Guy's and St Thomas'
NHS Foundation Trust

KING'S College LONDON

New horizons for treating obesity

Barbara McGowan
Consultant Endocrinologist
Professor of Diabetes and Endocrinology

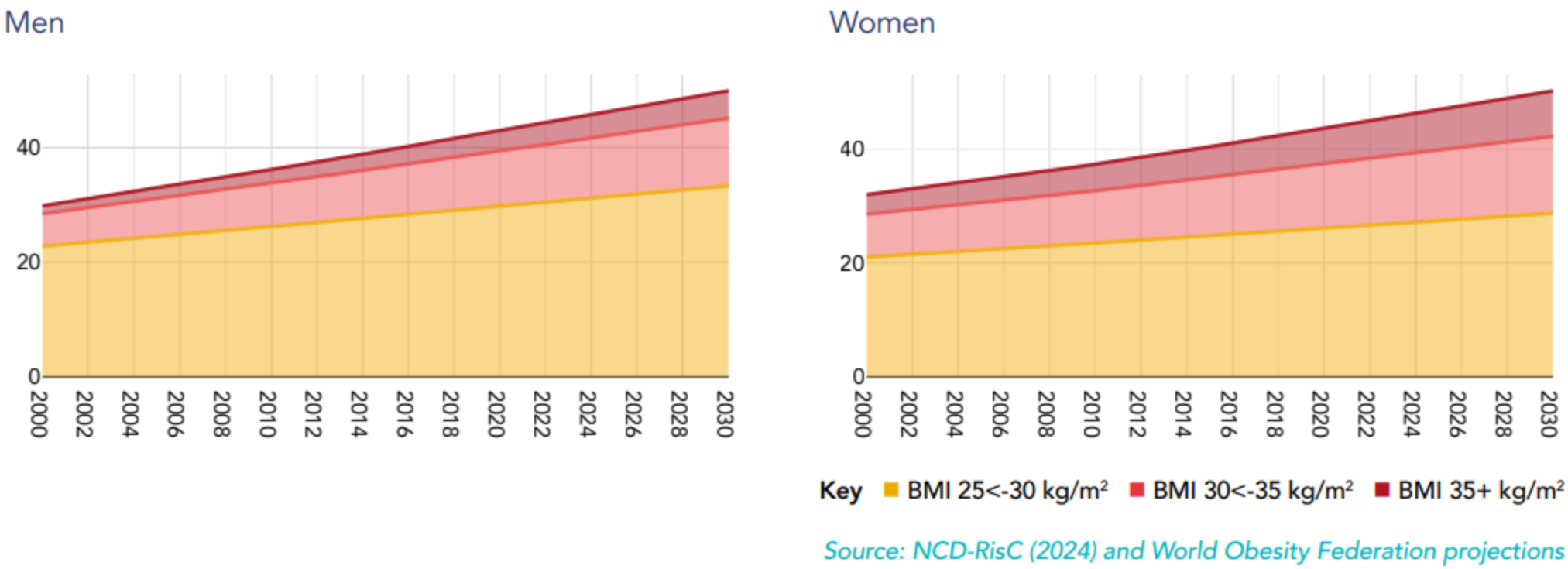
Guy's and St Thomas Hospital
King's College London

Conflicts of interest

- Advisory work Novonordisk, Astra Zeneca, J&J Ethicon, Lilly, Pfizer
- Educational work: Lilly, Novonordisk, BI, Janssen, MSD, Sanofi, Astra Zeneca
- Institutional Research grant support: Novonordisk
- Shareholder Reset Health and board member

World Obesity Atlas 2025

Figures 1.1 and 1.2: Percentages of men and women (aged 20+) living with high BMI, 2000-2030



Source: NCD-RisC (2024) and World Obesity Federation projections

- Nearly 3 billion adults will be affected by overweight and obesity by 2030 (50% of population)
- This compares with < 2 billion in 2015 (40%) and 1.6 billion in 2010 (36%)

Obesity affects many organ systems and contributes to over 200 complications[1,2]

Complications occur through multiple effects of adiposity and may have more than one origin[2–4]

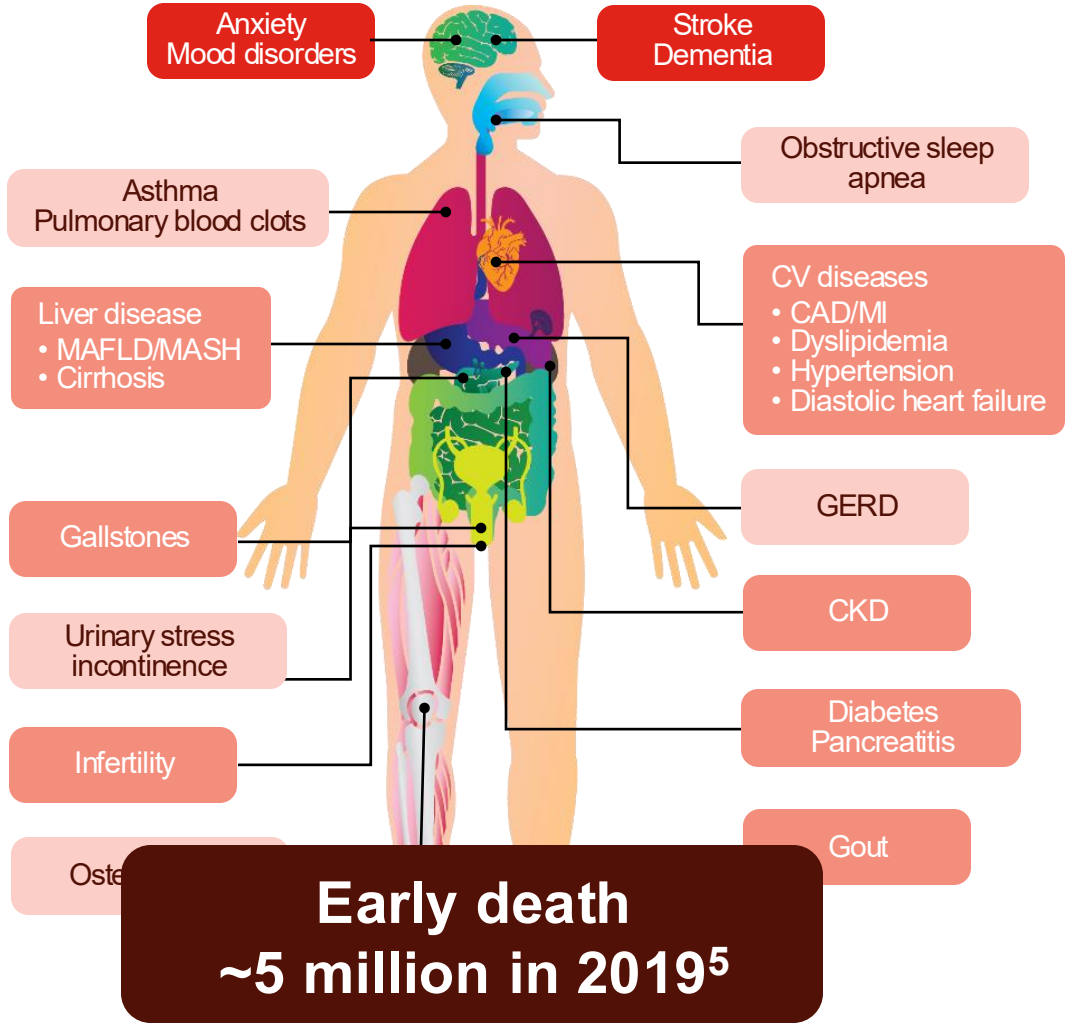
Multiple cancers[3]

- Breast
- Cervical
- Colorectal
- Endometrial
- Gallbladder
- Gastric
- Kidney
- Liver
- Esophageal
- Ovarian
- Pancreas
- Thyroid
- Uterus

Biomechanical effects
(strain at various body sites)

Metabolic effects
(inflammation and lipotoxicity)

Psychosocial effects



Early death
~5 million in 2019[5]

CAD=coronary artery disease; CKD=chronic kidney disease; CV=cardiovascular; GERD=gastroesophageal reflux disease; MAFLD=metabolic dysfunction-associated fatty liver disease; MASH=metabolic dysfunction-associated steatohepatitis; MI=myocardial infarction. 1. Jastreboff AM, et al. Obesity (Silver Spring). 2019;27(1): 7–9. 2. Ansari S, et al. Ther Adv Endocrinol Metab. 2020;11: 2042018820934955. 3. Fitch AK, Bays HE. Obes Pillars. 2022;1: 100004. 4. Hotoleanu C. Med Pharm Rep. 2020;93(2): 162–168. 5. Ritchie H, Roser M. 2017. Available from: https://ourworldindata.org/obesity. Accessed February 2025.

The effect of weight loss on complications

Towards greater weight loss and overall health improvement

- **0–5%**
  - Hypertension
  - Hyperglycaemia
- **5–10%**
  - Prevention of T2D
  - NAFLD
  - PCOS
  - Dyslipidaemia
- **10–15%**
  - Cardiovascular disease
  - Urinary stress incontinence
  - NASH
  - OSAS
  - GERD
  - Knee OA
- **>15%**
  - T2D remission
  - CV mortality
  - HFpEF

Weight loss

Weight loss of 16% is associated with reduction in all-cause mortality

CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; TG, triglycerides.

Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–51; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85; Ryan D and Yockey S. Curr Obes Rep 2017;6:187-94.

Obesity Drugs Timeline

1933
2,4- Dinitrophenol
Discontinued in 1938 due to side effects like cataracts, hyperthermia, and others

1941
Rainbow Pills
Discontinued in 1968 due to anxiety, and death

1947
Methamphetamine
Discontinued in 1979 due to high risk of abusiveness & addiction

1956
Amphetamine Congeners
Phenmetrazine
(1956-1965)
Phenylpropanolamine
(1976-2000)

1973
Fenfluramine
Dexfenfluramine
Discontinued in 1997 due to cardiac valvular insufficiency, Pulmonary hypertension, and cardiac fibrosis

1997
Sibutramine
Discontinued in 2011 due to non-fatal myocardial infarction, stroke, and other side effects

1999
Orlistat
(Xenica; Alli)
Commercially available

2006
Rimonabant
Discontinued in 2009 (Europe) due to side effects like suicidal thoughts, and depression

2012
Lorcaserin
Discontinued in 2020 due to increased cancer risk
Phentermine and Topiramate
(Qsymia)
Commercially available

2014
Naltrexone/ bupropion and liraglutide commercially available

2021
Semaglutide
(Wegovy)
Commercially available

2023
Tirzepatide
(Zepbound)
Commercially available

Red color indicates discontinued drugs Blue color indicates commercially available drugs

Currently EMA approved pharmacotherapy for obesity

- Orlistat 120 mg tds
- Liraglutide 3mg od
- Naltrexone/Bupropion 8/90 mg x2 bd
- Semaglutide 2.4 mg
- Tirzepatide 5, 10, 15mg

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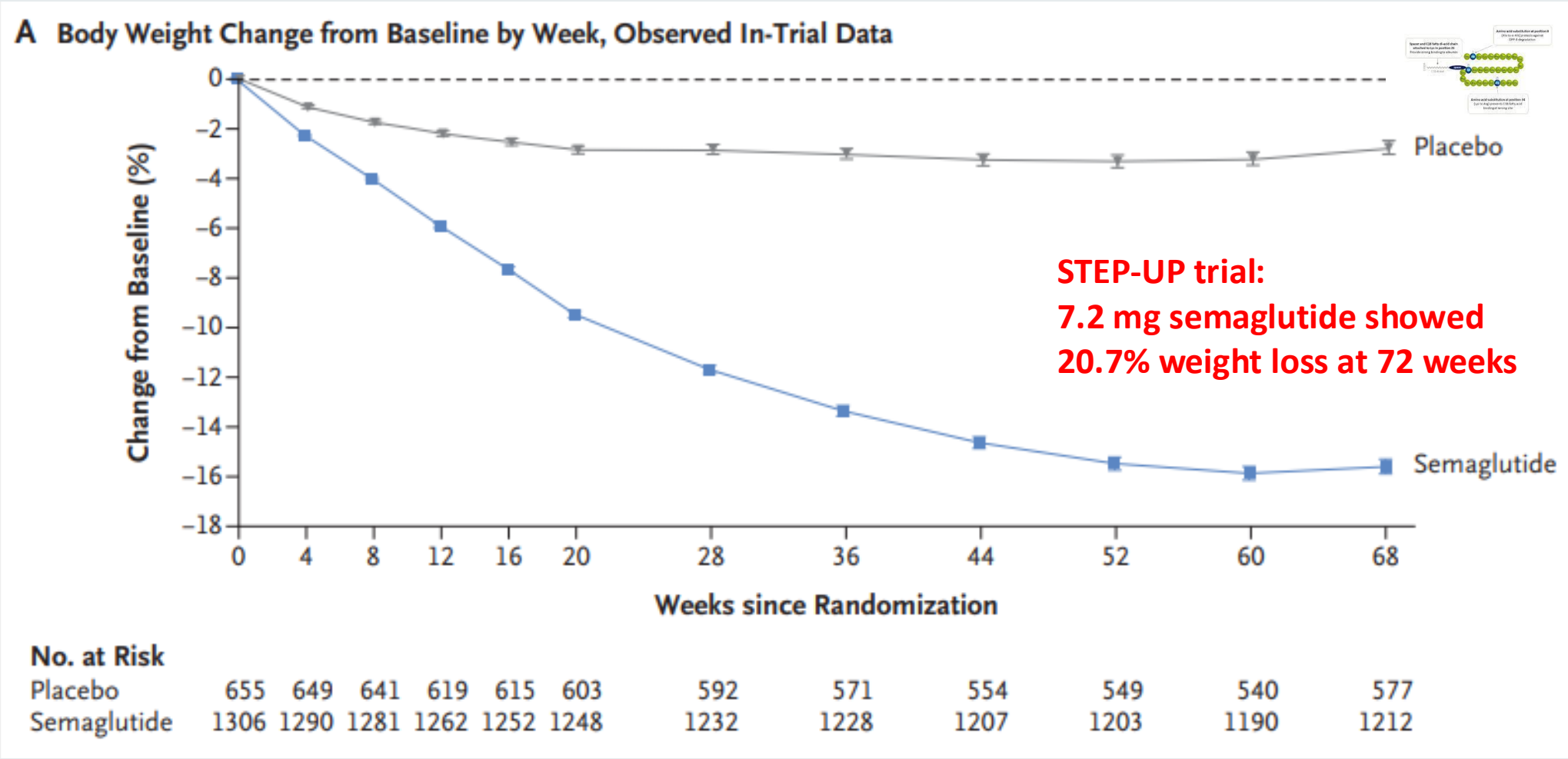
Semaglutide 2.4 mg: STEP 1 (n=1961)



FDA approval June 2021, MHRA September 2021, NICE recommended Sep 2023

Wilding JPH, McGowan et al. N Engl J Med 2021;384:989-1002

Tirzepatide: SURMOUNT 1 trial: 2,539 patients, mean BMI 38, no diabetes, 72 weeks

FDA/EMA/MHRA approved for obesity Nov 2023

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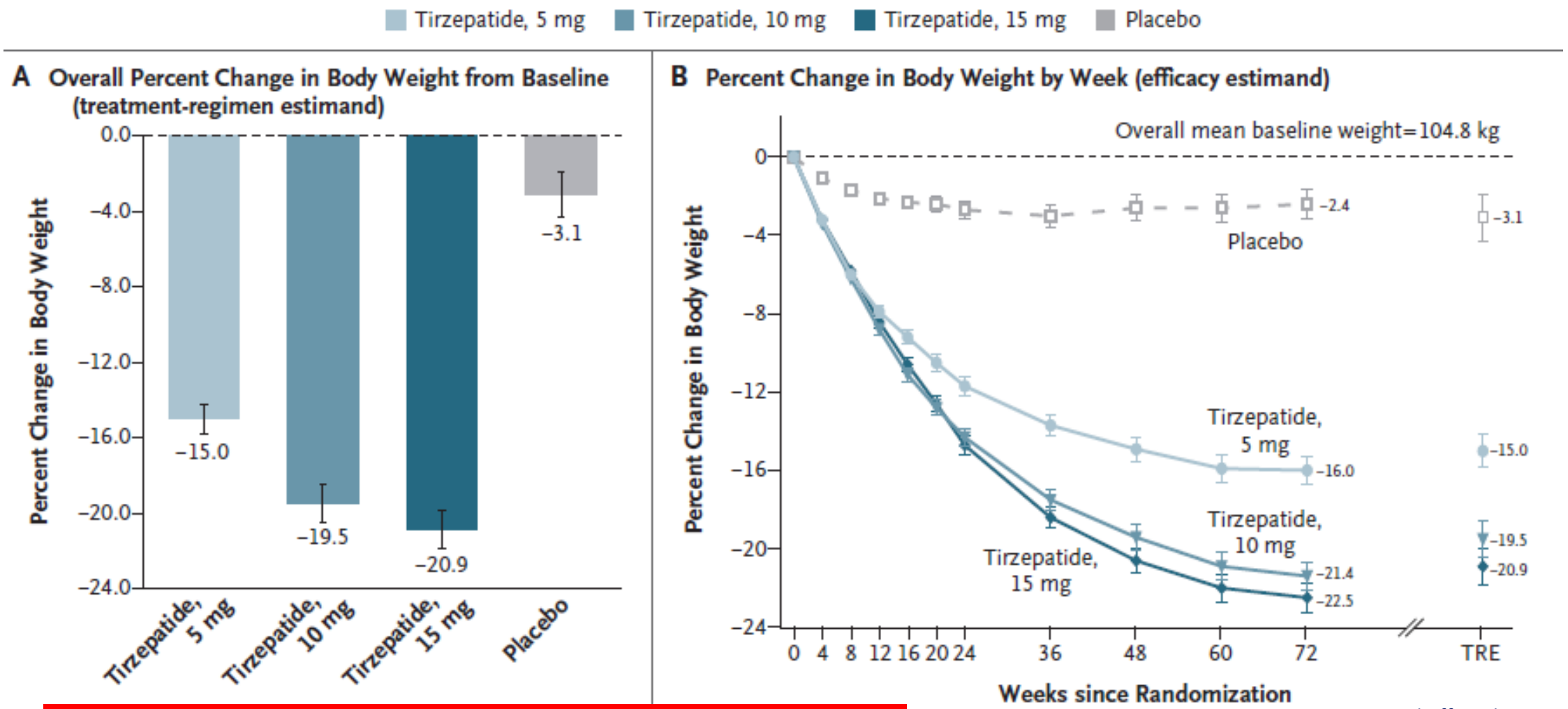
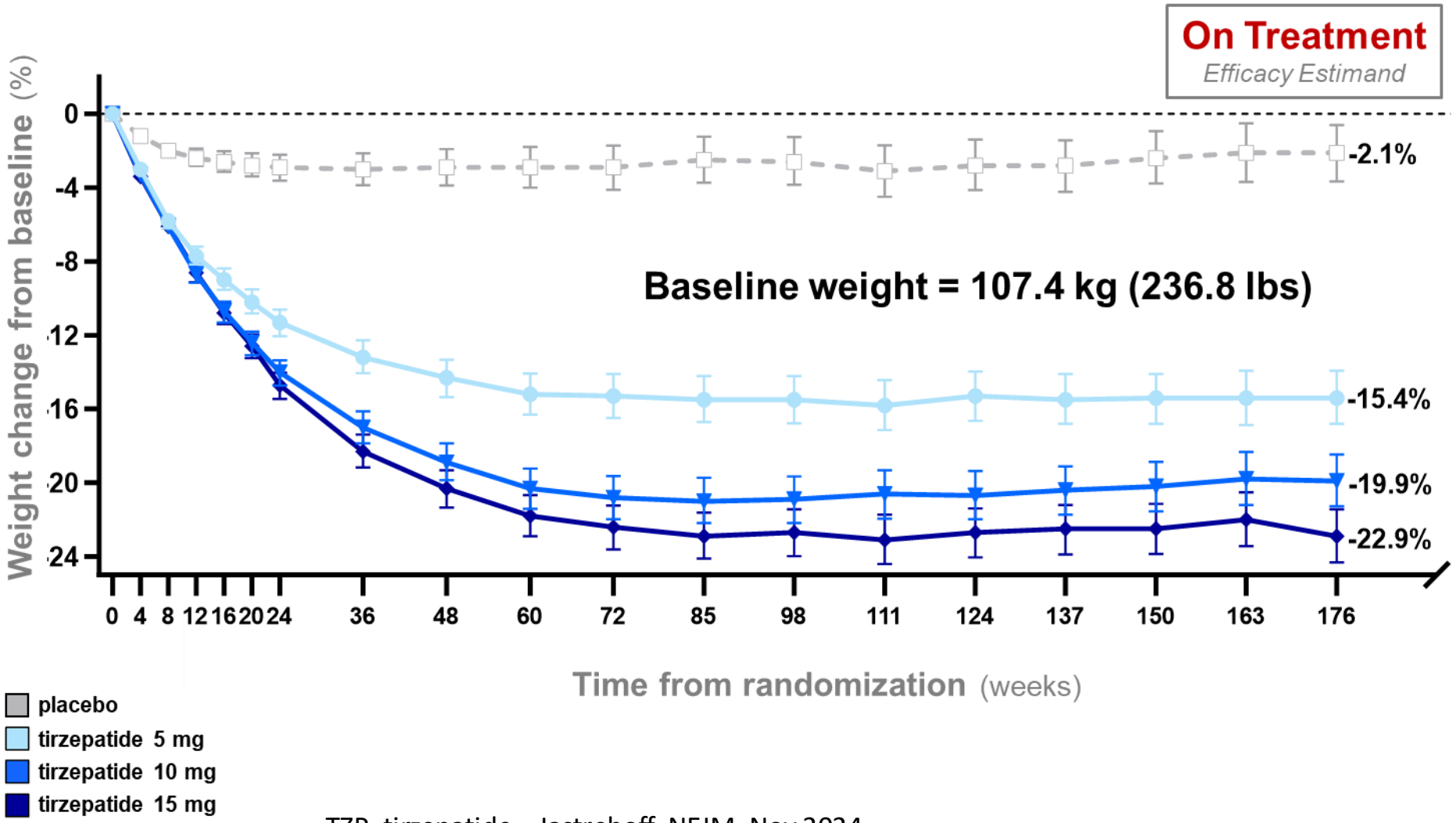
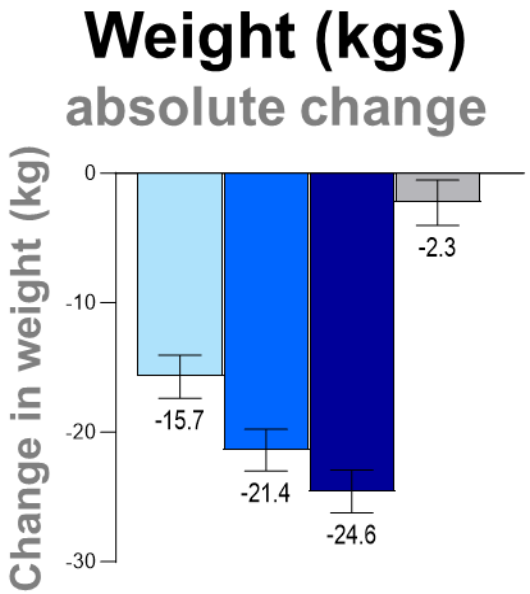


22.5% weight loss at 72 weeks with tirzepatide

Jastreboff et al, NJEM, June 2022

Tirzepatide weight Reduction maintained at 176 Weeks





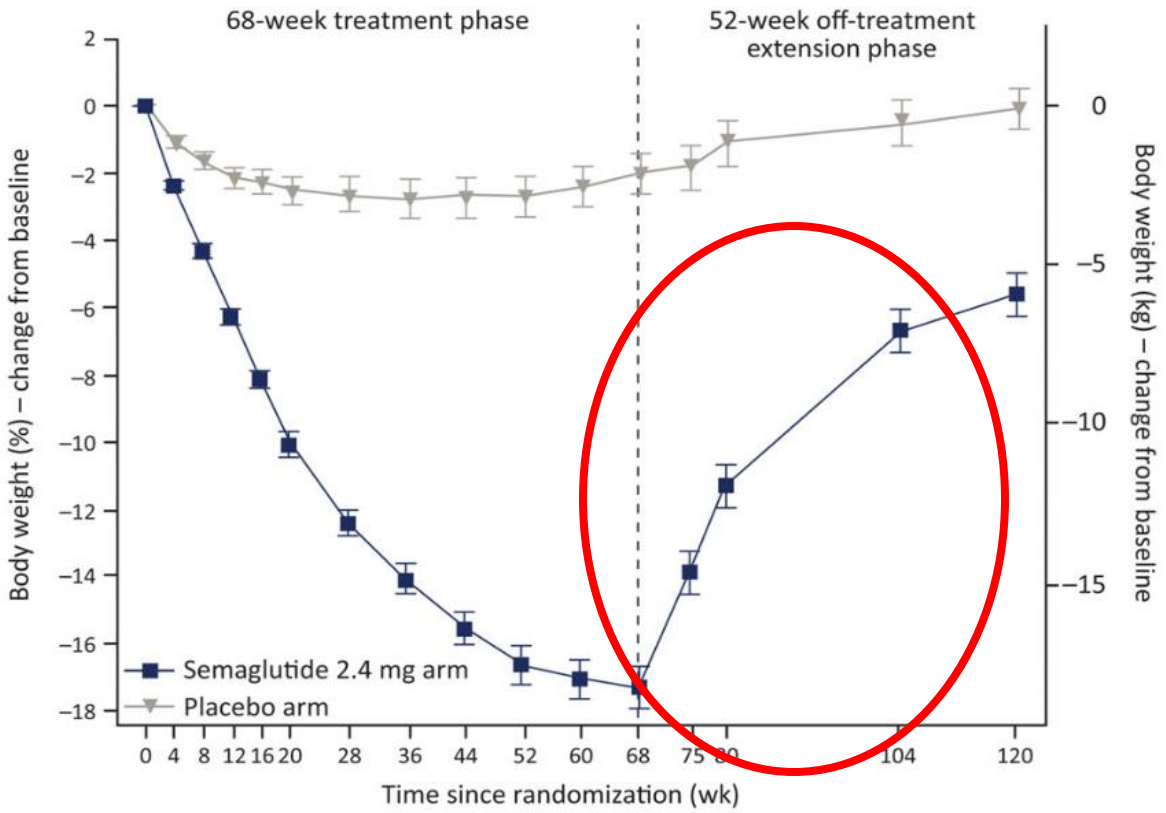
Average Weight Reduction from baseline 34.6-54.2 lbs
(15.7-24.6 kgs)
(range from 5-15 mg TZP dose arms)

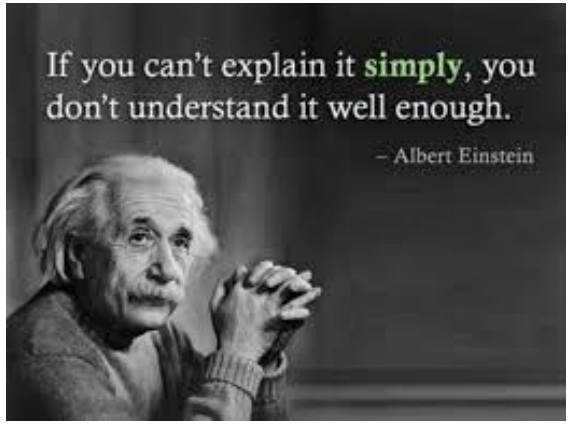
TZP=tirzepatide. Jastreboff, NEJM. Nov 2024.

Semaglutide 2.4 mg: The STEP 1 trial extension

GLP-1R

Weight Loss %

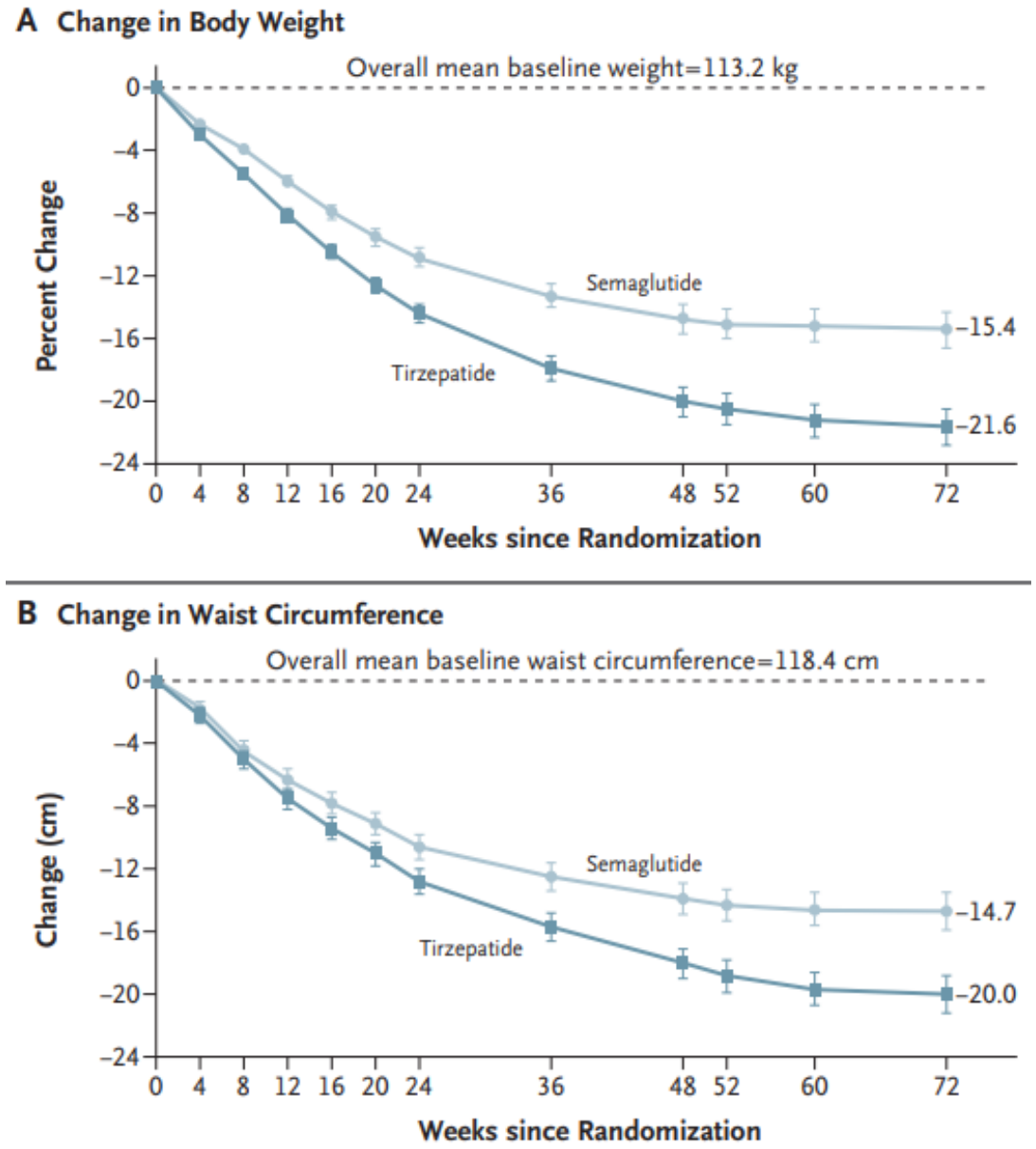




Weight regain towards baseline (-5% from baseline) 1 year after stopping semaglutide

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

Surmount 5: tirzepatide (10/15mg) vs semaglutide 2.4 mg



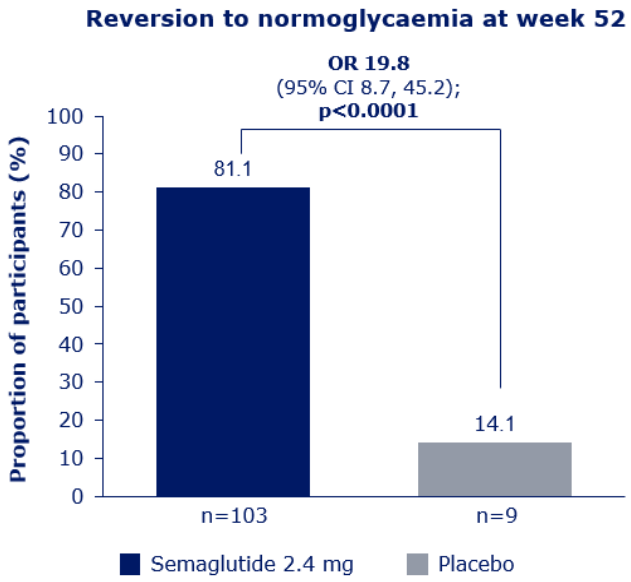
15.4% mean weight loss sema vs 21.6% tirze

NEJM May 2025

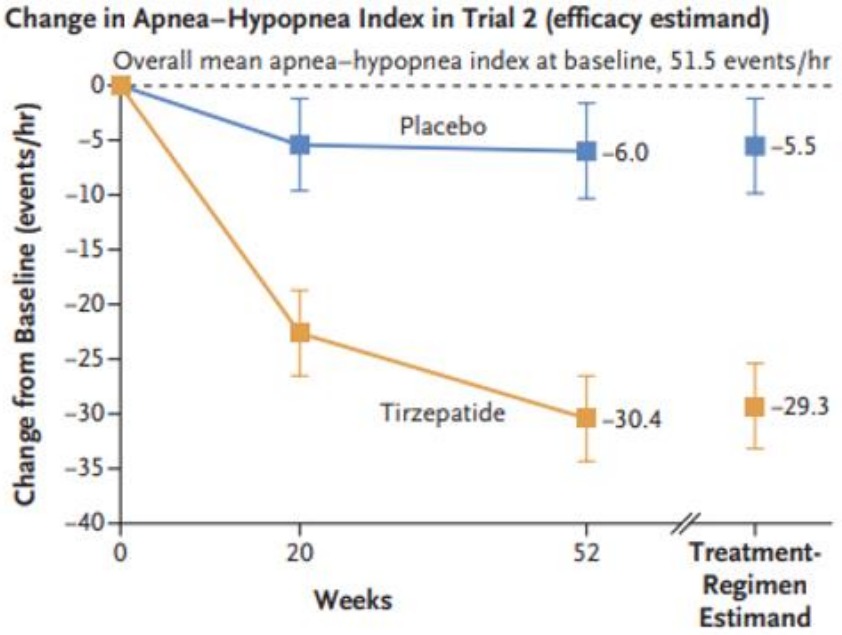
Beyond weight loss: evidence for cardiovascular benefit and other health outcomes

So much more than weight loss……..

STEP-10, semaglutide 2.4 mg, reversion of prediabetes McGowan et al, Lancet D&E, Sep 2024

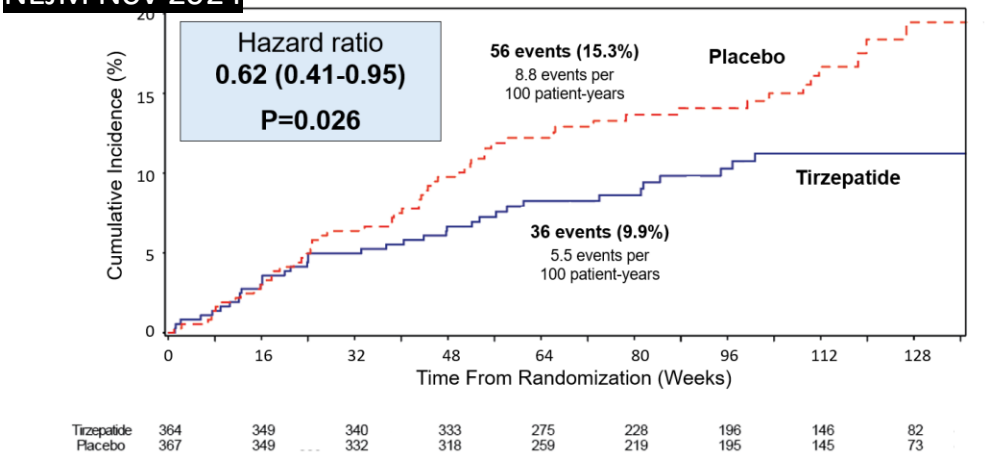


SURMOUNT-OSA, Tirzepatide, improvement in AHI, June 2024

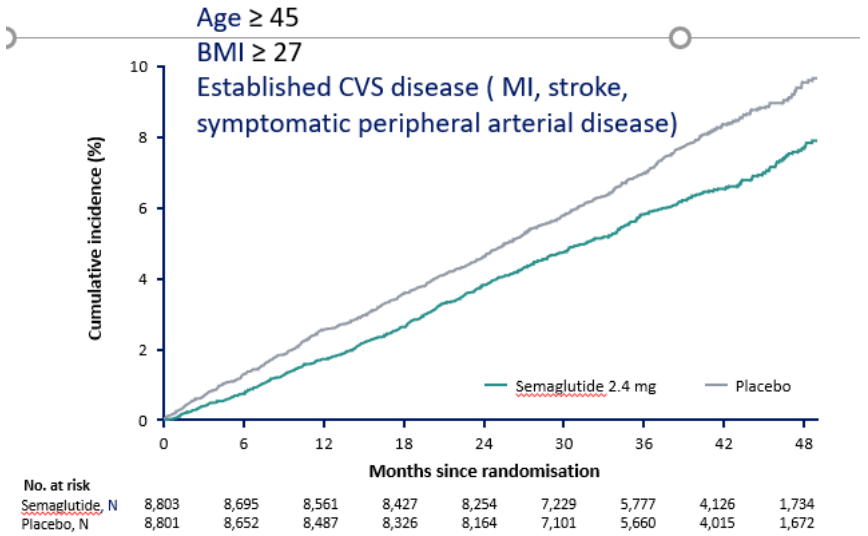


SUMMIT Primary Endpoint: Time-to-First-Event for Cardiovascular Death or Worsening Heart Failure (α=0.04)

NEJM Nov 2024

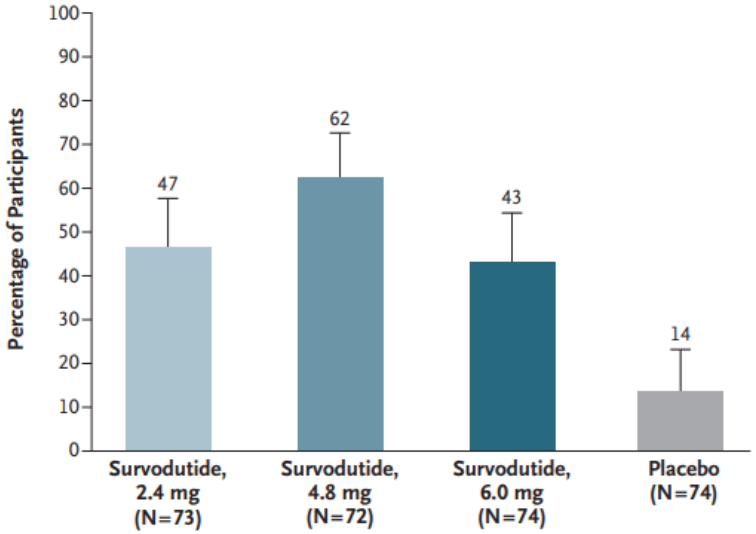


SELECT, semaglutide 2.4 mg, reduction in CVS risk, NEJM Nov 2023

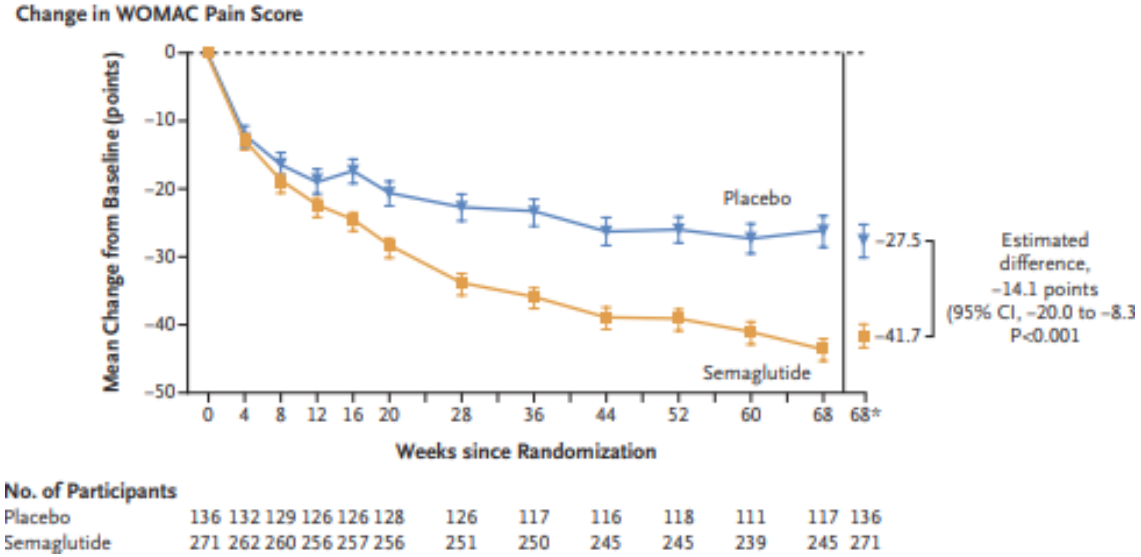


So much more than weight loss……

Phase 2 Survodutide, histological improvement in MASH and no worsening of Fibrosis, NEJM June 2024



STEP-9 Semaglutide 2.4 mg improvement in osteoarthritis , NEJM Oct 2024



Semaglutide 2.4 mg in CKD reduced UACR by 52% at 24 wks, Nature Med, Jan 2025

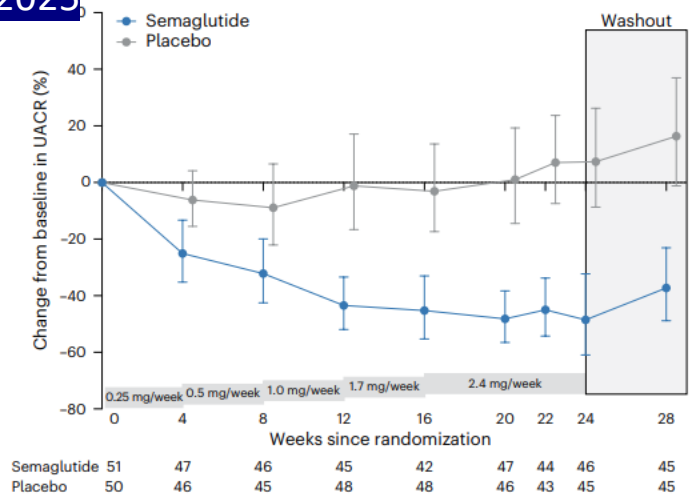
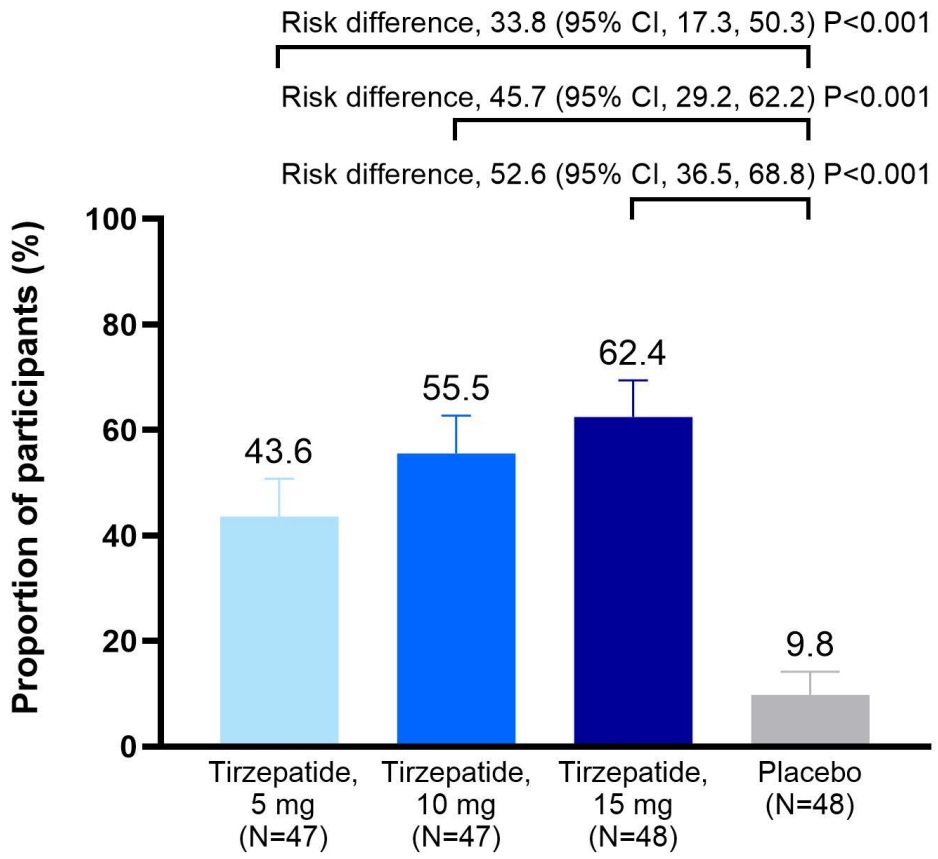


Fig. 1 | Change from baseline in UACR over the study treatment period.

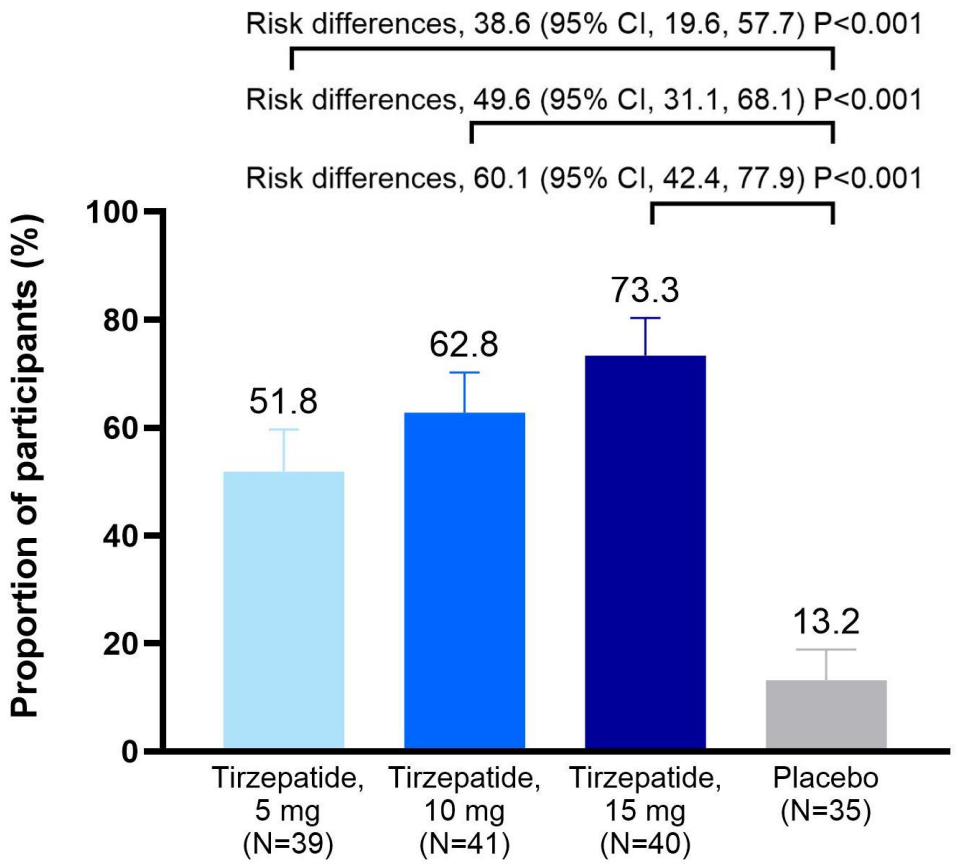
SYNERGY-NASH: TIRZEPATIDE FOR TREATMENT OF MASH WITH STAGE 2/3LIVER FIBROSIS (Phase 2)

PRIMARY ENDPOINT: Resolution of MASH and no worsening of fibrosis

Treatment Regimen Estimand



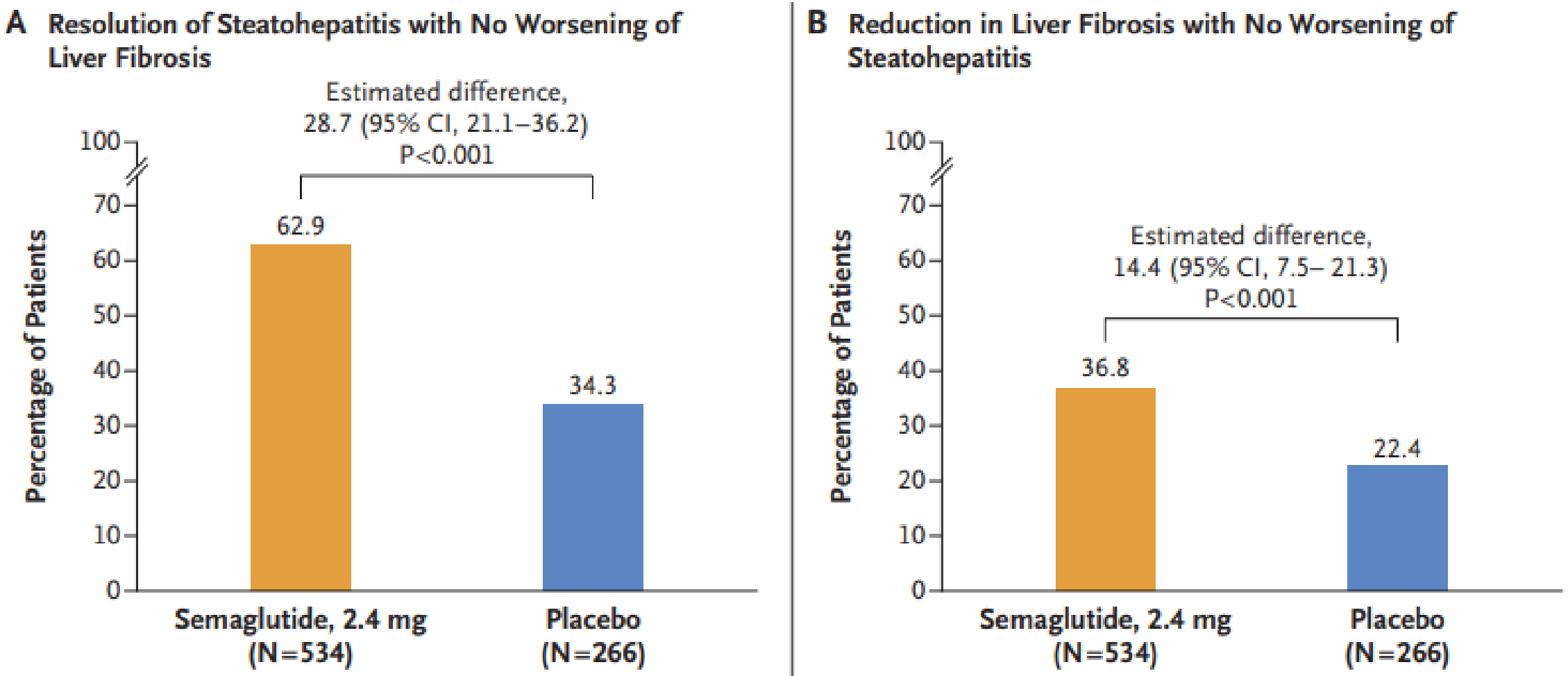
Efficacy Estimand



Data are estimates; risk differences with 95% CI are presented. The CIs are not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Proportion estimate and risk difference are estimated based on logistic regression model. For the efficacy estimand, 155 participants completed treatment and had evaluable end-of-treatment liver biopsies. MASH = metabolic dysfunction-associated steatohepatitis; N = number of participants in the analysis population.

ESSENCE: SEMAGLUTIDE 2.4 MG FOR TREATMENT OF MASH WITH STAGE 2/3 LIVER FIBROSIS (Phase 3)

PRIMARY ENDPOINT: Resolution of MASH and no worsening of fibrosis and reduction in liver fibrosis with no worsening of steatohepatitis

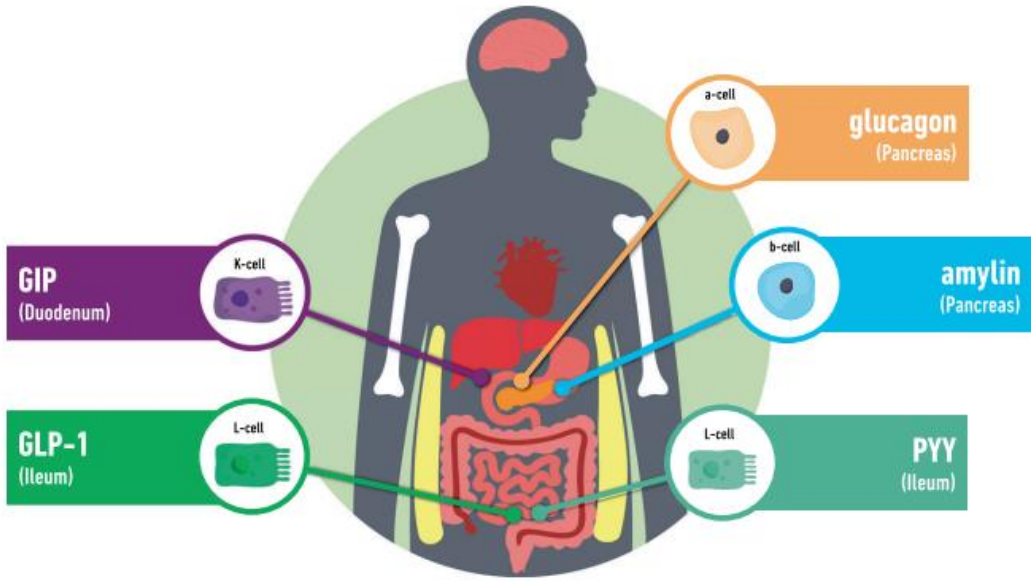


FDA approved August 2025 for MASH with moderate to advanced fibrosis

NEJM June 2025

What’s the Future of obesity pharmacotherapy?

Nutrient-stimulated Hormone (NUSH- based therapies)

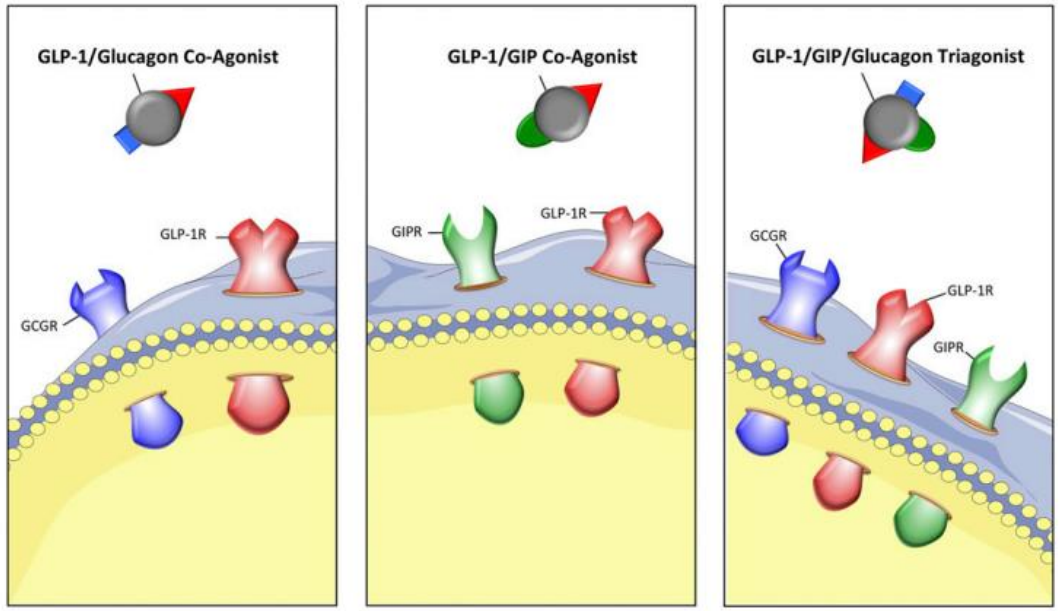


GLP-1R and GIP-R[a,b]
- Phase 1
- Phase 2
- Phase 3

GLP-1R and amylin receptor[c]
- Phase 3

GLP-1R and glucagon[d]
- Phase 1
- Phase 2

GLP-1R, GIP-R and glucagon[e]
- Phase 3



Improves

Body weight
Energy Expenditure
Glycemic control
Cholesterol

Improves

Glycemic control
Body weight
Lipolysis
Cholesterol

Improves

Body weight
Glycemic control
Hepatosteatosis
Cholesterol
Energy Expenditure
Lipolysis

How many OMMS are currently in development?

1.~ 40

2.~ 70

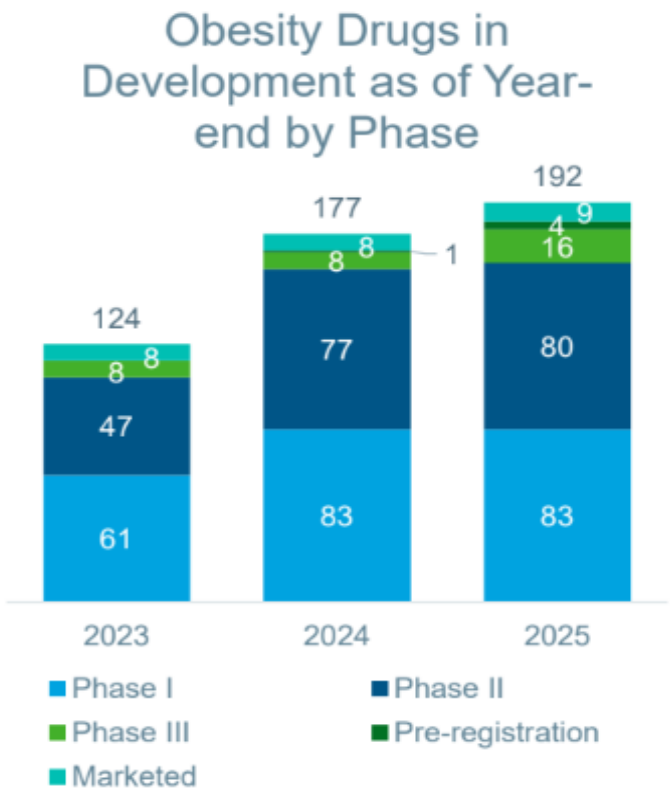
3.~ 100

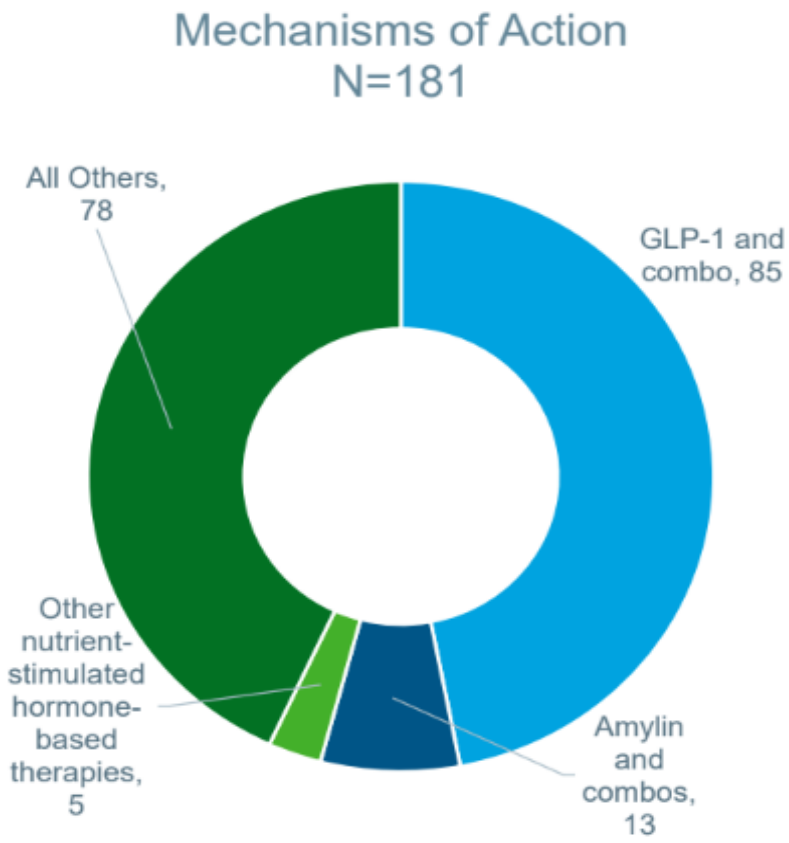
4.~ 180

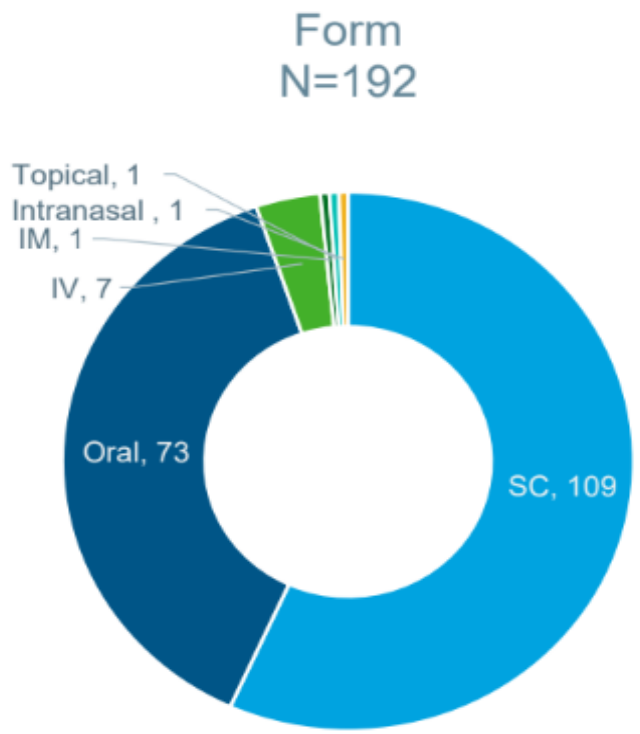
There are 181 obesity medicines in development or marketed with multiple mechanisms beyond the leading GLP-1 therapies

Obesity pipeline by phase, target and route of administration

+50 MOAs, 70+ companies







Source: Citeline Trialtrove; IQVIA Institute, June 2025.
Global Trends in R&D: Overview through 2025. Report by the IQVIA Institute for Human Data Science.

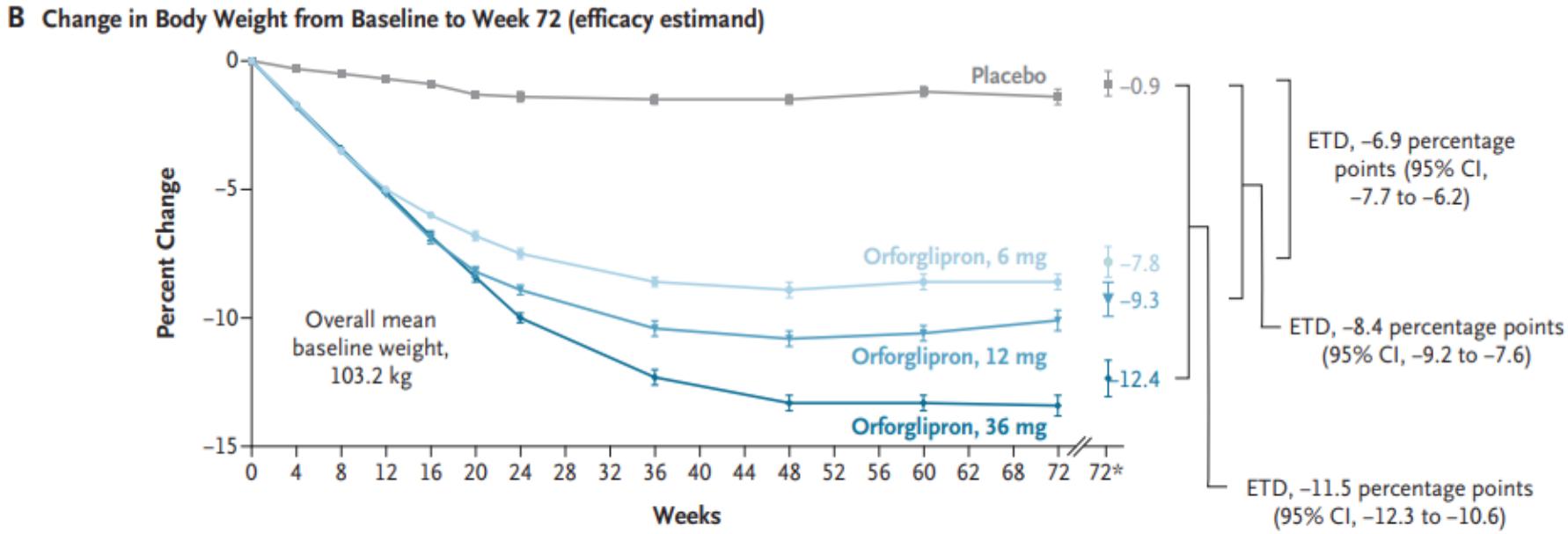
IQVIA INSTITUTE FOR HUMAN DATA SCIENCE

ATTAIN-1: Orforglipron, an Oral Small-Molecule GLP-1 for Obesity Treatment

3127 patients, mean age 45yrs, mean BMI 37.0, no diabetes, 72 weeks

Orforglipron:

- Novel, non-peptide, once daily, oral GLP1 receptor partial agonist, for weight loss
- Bioavailability 30-40%
- Can be taken with food, water or other medications



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

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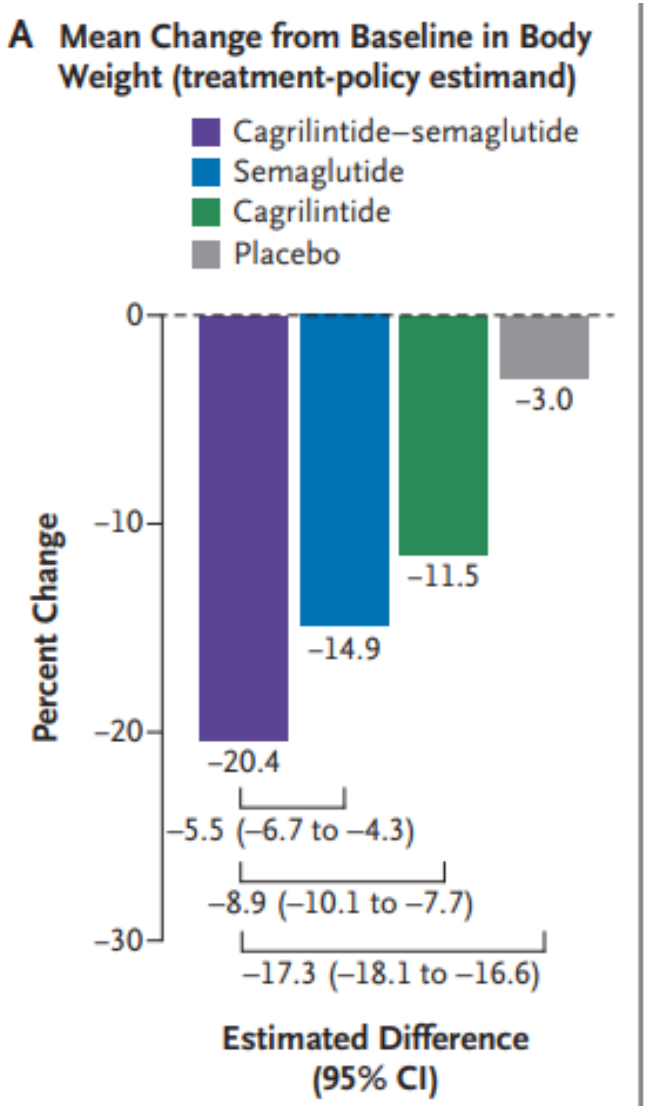
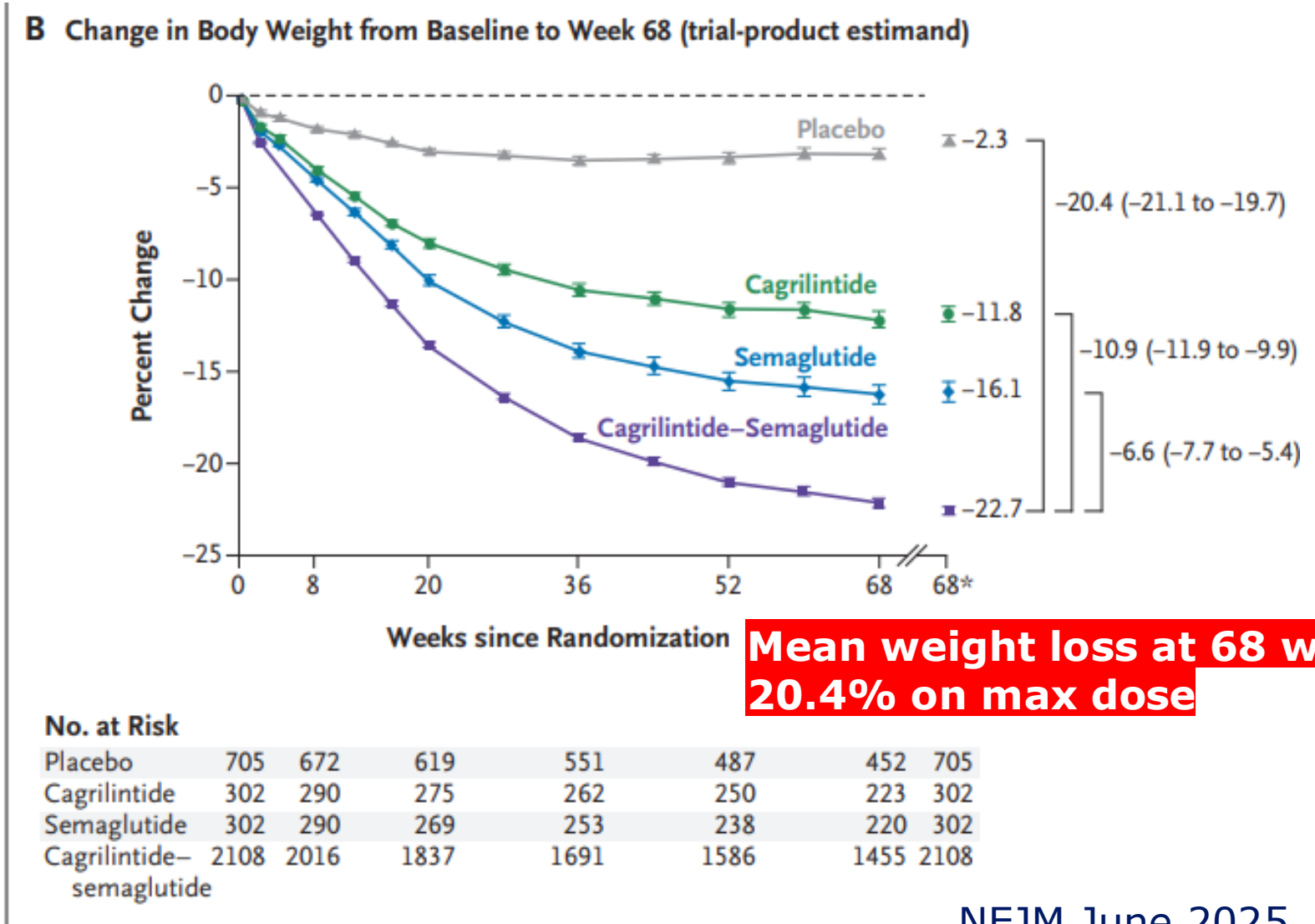
Phase 3: 12.4% (august 2025)

Redefine: CagriSema (GLP-1/Amylin agonist) Phase 3





Mean weight loss at 68 wks 20.4% on max dose

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

NEJM June 2025

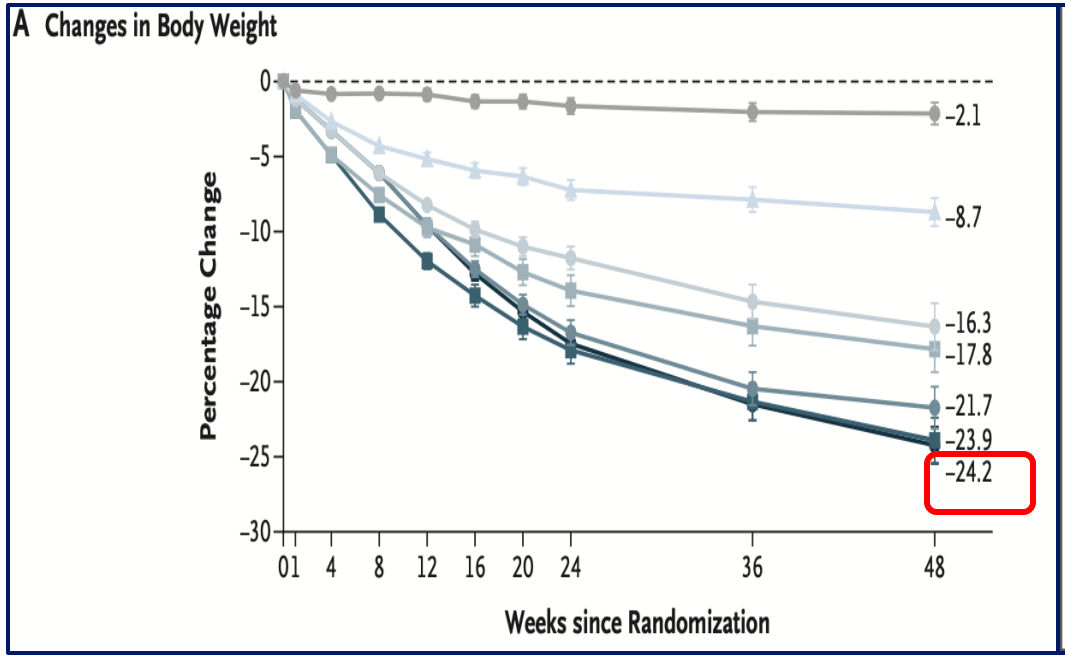
Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

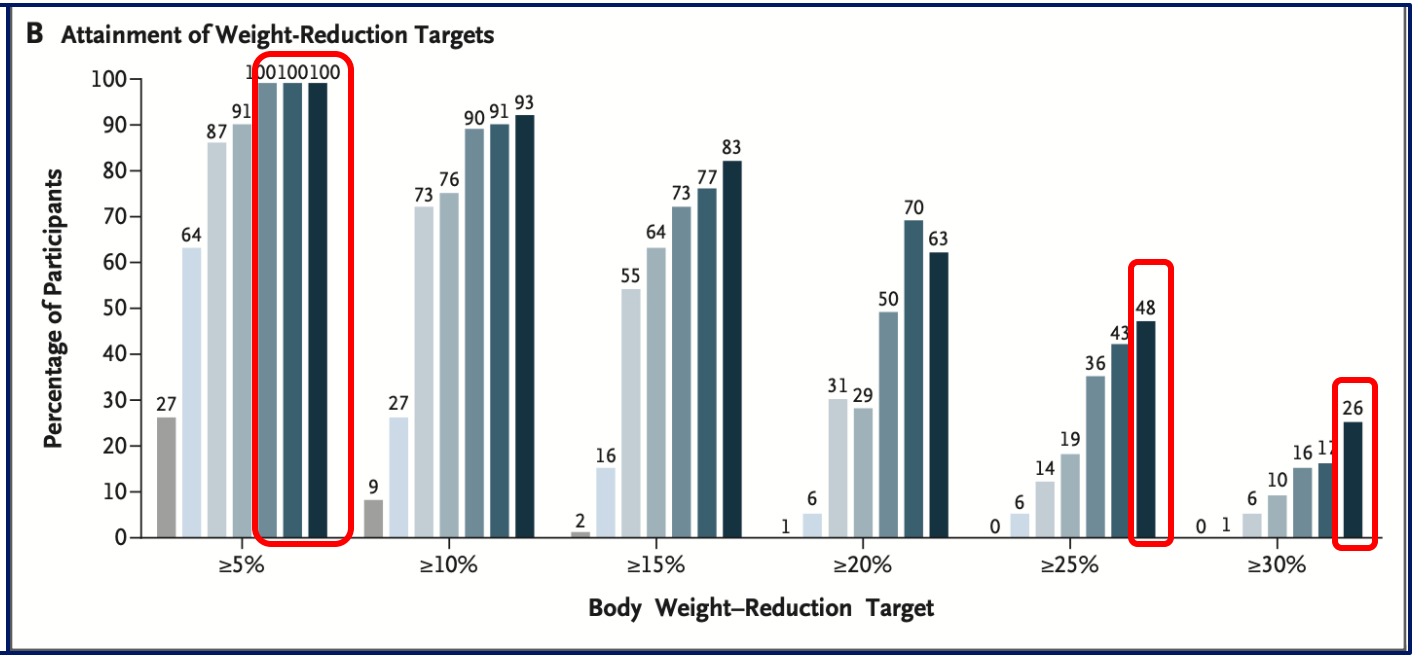
Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D. for the Retatrutide Phase 2 Obesity Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on June 26, 2023, at NEJM.org.

Retatrutide, triple G: 338 patients, mean age 48 yrs, mean BMI 37, no diabetes, 48 weeks

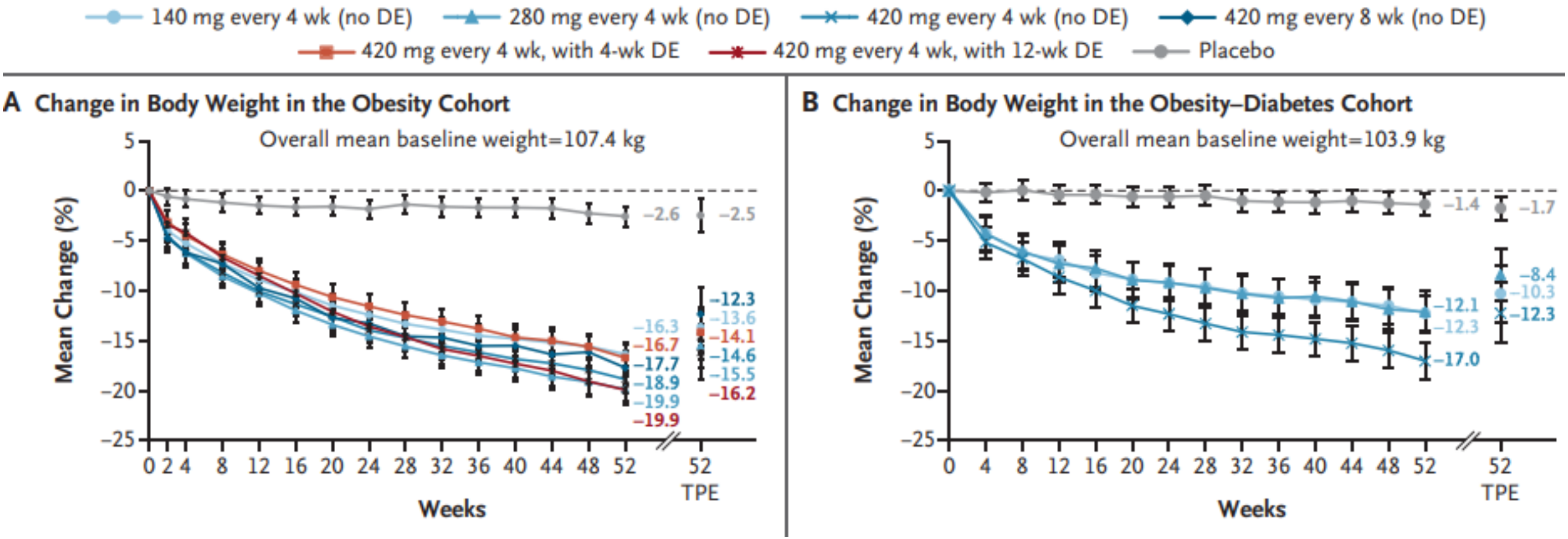




Placebo | Retatrutide, 1 mg | Retatrutide, 4 mg (ID, 2 mg) | Retatrutide, 4 mg (ID, 4 mg) | Retatrutide, 8 mg (ID, 2 mg) | Retatrutide, 8 mg (ID, 4 mg) | Retatrutide, 12 mg (ID, 2 mg)

> 24% mean weight loss at 48 weeks with Retatrutide

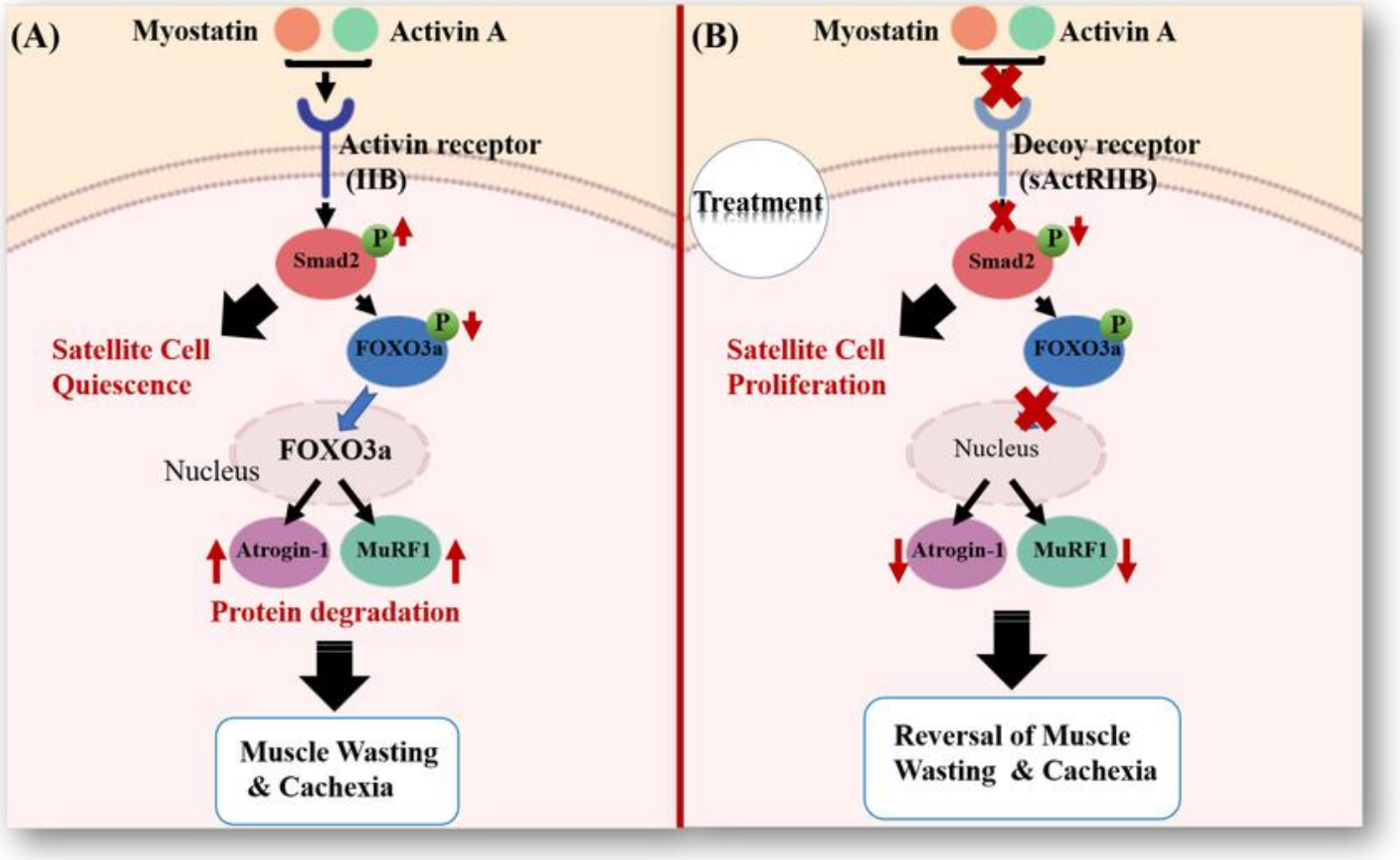
Once a month maritide (GLP-1/GIPR antagonist)-Phase 2



16.2% mean weight loss at 52 wks on max dose (12.3% in T2DM)

Jastreboff et al NEJM June 2025

Myostatin-Activin Pathway inhibitors



Myostatin and Activin A

- Potent inhibitors of muscle growth
- Treatments in development aim to disrupt myostatin and activin receptor signalling
- This leads to increase muscle cell protein synthesis and preservation of muscle function

Farhang-Sardroodi et al, J Clin Medicine 2020

Bimagrumab, an antibody that blocks activin type II receptors and stimulates skeletal muscle growth

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

POPULATION

40 Men, 35 Women

Adults with BMI of 28-40, type 2 diabetes, glycated hemoglobin levels of 6.5%-10.0%, and stable body weight of 65-140 kg

Mean (SD) 60.4 (7.7) y

INTERVENTION

58 Individuals randomized and analyzed

27 Bimagrumab
Bimagrumab 10 mg/kg, up to a maximum of 1200 mg, in 5% dextrose solution, IV infusion over 30 minutes, every 4 wk for 48 weeks (12 doses)

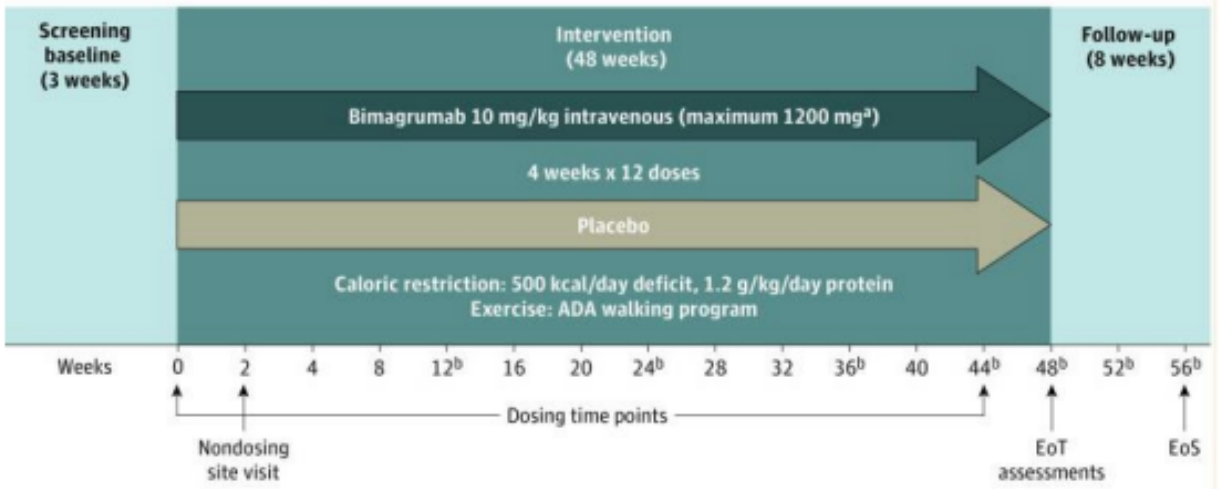
31 Placebo
5% dextrose solution, IV infusion over 30 minutes, every 4 weeks for 48 wk (12 doses)

SETTINGS / LOCATIONS

9 sites, 8 in the US and 1 in Wales, UK

PRIMARY OUTCOME

Primary end point was least squares mean change from baseline in total body fat mass in kg at 48 wk



Heymsfield SB, Coleman LA, Miller R, et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw Open*. 2021;4(1):e2033457. doi:10.1001/jamanetworkopen.2020.33457

Promotes muscle growth, causes beigeing (WAT shifts phenotype towards BAT)
Uncoupling effect, which means ox phos is disrupted, increased EE as you have to go through the Krebs cycle more often leading to weight loss
Also has anti-inflammatory and positive metabolic effects

- **-20.5% FAT MASS LOSS bimagrumab vs -0.5 % placebo**
- **+3.6 % LEAN MASS bimagrumab vs -0.8% placebo**

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

Anti-Obesity Medications / Mystatin-activin pathway inhibitors (upcoming in next years)

	Mode of action
Bimagrumab	Monoclonal antibody that binds activin type 2 Receptor (ACTR2)
Taldefgrobep	Fusion protein that binds active myostatin
SRK-439	Myostatin inhibitor
Garetosmab	Human monoclonal antibody that inhibits activin A
Trevogrumab	Human monoclonal antibody that inhibits myostatin
GYM329/RG6237	Anti –latent myostatin antibody

Slide Barbara McGowan, MD, PhD

….Generally safe but are we storing trouble for the future?

- Nutritional deficiencies- unknown
- Impact on muscle health-unknown
- Impact on bone health-unknown
- Impact on psychological health-unknown

Access to obesity pharmacotherapy

How many private prescriptions for GLP-1 have been issued per month (August 2025)

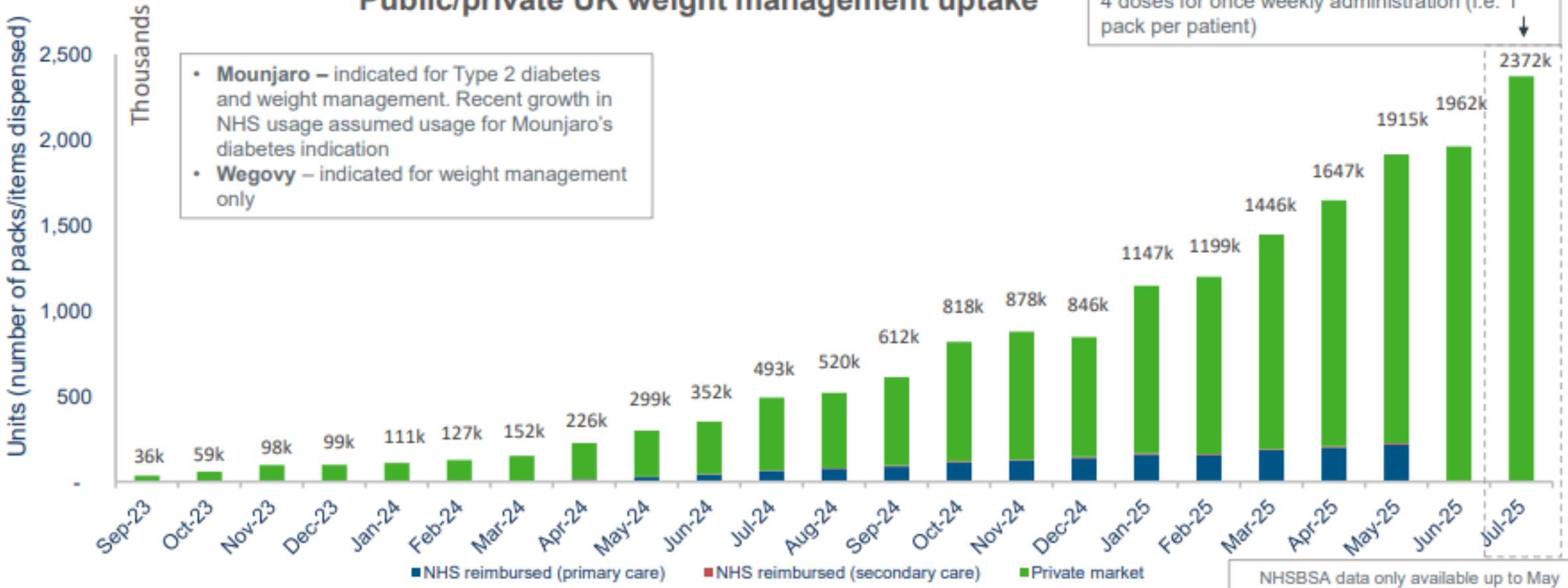
1. 50,000
2. 250,000
3. 1 million
4. 2.3 million

The UK weight management* market has seen an average monthly volume growth of 22.2% since October 2023

Growth driven by GLP1s being used to treat weight management

2,372k packs in July 2025, Mounjaro and Wegovy packs contain 1x Pre-filled syringe with 4 doses for once weekly administration (i.e. 1 pack per patient)

Public/private UK weight management uptake



NHSBSA data only available up to May 2025 (Scotland April 2025) Private market reflects **all supply** for these months

* Weight Management defined as combined dispensing/purchasing of Mounjaro and Wegovy, does not include off-label use of Ozempic (licensed for diabetes) in the private market which may be for weight management.

Source: NHS reimbursed (primary care): NHSBSA data, Items dispensed, May 2025, NHS reimbursed (secondary care): IQVIA Hospital Pharmacy Audit (HPA), units, Jun 2025, Private market: IQVIA Supply Chain Manager (SCM), units, Jul 2025

OMMs phased rollout in uk- Phase 1

Mounjaro roll-out 12 yrs: BMI ≥ 40 + 4/5 complications (T2DM, OSA, BP, hyperlipidemia, established CVD)

- **Active malignancy**
  - where rapid weight loss is required for planned therapy, for example radiotherapy or surgery
- **Organ transplant**
  - Patients requiring urgent weight loss for organ transplant
- **Idiopathic intracranial hypertension (IIH)**
  - Requiring frequent lumbar punctures and/or visual compromise
- **Time-sensitive surgery for life-limiting conditions**
  - Patients undergoing planned time-sensitive surgery for life-limiting conditions, where high BMI is the primary barrier to surgery and weight loss would be beneficial
- **Assisted conception**
  - Weight loss required for assisted conception in women under the care of a fertility service, in cases where weight loss is necessary for therapy
- **Severe sleep apnoea / Obesity hypoventilation syndrome**

Conclusions

- Current and future medical therapies for obesity have bridged the gap between lifestyle and bariatric surgery
- Incretin therapies for weight loss have benefits beyond weight loss
- Inequalities of obesity care including lack of access to services and funding likely to continue for several years

33rd EUROPEAN CONGRESS ON OBESITY
ECO 2026
12-15 May 2026 - Istanbul, Türkiye

Thank you