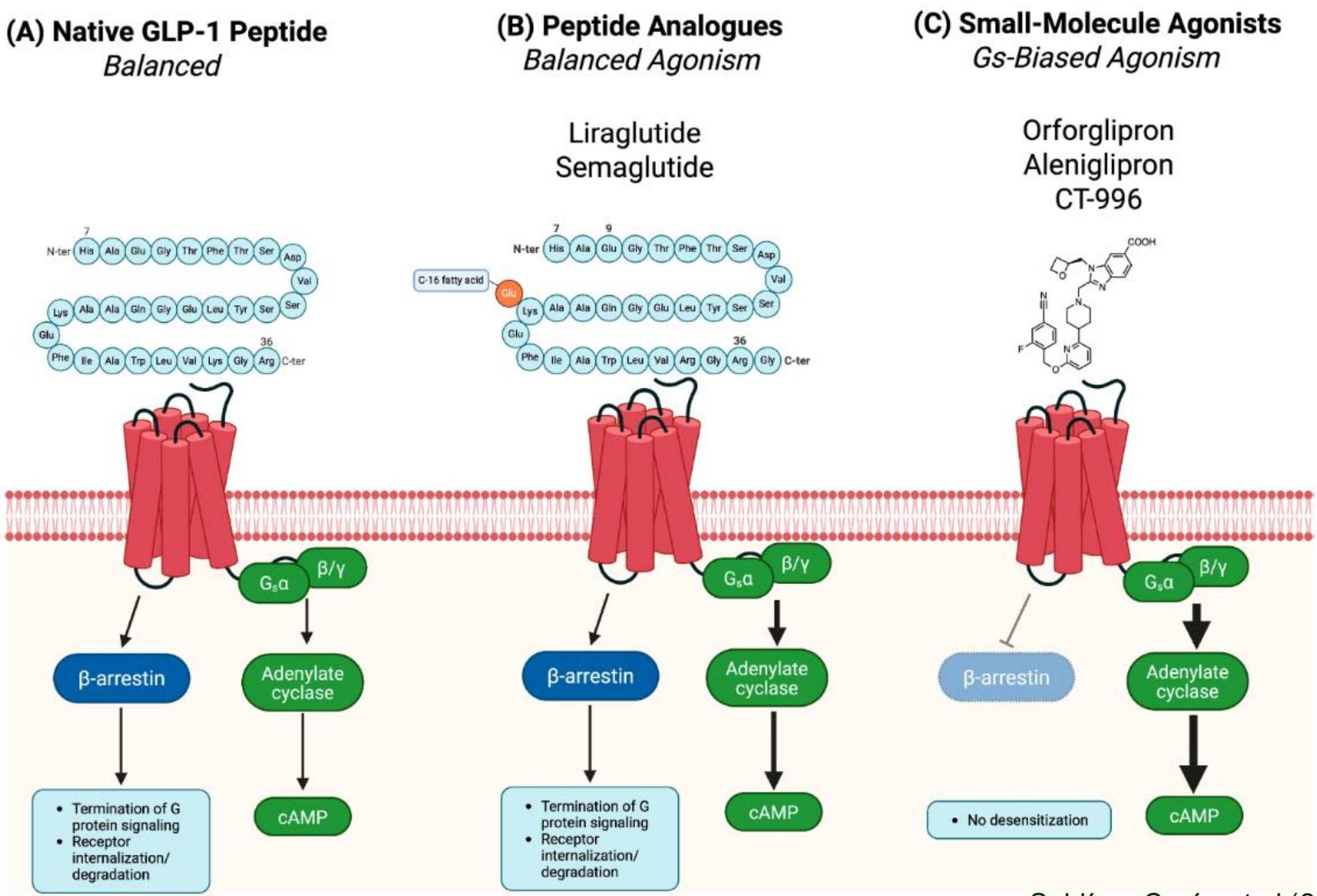


Rosenstock J, et al.

Lancet (Epub ahead of print, 2026)



Saldívar-Cerón et al (2025)