Terapia farmacologica: oggi e domani

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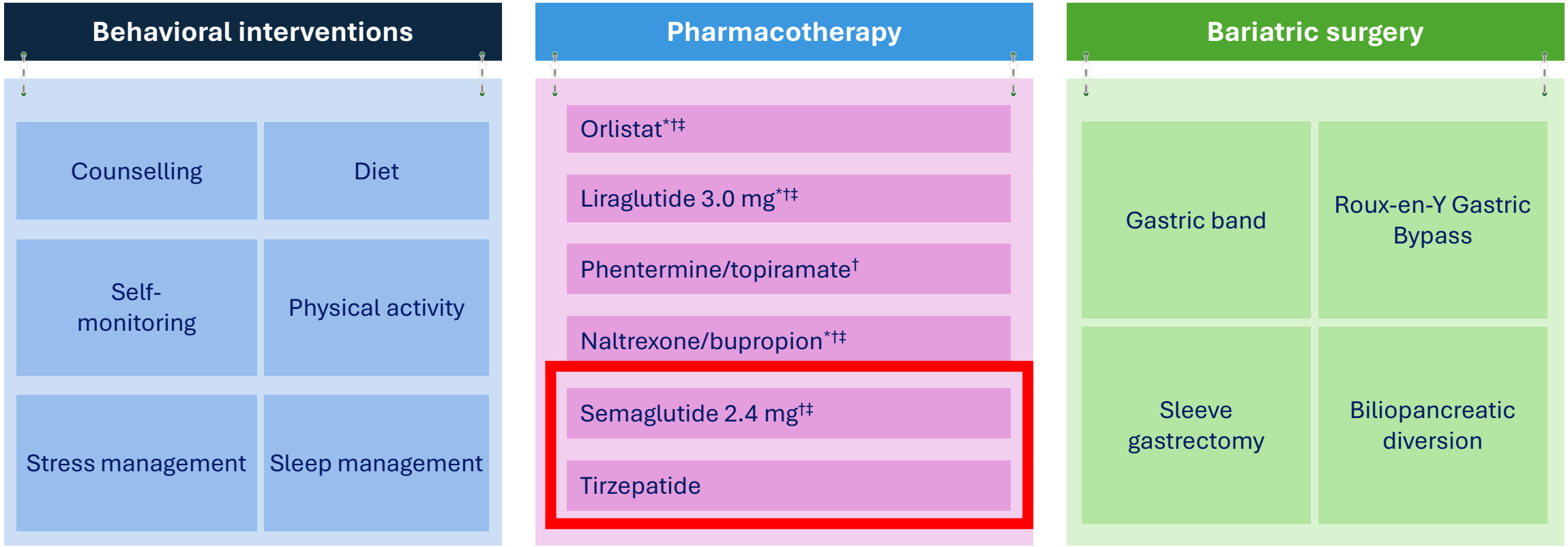
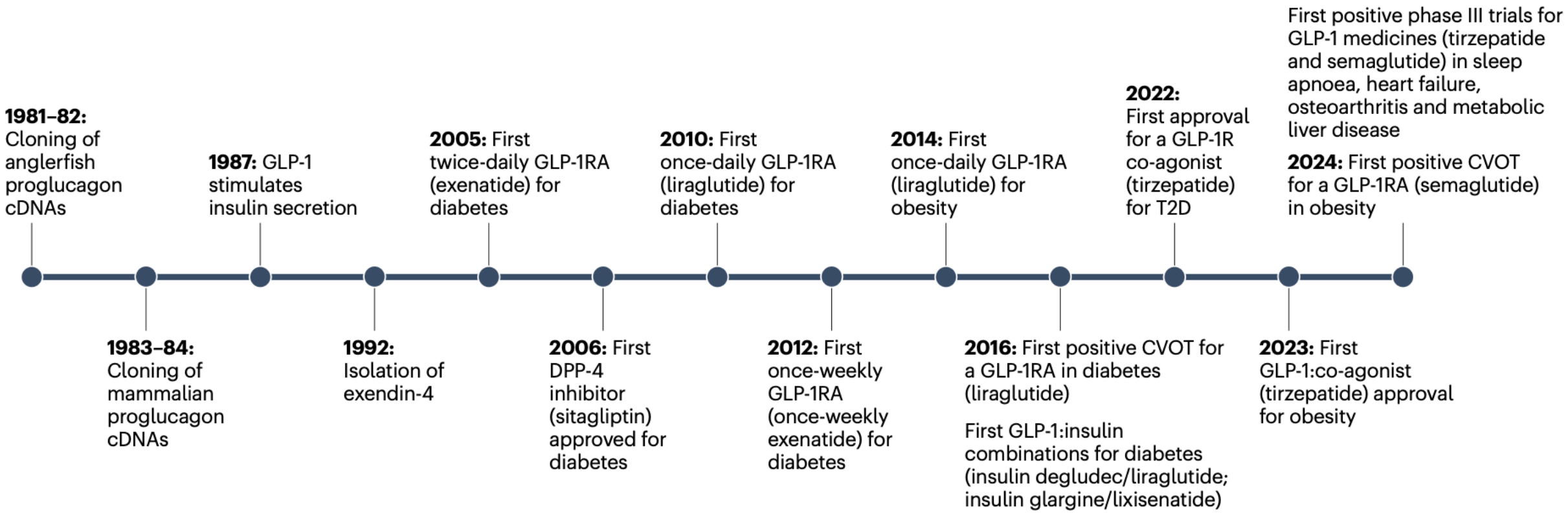
Treatment strategies for obesity



*approved by the EMA; †approved by the FDA; ‡approved by Health Canada.

1. Garvey et al. Endocr Pract. 2016:1–203; 2. Mechanick JI et al. SOARD. 2020;16:175-247; 3. Wharton et al. CMAJ. 2020;192:E875-91; 4. FDA approved drugs. Available at: http://www.fda.gov/Drugs/default.htm. Accessed October 2022; 5. Pharmacotherapy in Obesity Management. Obesity Canada. 2022. Available at: https://obesitycanada.ca/wp-content/uploads/2022/10/Pharmacotherapy-CPG-2022_final.pdf. Accessed November 2022; 6. EMA approved drugs. Available at: http://www.ema.europa.eu/. Accessed October 2022.

GLP-1 DISCOVERIES LANDMARKS



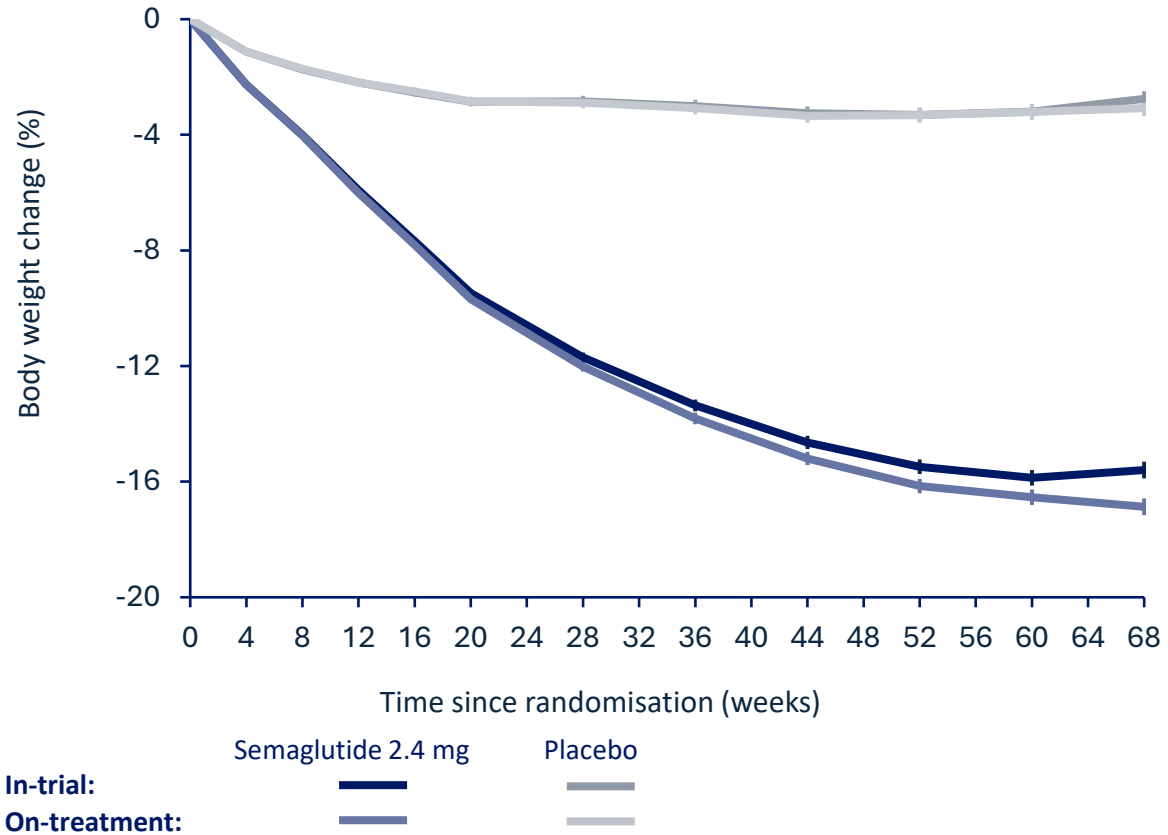
Drucker DJ, Nature Reviews Drug Discovery, vol. 2 , August 2025, 631–650

Change in body weight with semaglutide 2,4 mg

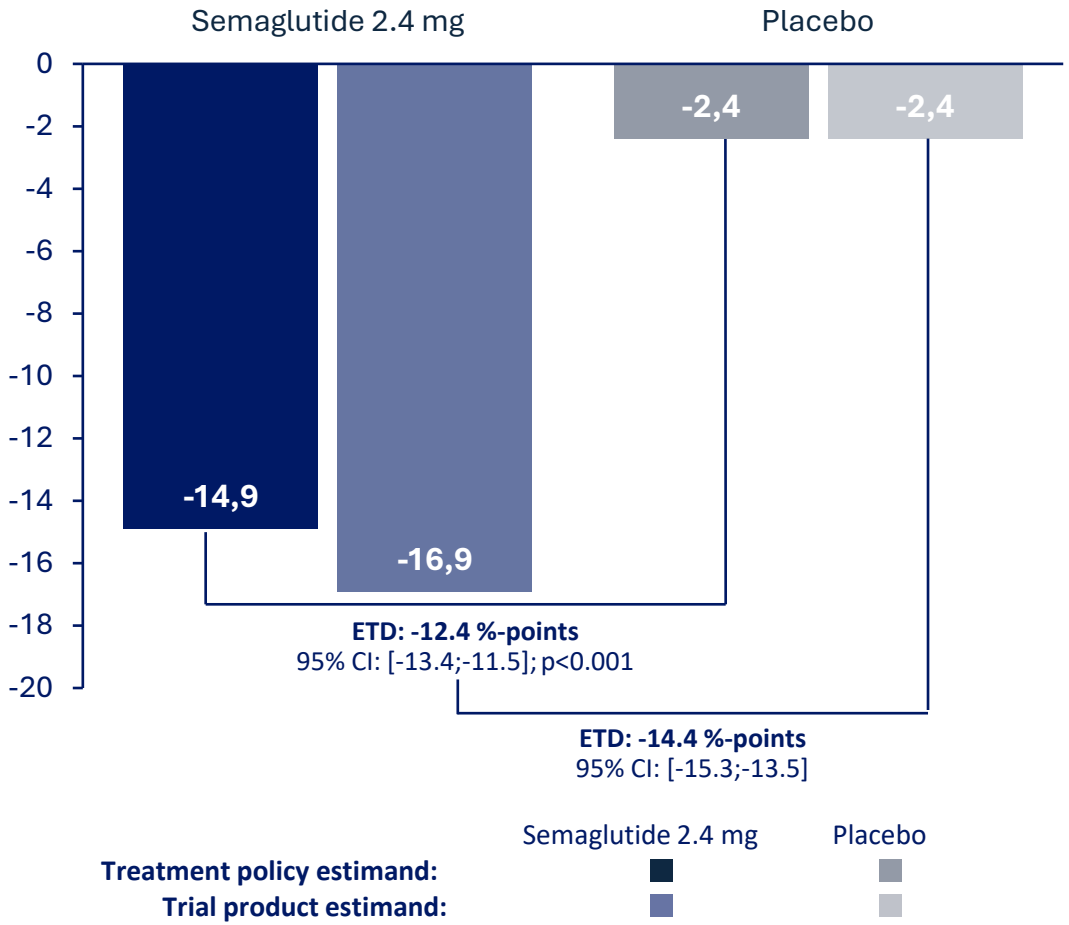
STEP 1

Observed body weight change over time

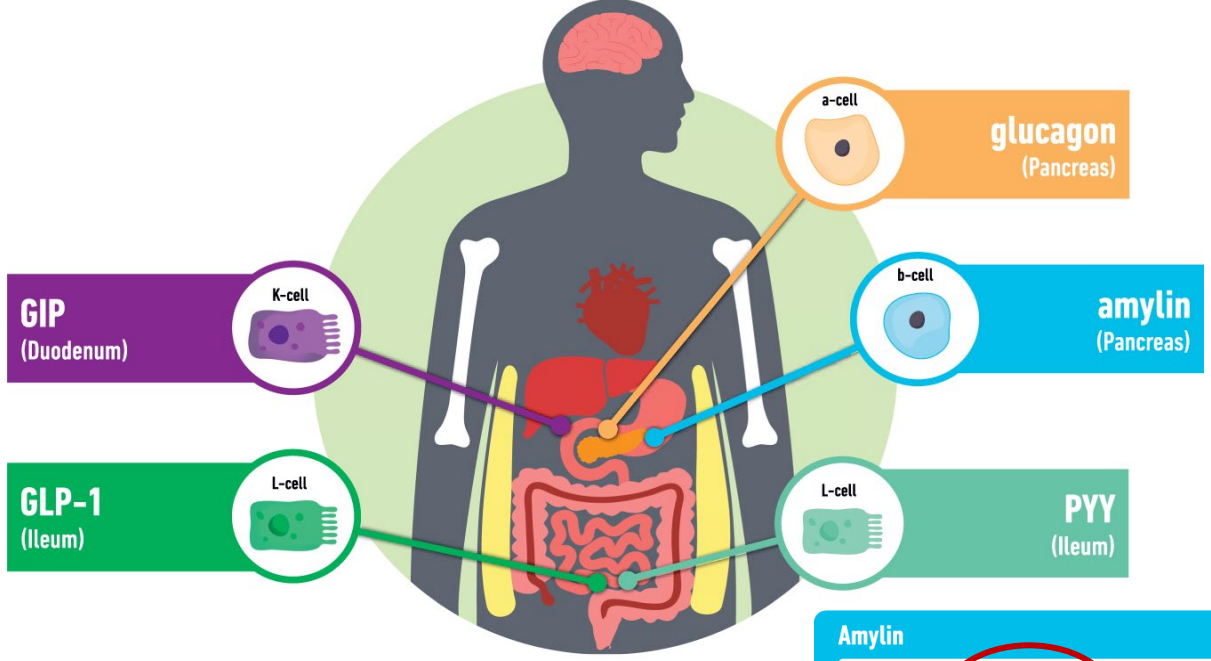
(Mean at baseline: 105.8 kg)



Estimated change from baseline to week 68



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



GLP-1

- ↓ appetite, ↓ food intake; ↑ nausea
- ↑ insulin; ↓ glucagon
- ↓ gastric emptying
- ↑ lipolysis
- ↑ cardioprotection; ↑ heart rate

GIP

- ↓ appetite*; ↓ nausea
- ↑ insulin; ↑ glucagon
- ↓ gastric acid secretion
- ↑ lipid deposition; ↑ lipogenesis
- ↓ bone resoption

Amylin

- ↓ appetite; ↓ food intake
- ↓ glucagon
- ↑ energy expenditure*
- ↓ gastric emptying
- ↓ osteoclast activity; ↑ osteoblast activity

PYY

- ↓ appetite, ↓ food intake; ↑ nausea
- ↓ gastric emptying
- ↑ energy expenditure*

Glucagon

- ↓ appetite, ↓ food intake; ↑ nausea
- ↑ insulin
- ↑ hepatic glucose production; ↑ lipid oxidation, ↓ hepatic lipid synthesis
- ↓ gastric emptying
- ↑ energy expenditure
- ↑ heart rate

PIPELINE FOR FUTURE OBESITY MEDICATIONS

Name	Dose	Administration	Mechanism of action	Company	Expected completion date	Clinical Trials gov	Other indication(s)
Phase 3 obesity trials							
Semaglutide*	50 mg	PO, OD	GLP-1 RA	Novo Nordisk	Completed	NCT05035095	Phase 3 - T2D
Orforglipron	NA	PO, OD	GLP-1 RA	Eli Lilly	September-2027	NCT05869903	Phase 3 - T2D, CV outcomes in T2D
Semaglutide	7.2 mg	SC, OW	GLP-1 RA	Novo Nordisk	NA	NA	NA
Tirzepatide*	5–15 mg	SC, OW	GLP-1 RA + GIP RA	Eli Lilly	Completed	NCT04184622	Phase 3 - T2D, HFpEF, OSA, CV outcomes in T2D, morbidity and mortality in obesity Phase 2 - MASH, CKD
CagriSema	2.4 mg/2.4 mg	SC, OW	GLP-1 RA + Amylin RA	Novo Nordisk	October-2026	NCT05567796	Phase 3 - T2D, CV outcomes
Survodutide	3.6–6 mg	SC, OW	GLP-1 RA + GCG RA	Boehringer Ingelheim	Completed	NCT04667377	Phase 2 - T2D, MASH
Mazdutide	4–6 mg	SC, OW	GLP-1 RA + GCG RA	Innovent Biologics	April-2024	NCT05607680	Phase 3 - T2D Phase 1 CKD
Mazdutide	9 mg	SC, OW	GLP-1 RA + GCG RA	Innovent Biologics	September 2025	NCT06164873	NA
Retatrutide	4–12 mg	SC, OW	GLP-1 RA + GIP RA + GCG RA	Eli Lilly	May-2026	NCT05929066	Phase 3 - T2D, OA Phase 2 - CKD
Phase 2 obesity trials							
Danuglipron	40–200 mg	PO, BD	GLP-1 RA	Pfizer	Completed	NCT04707313	NA
Cagrilintide	0.3–4.5 mg	SC, OW	Amylin RA	Novo Nordisk	Completed	NCT03856047	Phase 1 - MASH
PYY 1875	0.03–2.4 mg	SC, NA	PYY RA	Novo Nordisk	Completed	NCT03707990	NA
Efinopegdutide	5–10 mg	SC, OW	GLP-1 RA + GCG RA	Hanmi Pharmaceutical	Completed	NCT03486392	Phase 2 - T2D, MASH, MASLD
Pemvidutide	1.2–2.4 mg	SC, OW	GLP-1 RA + GCG RA	Altimmune	Completed	NCT05295875	Phase 2 - MASH, MASLD Phase 1 – T2D
AMG 133	NA	SC, once monthly	GLP-1 RA + GIP receptor antagonist	Amgen	January-2025	NCT05669599	NA
NNC0165-1875 + Semaglutide	1–2 mg + 2.4 mg	SC, every 2 to 4 weeks	GLP-1 RA + PYY RA	Novo Nordisk	Completed	NCT04969939	NA
Dapiglutide	4–6 mg	SC, OW	GLP-1 RA + GLP2 RA	Zealand Pharma	August-2024	NCT05788601	NA
Bimagrumab + Semaglutide	30 mg/kg + 1–2.4 mg	IV, every 4 weeks (Bimagrumab) + SC, OW	Activin receptor II inhibition + GLP-1 RA	Versanis Bio	September-2025	NCT05616013	NA
S-309309	NA	PO, OD	MGAT2	Shionogi	May-2024	NCT05925114	NA
Phase 1 obesity trials							
CT-996	NA	PO, OD	GLP-1 RA	Carmot Therapeutics	November-2024	NCT05814107	NA

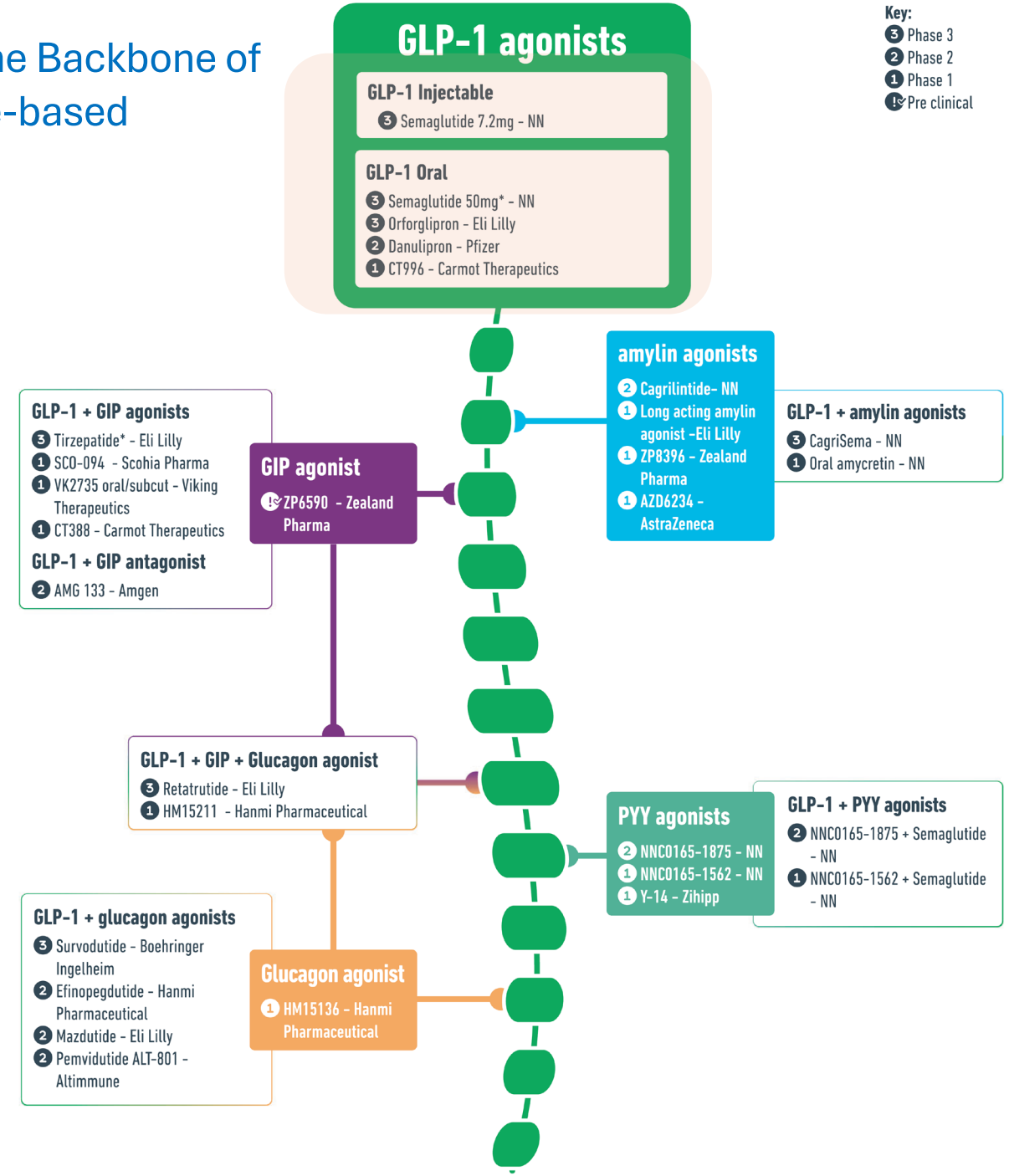
PIPELINE FOR FUTURE OBESITY MEDICATIONS (2)

Name	Dose	Administration	Mechanism of action	Company	Expected completion date	Clinical Trials gov	Other indication(s)
Long-acting amylin agonist	NA	NA	Amylin RA	Eli Lilly	NA	NA	NA
AZD6234	NA	SC, OW	Amylin RA	AstraZeneca	December-2023	NCT05511025	NA
ZP8396	NA	SC, OW	Amylin RA	Zealand Pharma	May-2024	NC 05613387	NA
HM15136	NA	SC, frequency not stated	Glucagon RA	Hanmi Pharmaceu	Complet	04032782	NA
NNC0165-1562	NA	SC, OW	PYY RA	Novo Nordisk	Compl	02568306	NA
Y-14	9-36mg	SC, OW/every 2 weeks	PYY RA	Zihipp			NA
VK2735	NA	PO, frequency not stated	GLP-1 RA + GIP RA	Viking Therapeutics			Phase 1 – MASH
VK2735	NA	SC, OW	GLP-1 RA + GIP RA	Viking Therapeutics			Phase 1 – MASH
SCO-094	NA	PO, frequency not stated	GLP-1 RA + GIP RA	Scohia Pharma			Phase 1 - T2D, MASH
CT-388	5–12 mg	SC, OW	GLP-1 RA + GIP RA	Carmot Therapeutics		5	Phase 1 - T2D
Amycretin (NNC0487-0111)	1–100 mg	PO, OD	GLP-1 RA + Amylin RA	Novo Nordisk	em 24	T0536	NA
Dacra QW II	NA	NA	Amylin RA + calcitonin RA	Eli Lilly	NA	A	NA
NNC0165-1562 and Semaglutide	NA	SC, OW	PYY RA + GLP-1RA	Novo Nordisk	Complet d	NCT03574584	NA
HM15211	NA	SC, OW	GLP-1 RA + GIP RA + GCG RA	Hanmi Pharmaceutical	Completed	NCT03374241	Phase 2 – MASH
NNC0247-0829	NA	SC, OW	GDF15 analogue	Novo Nordisk	Completed	NCT04010786	NA
JNJ-9090/CIN-109	NA	SC, OW/Twice weekly	GDF15 analogue	CinRx Pharma	NA	NA	NA
SCO-267	NA	PO, OD	G-protein-coupled receptor 40	Scohia Pharma	Completed	JapicCTI-195057	Phase 1 - MASH
Preclinical status							
ZP6590	NA	NA	GIP RA	Zealand Pharma	NA	NA	NA

*Completed phase 3 trials for obesity

T2D type 2 diabetes, *HFpEF* heart failure with preserved ejection fraction, *MASH* metabolic dysfunction-associated steatohepatitis, *MASLD* metabolic dysfunction-associated steatotic liver disease, *CKD* chronic kidney disease, *CV* cardiovascular, *OA* osteoarthritis, *OSA* obstructive sleep apnoea, *RA* receptor agonist, *GLP-1* glucagon-like peptide-1, *GIP* glucose-dependent insulinotropic polypeptide, *GCG* glucagon, *PYY* peptide YY, *GDF15* Growth/differentiation factor-15, *MGAT2* Monoacylglyceroltransferase 2, *SC* subcutaneous, *PO* oral, *IV* intravenous, *OD* once-daily, *BD* twice daily, *OW* once-weekly, *NA* data not available.

Glucagon-like peptide-1 as the Backbone of the Pipeline for Gut Hormone-based Obesity Treatments

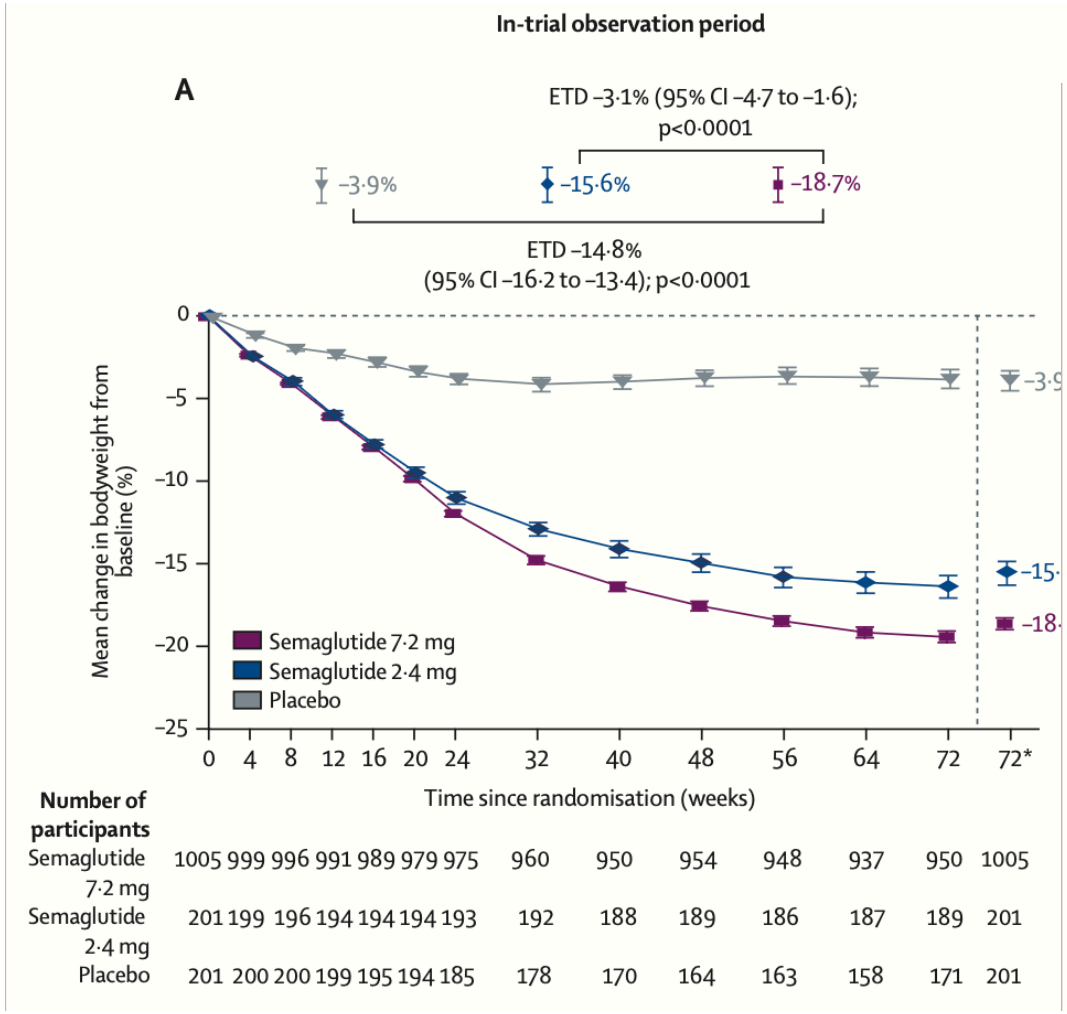


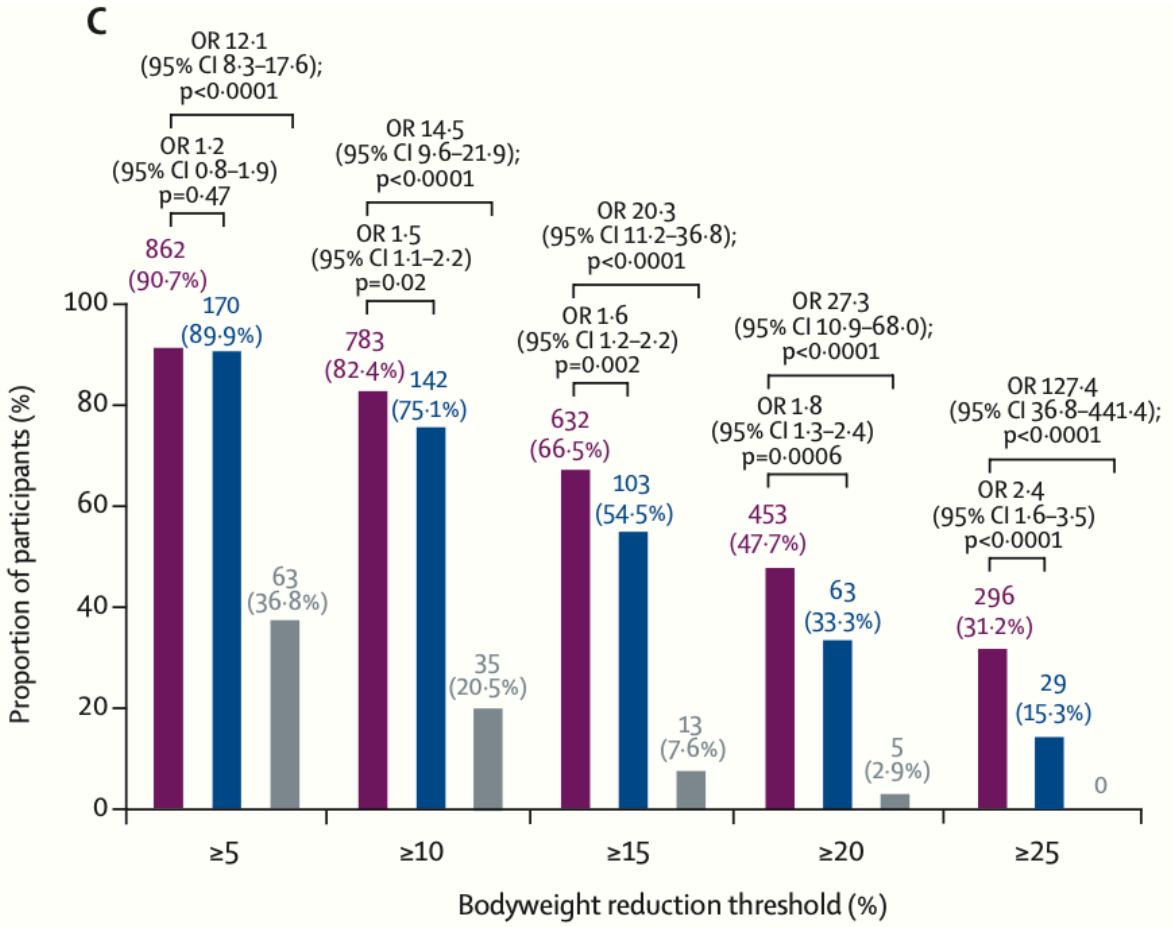
GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: Novo Nordisk, *completed phase 3 trials for obesity.

Melson E, et al, *Int J Obes* 2024

Once-weekly semaglutide 7·2 mg in adults with obesity (STEP UP): a randomised, controlled, phase 3b trial

*Sean Wharton, Paula Freitas, Jøran Hjelmesæth, Maria Kabisch, Kristian Kandler, Ildiko Lingvay, Maria Quiroga, Julio Rosenstock, W Timothy Garvey, on behalf of the STEP UP trial group**





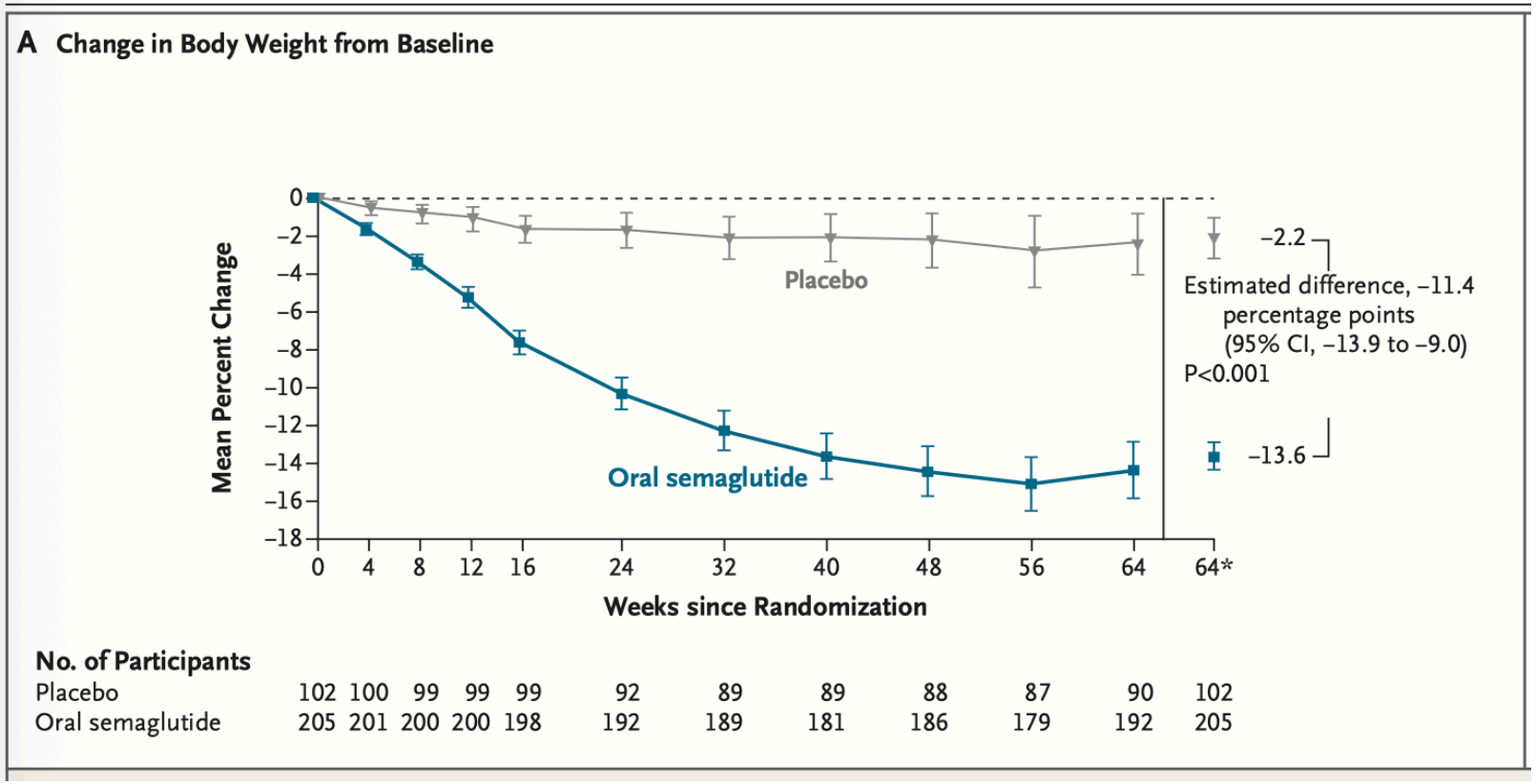
www.thelancet.com/diabetes-endocrinology Published online September 14, 2025 https://doi.org/10.1016/S2213-8587(25)00226-8

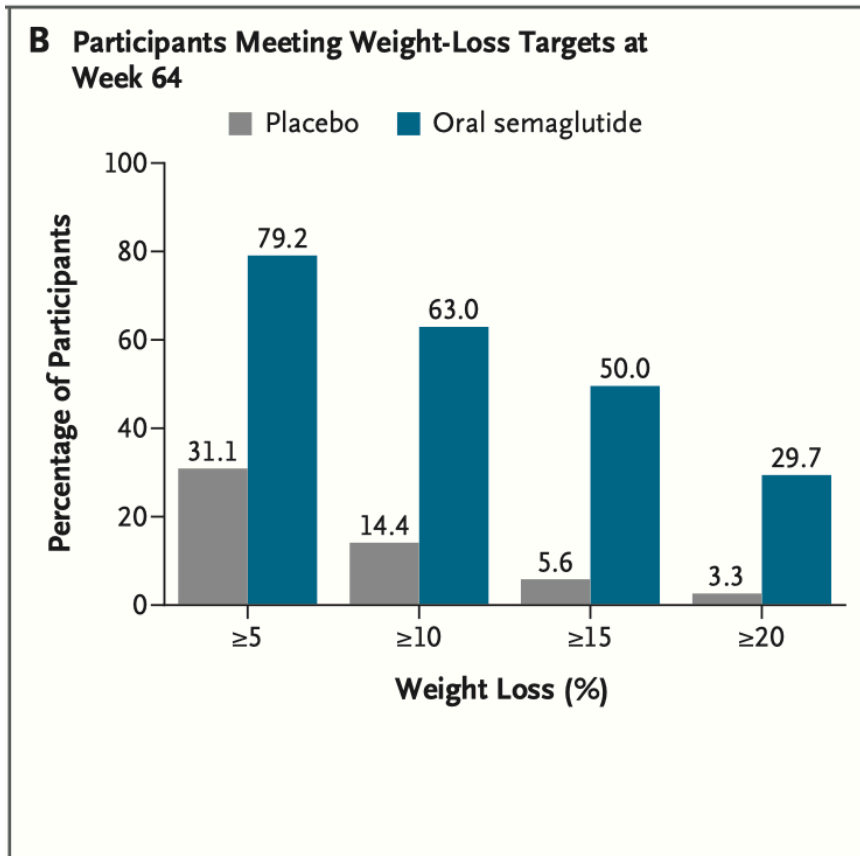
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity

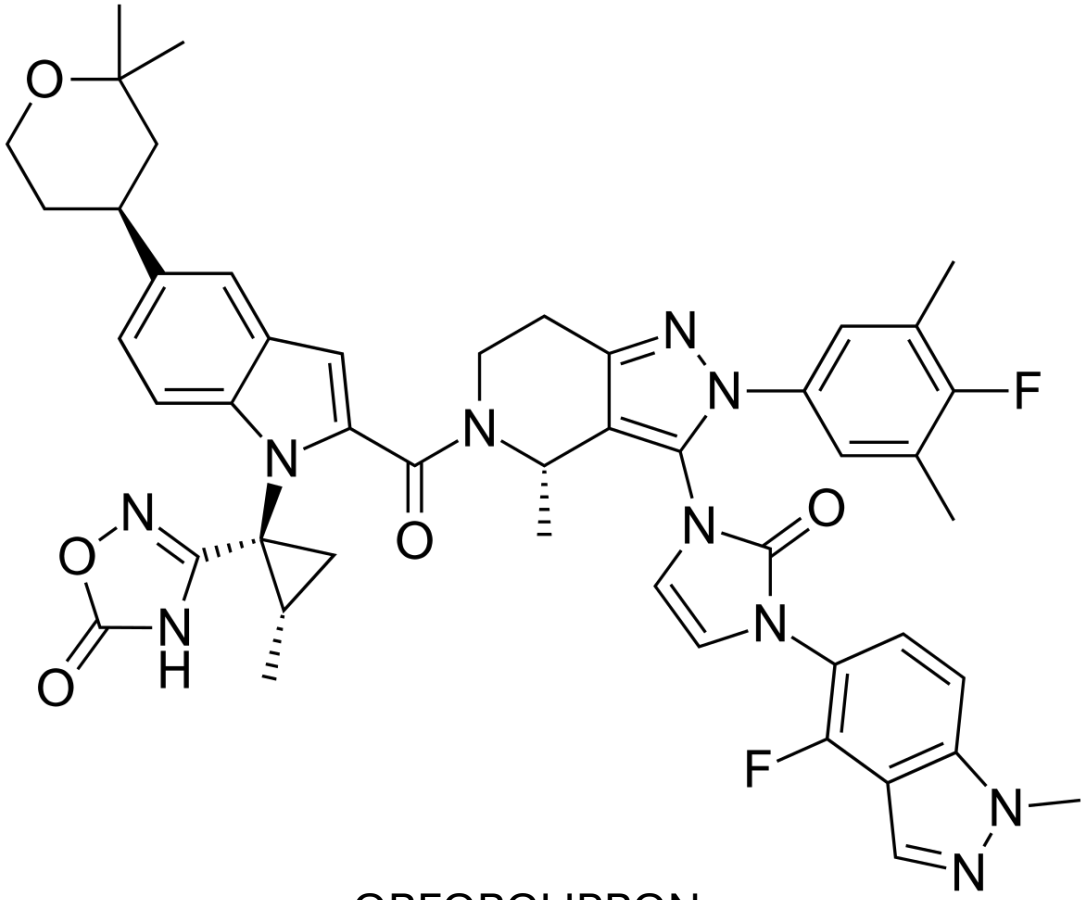
Sean Wharton, M.D.,[1-4] Ildiko Lingvay, M.D.,[5,6] Pawel Bogdanski, M.D.,[7] Ruben Duque do Vale, M.D.,[8] Stephan Jacob, M.D.,[9] Tobias Karlsson, M.D.,[8] Chaithra Shaji, M.Sc.,[10] Domenica Rubino, M.D.,[11] and W. Timothy Garvey, M.D.,[12] for the OASIS 4 Study Group*



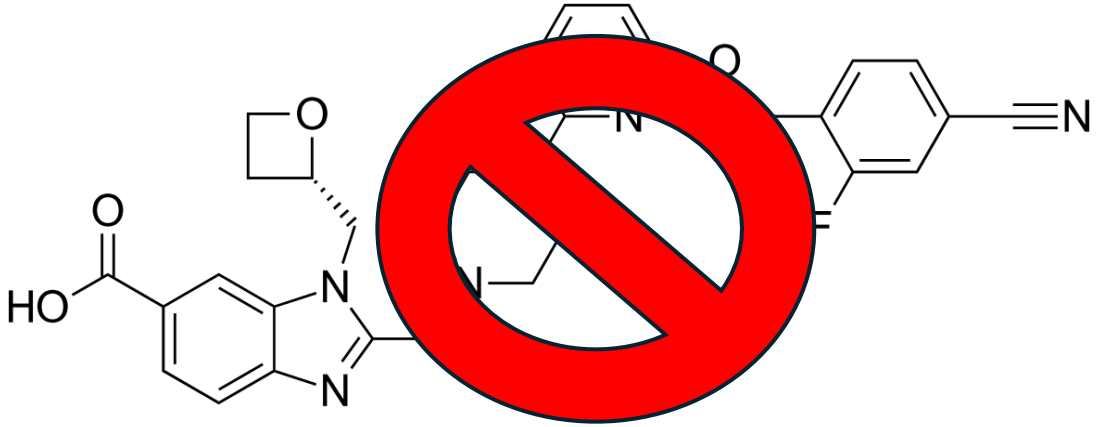


N Engl J Med. 2025 Sep 18;393(11):1077-1087

NON PEPTIDIC GLP-1 AGONISTs

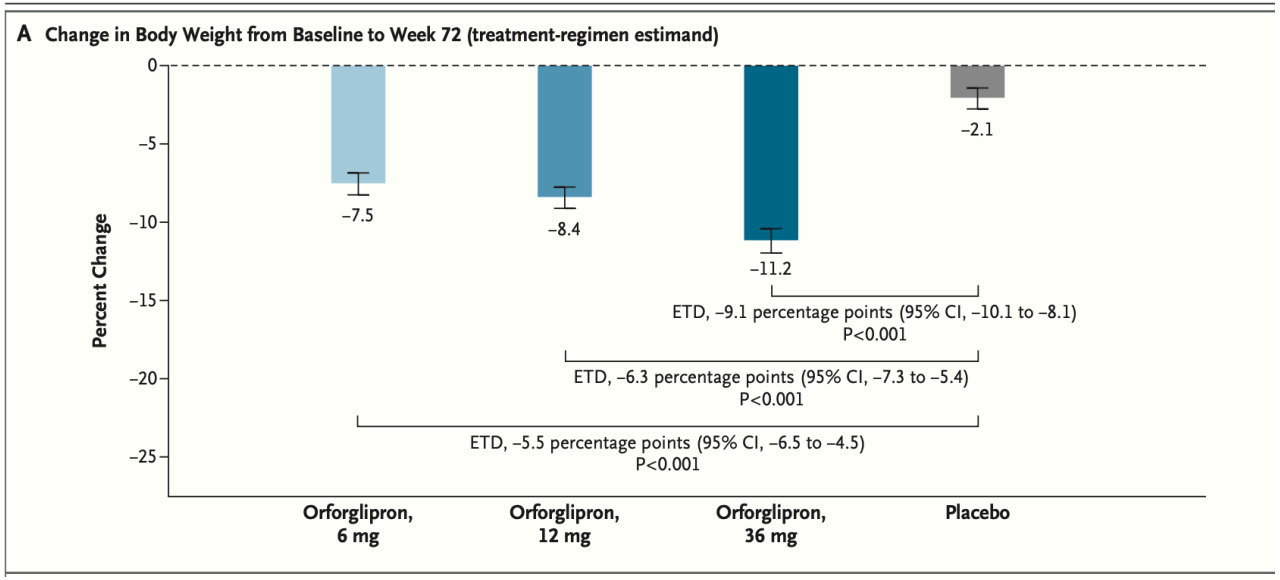


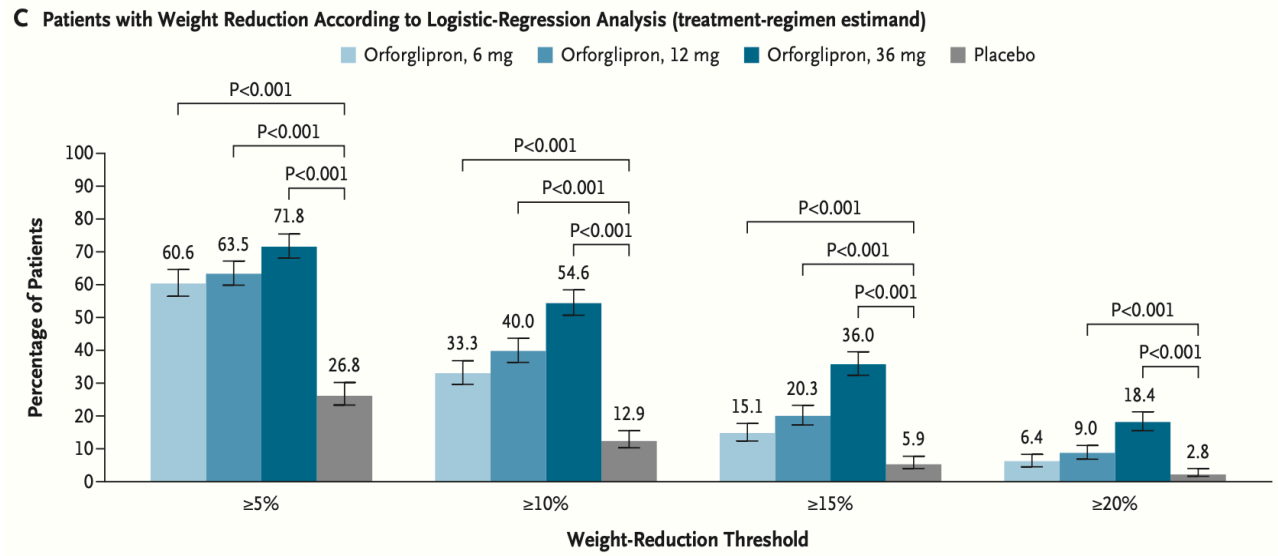
ORFORGLIPRON



DANUGLIPRON

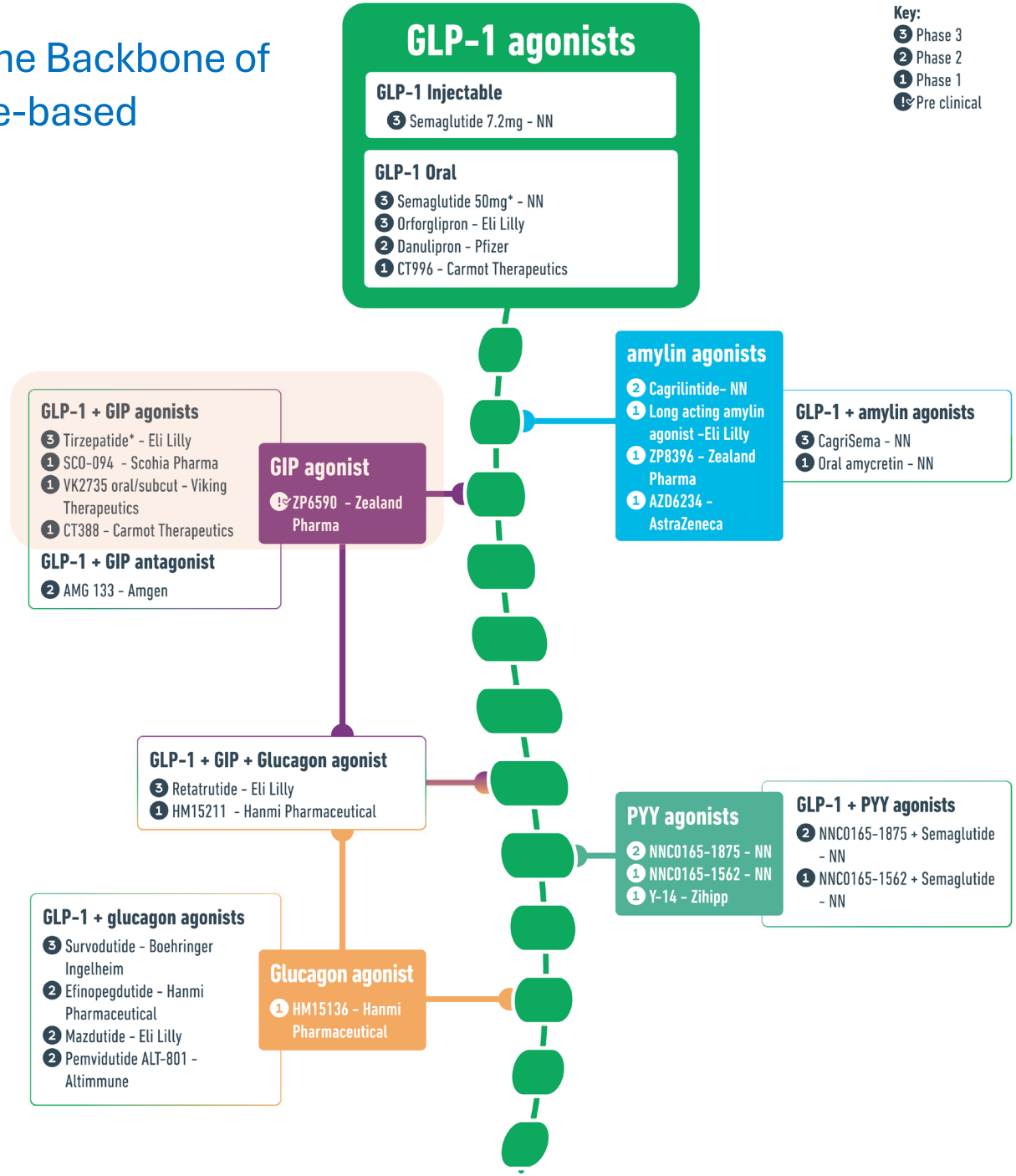
Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment





N Engl J Med. 2025 Sep 16. doi: 10.1056/NEJMoa2511774. Online ahead of print

Glucagon-like peptide-1 as the Backbone of the Pipeline for Gut Hormone-based Obesity Treatments



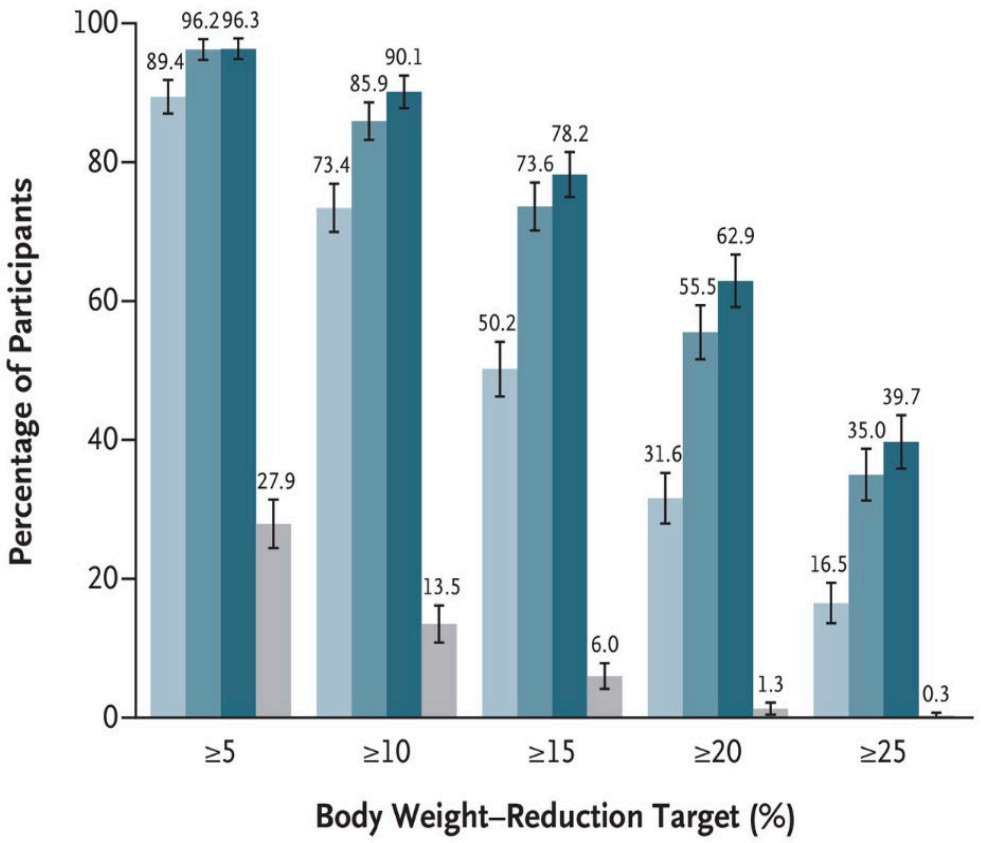
GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: Novo Nordisk, *completed phase 3 trials for obesity.

Melson E, et al, *Int J Obes* 2024

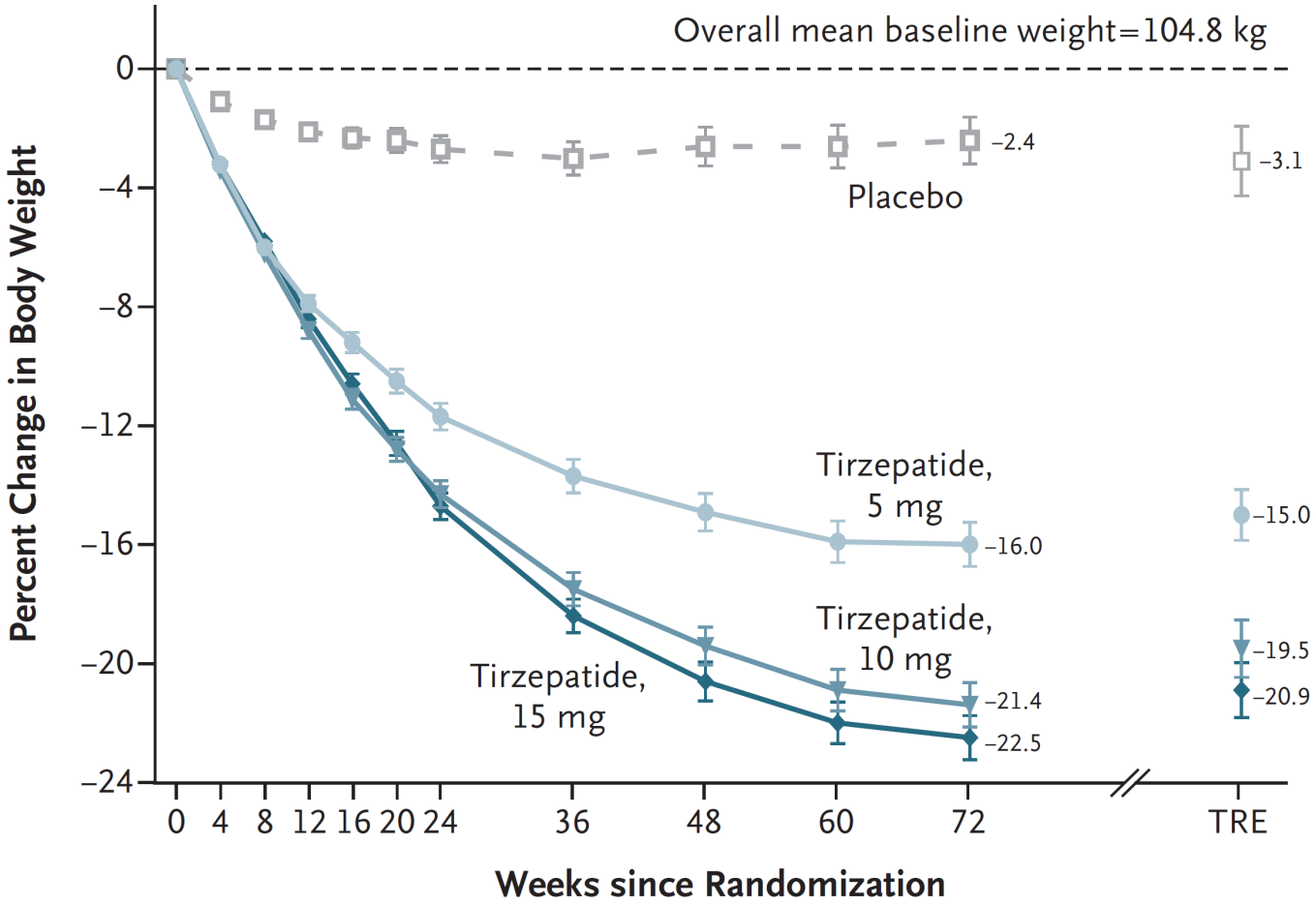
SURMOUNT-1: Effects of Tirzepatide on Body Weight in Obesity

Tirzepatide, 5 mg Tirzepatide, 10 mg Tirzepatide, 15 mg Placebo

Participants Who Met Weight-Reduction Targets (efficacy estimand)



Percent Change in Body Weight by Week (efficacy estimand)



Jastreboff AM, et al, *N Engl J Med* 2022

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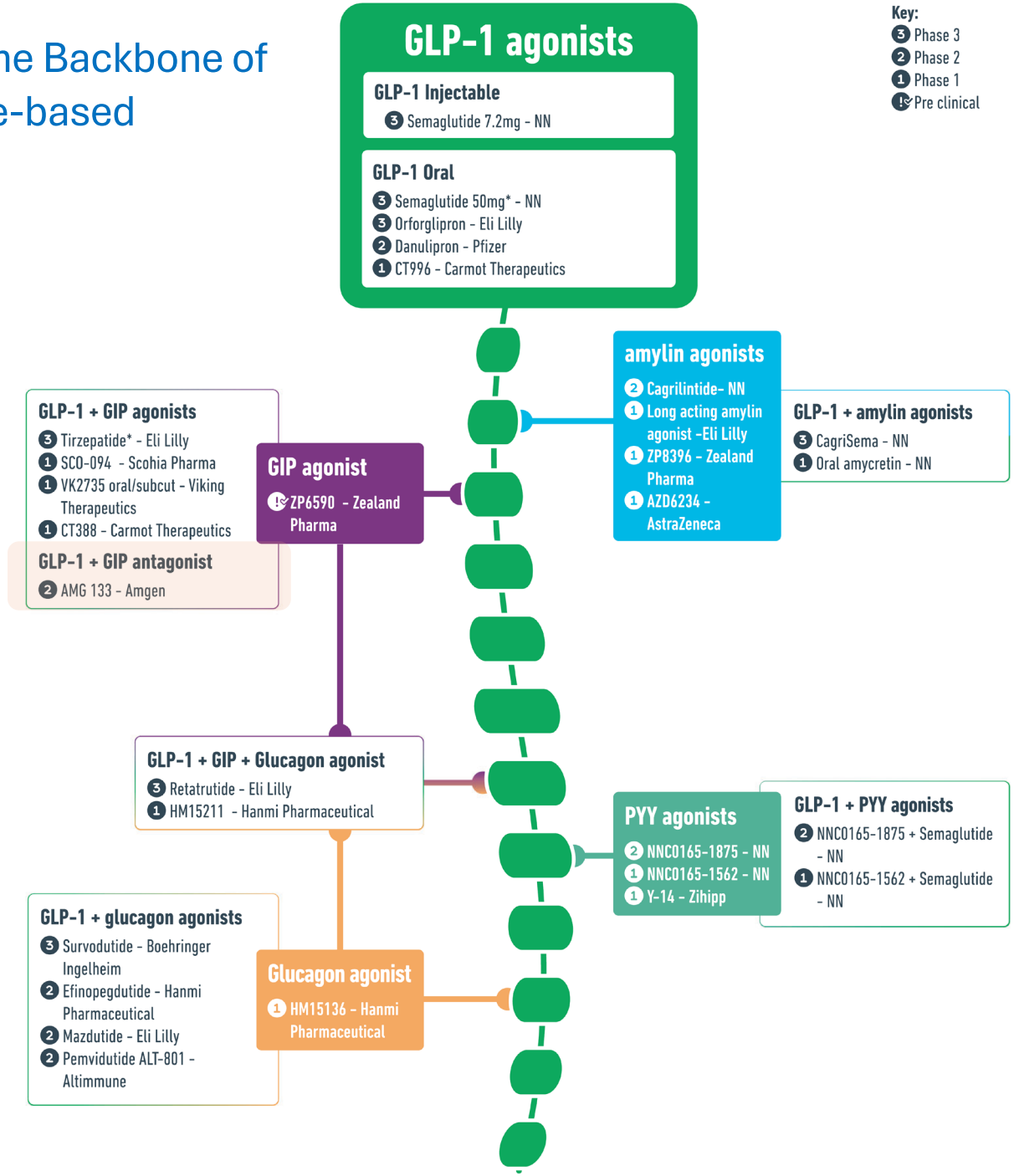

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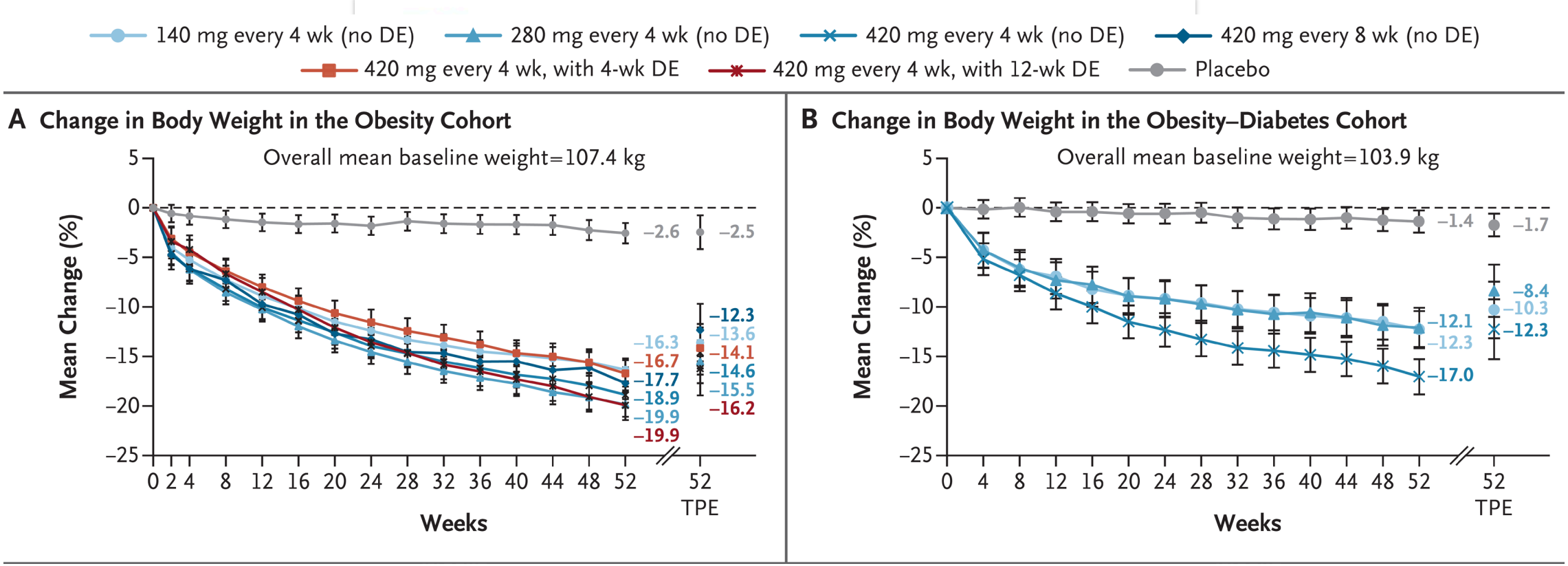
Melson E, et al, *Int J Obes* 2024

Rationale for Antagonizing GIP Receptor

- Genome-wide association studies in humans show that the *GIPR* locus contributes to body weight regulation **(Berndt S I et al, *Nat Genet* 2013; Saxena R et al, *Nat. Genet* 2010; Speliotes EK et al, *Nat Genet* 2010)**
- GIP/GIPR knockout mice are protected from diet-induced obesity (DIO) **(Althage MC et al, *J Biol Chem* 2008; Miyawaki K et al, *Nat Med* 2002)**
- Pharmacological inhibition of GIPR with anti-GIPR antibodies prevented body weight gain in DIO mice and obese cynomolgus monkeys **(Killion EA et al, *Sci Transl Med* 2018)**
- Bispecific molecules that antagonize GIPR and agonize GLP-1R pathways led to decreases in body weight and improvements in metabolic parameters in obese mice and monkeys **(Lu SC et al, *Cell Rep Med* 2021)**

Maridebart Cafraglutide in Obesity and Obesity With Type 2 Diabetes. A Phase 2 Study



Jastreboff AM, et al. *N Engl J Med* 2025

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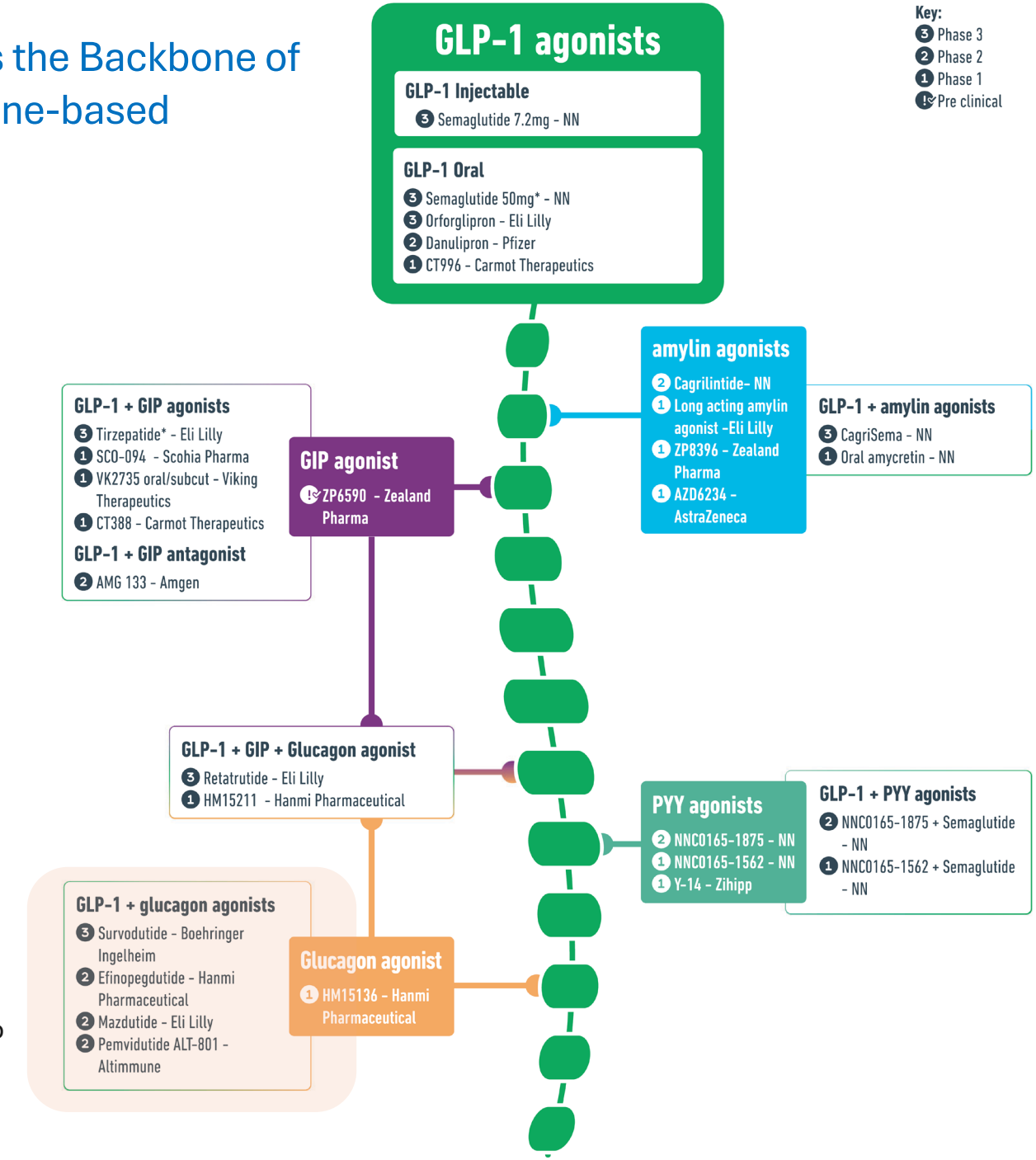

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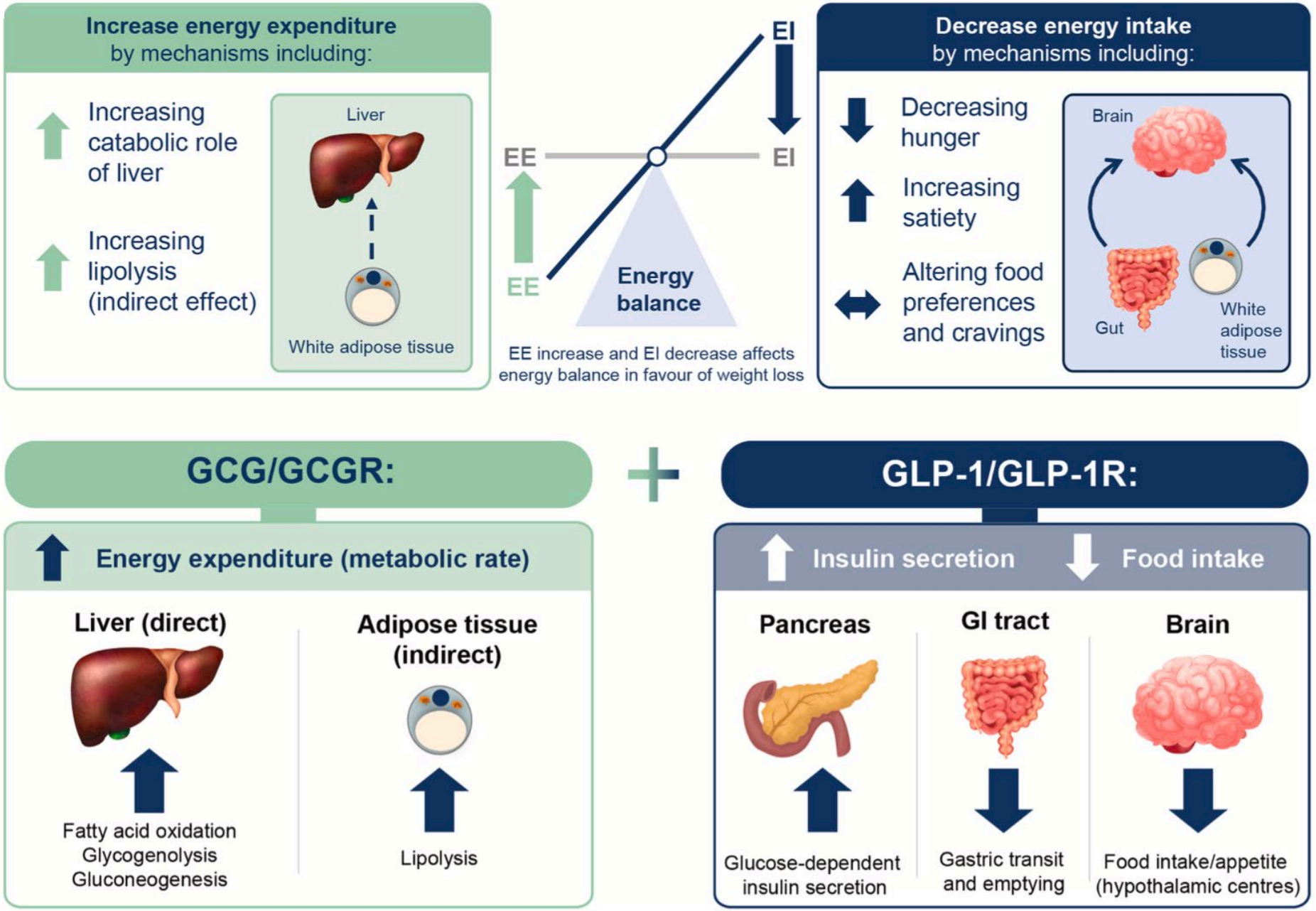
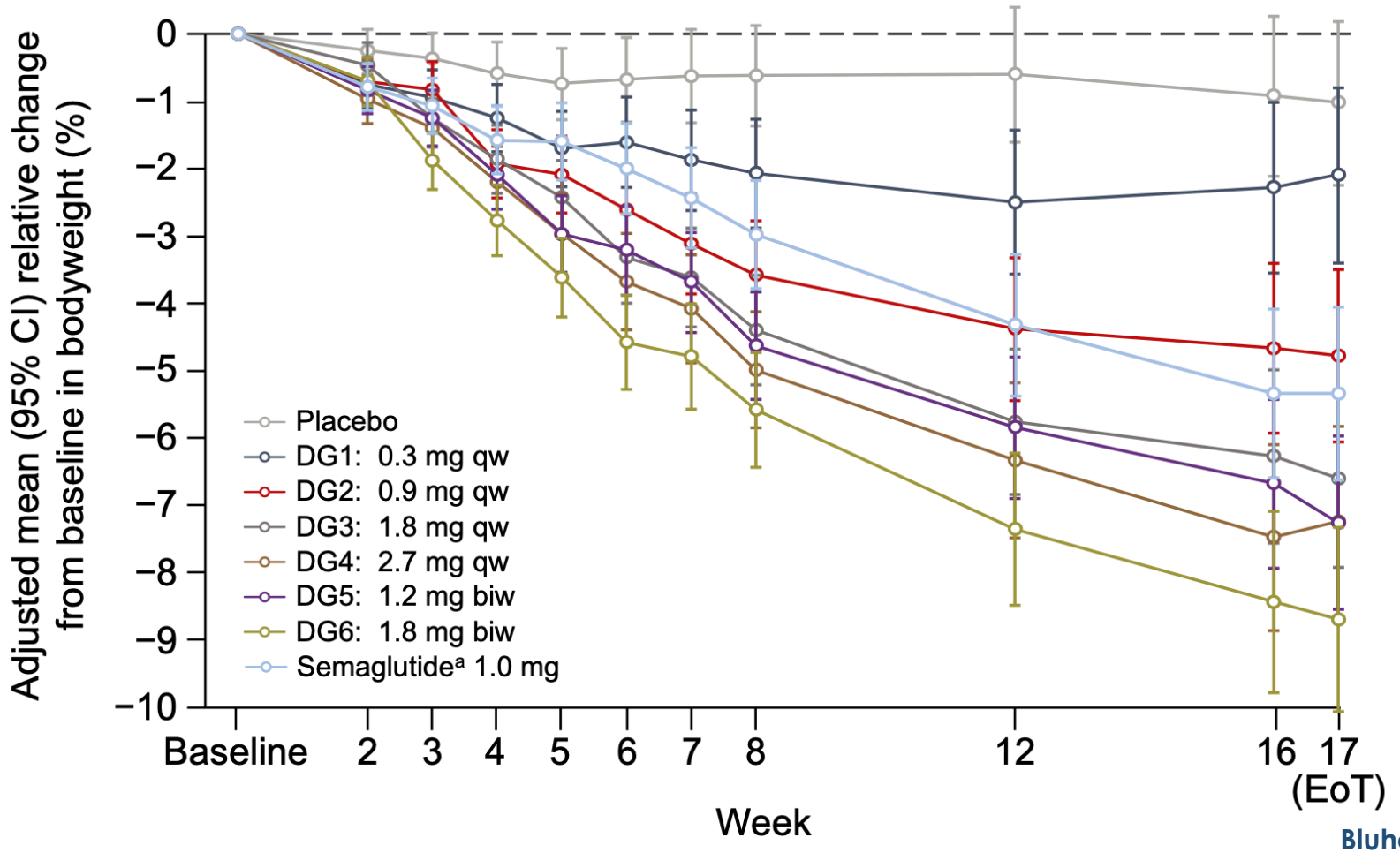
Melson E, et al, *Int J Obes* 2024



Klein T, et al, *Diabetes Res Clin Pract* 2024

A Phase 2 RCT of Survodutide in Adults with Type 2 Diabetes and Overweight or Obesity

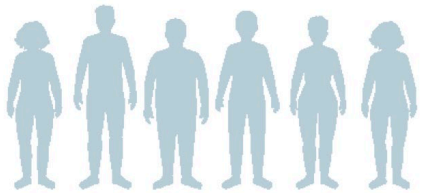
- 413 participants were randomised (DG1, n=50; DG2, n=50; DG3, n=52; DG4, n=50; DG5, n=51; DG6, n=50; semaglutide, n=50; placebo, n=60).
- **Survodutide reduced body weight vs. placebo and semaglutide 1 mg after 16 weeks of treatment.**



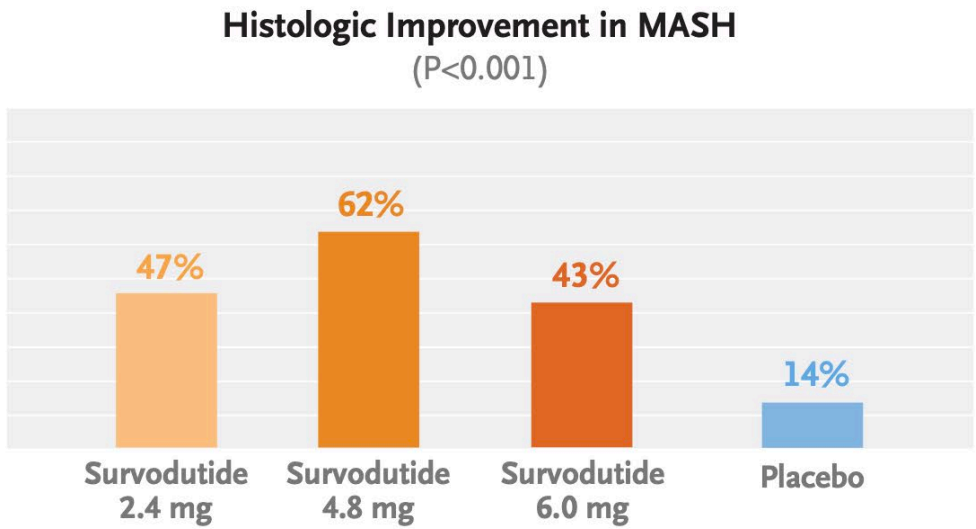
Bluher M, et al, *Diabetologia* 2023

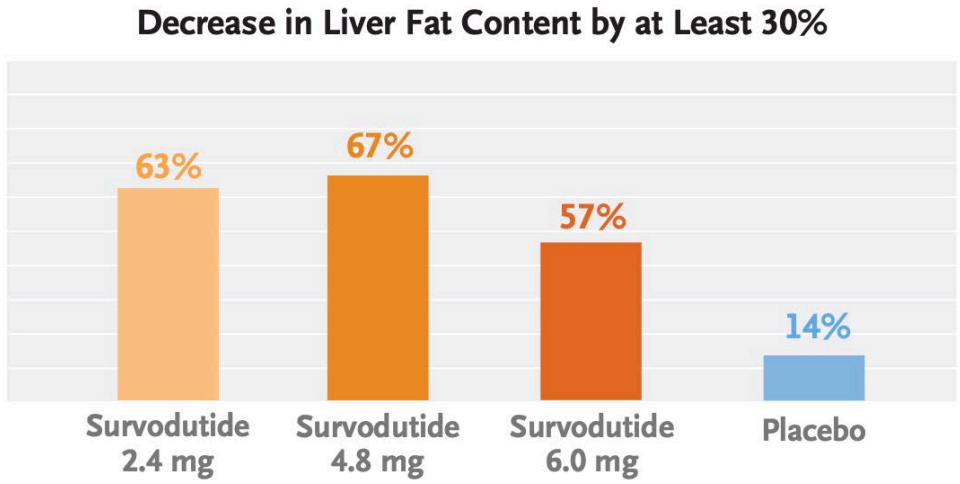
Survodutide Improved MASH without Worsening of Fibrosis at 48 Weeks Compared to Placebo

PARTICIPANTS



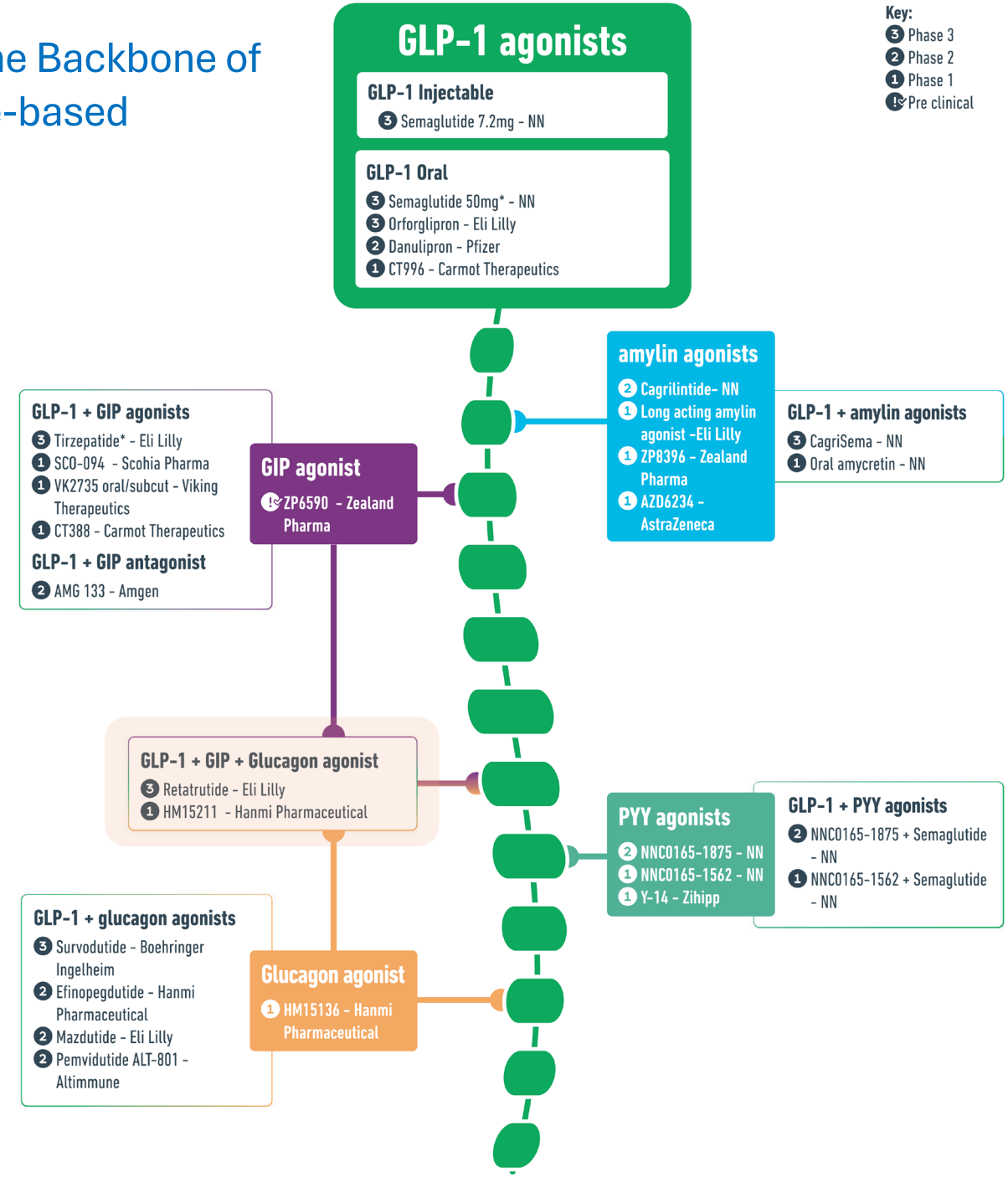
WHO	293 adults
	18–80 years of age
	Women: 53%; Men: 47%
CLINICAL STATUS	Biopsy-confirmed MASH
	Fibrosis stage F1 through F3





Sanyal AJ et al, *N Engl J Med* 2024

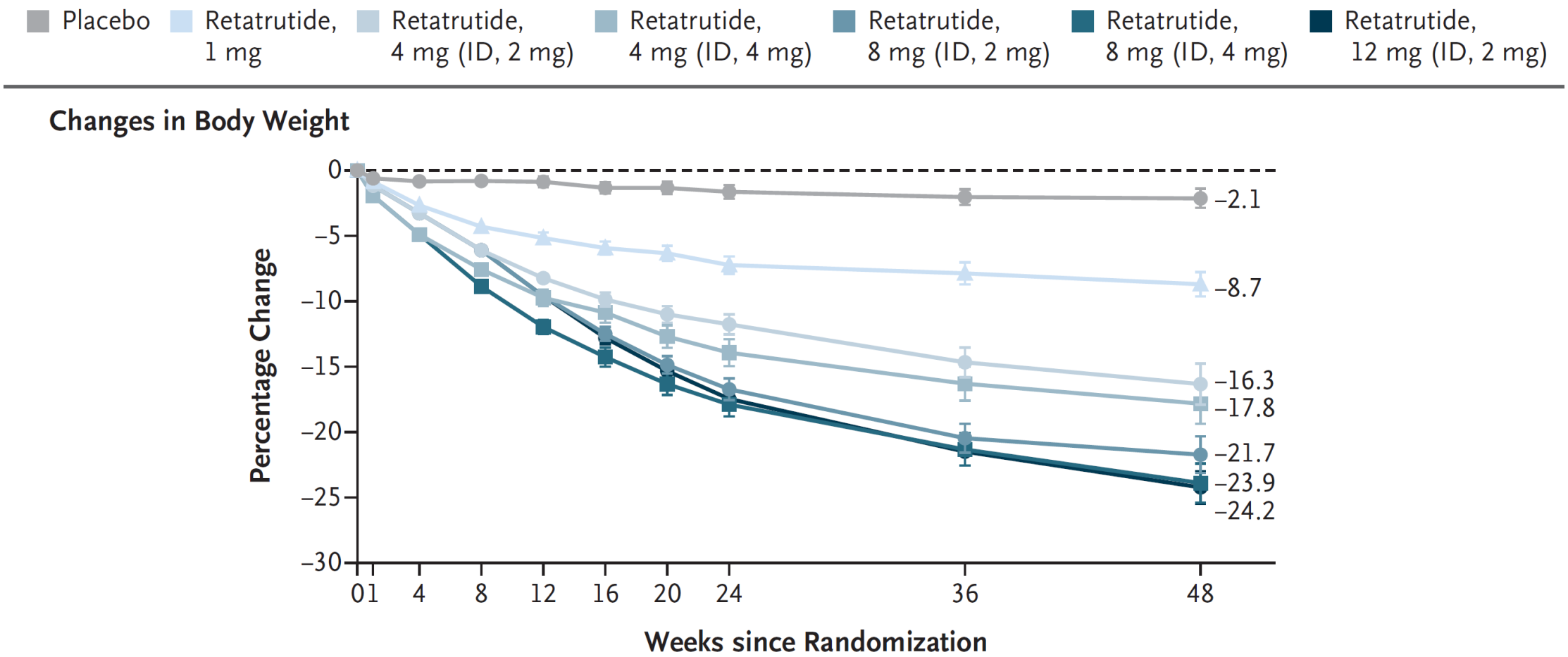
Glucagon-like peptide-1 as the Backbone of the Pipeline for Gut Hormone-based Obesity Treatments



GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: Novo Nordisk, *completed phase 3 trials for obesity.

Melson E, et al, *Int J Obes* 2024

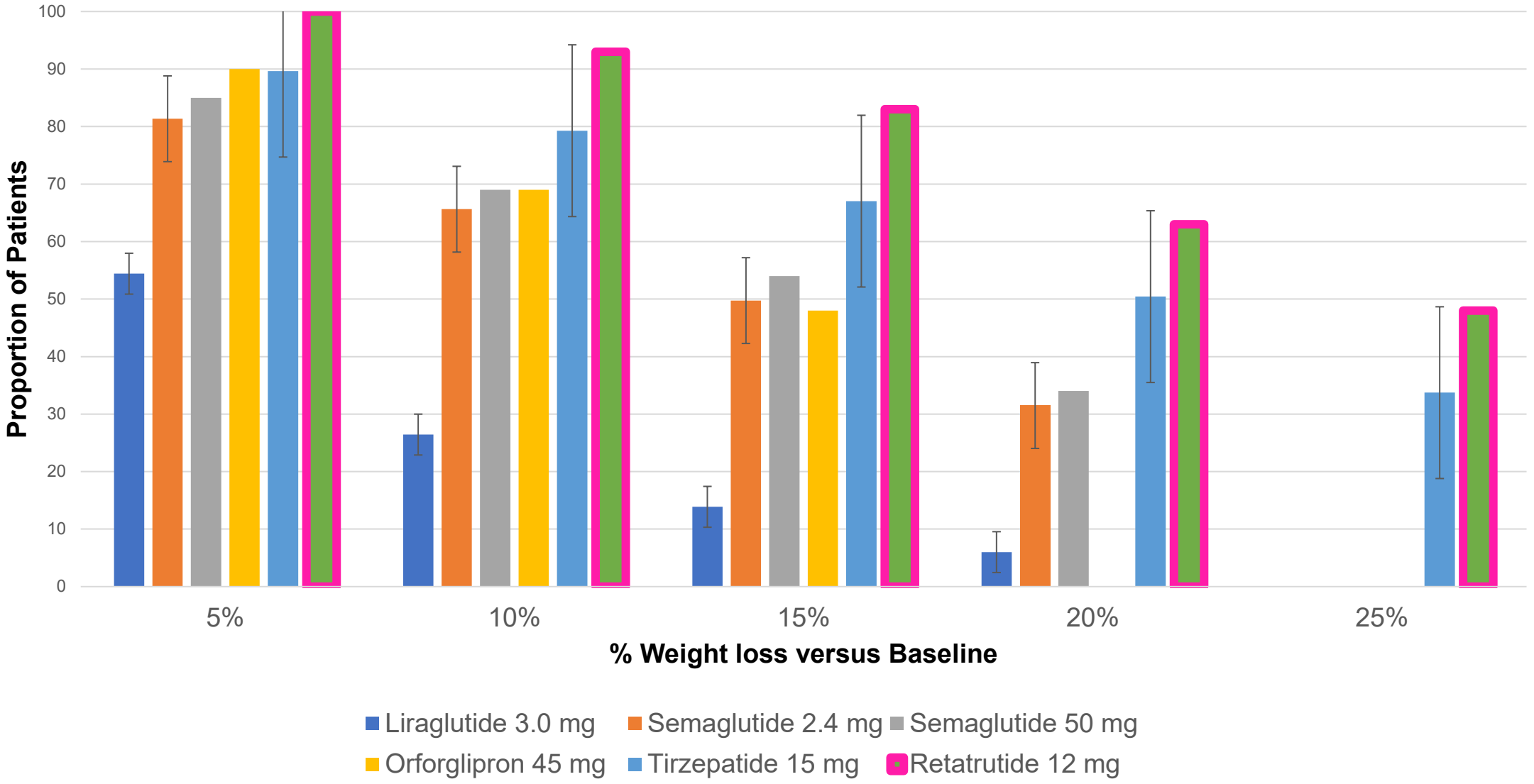
Triple–Hormone-Receptor Agonist Retatrutide for Obesity
A Phase 2 Trial



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. 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.

Jastreboff AM, et al, *N Engl J Med* 2023

Participants with 5-25% Body Weight Loss Across RCTs with Incretin-based Anti-obesity Medications -



Adapted from **Caruso *et al. NPJ Metab Health Dis* 2024**

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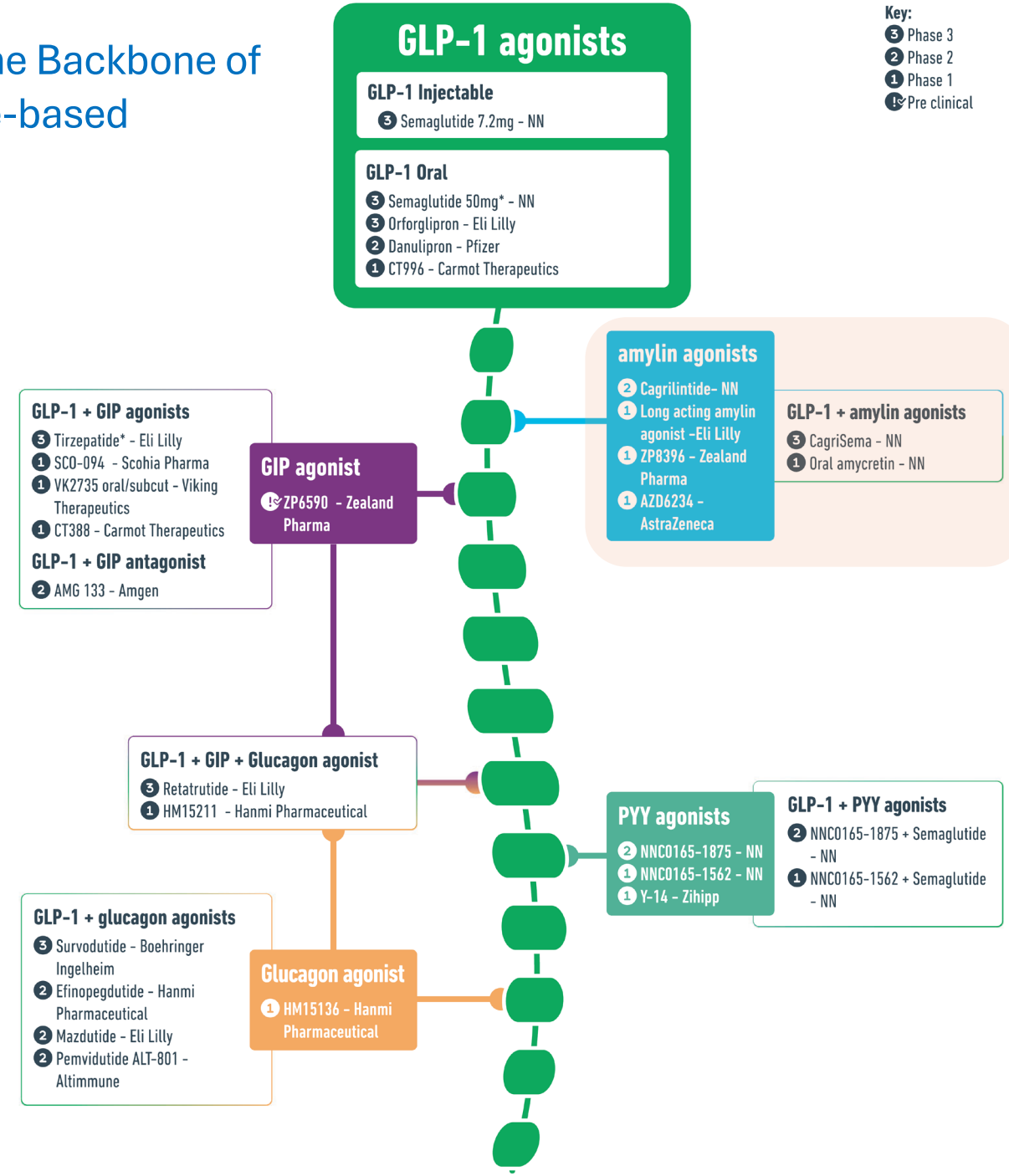

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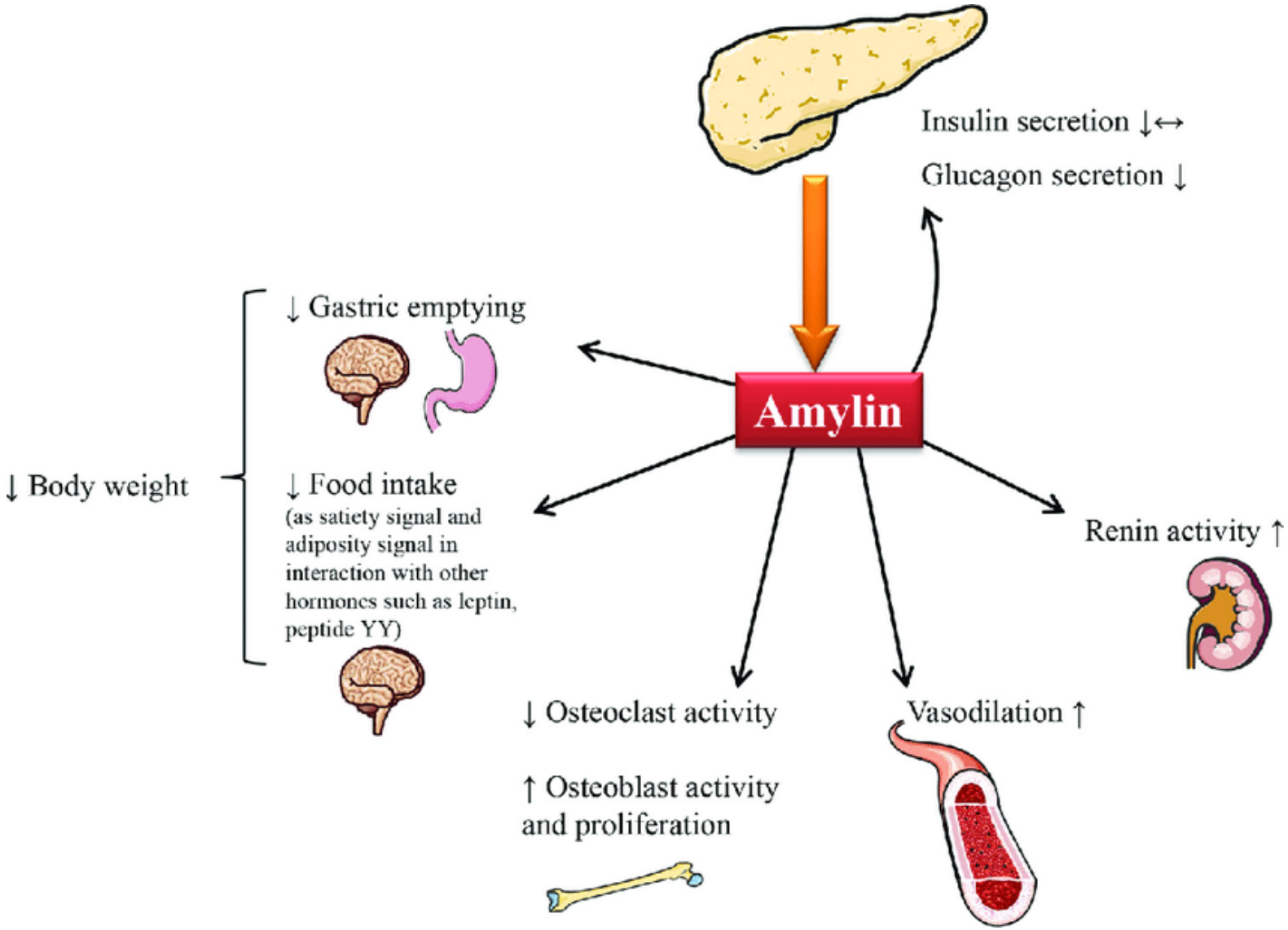
Melson E, et al, *Int J Obes* 2024

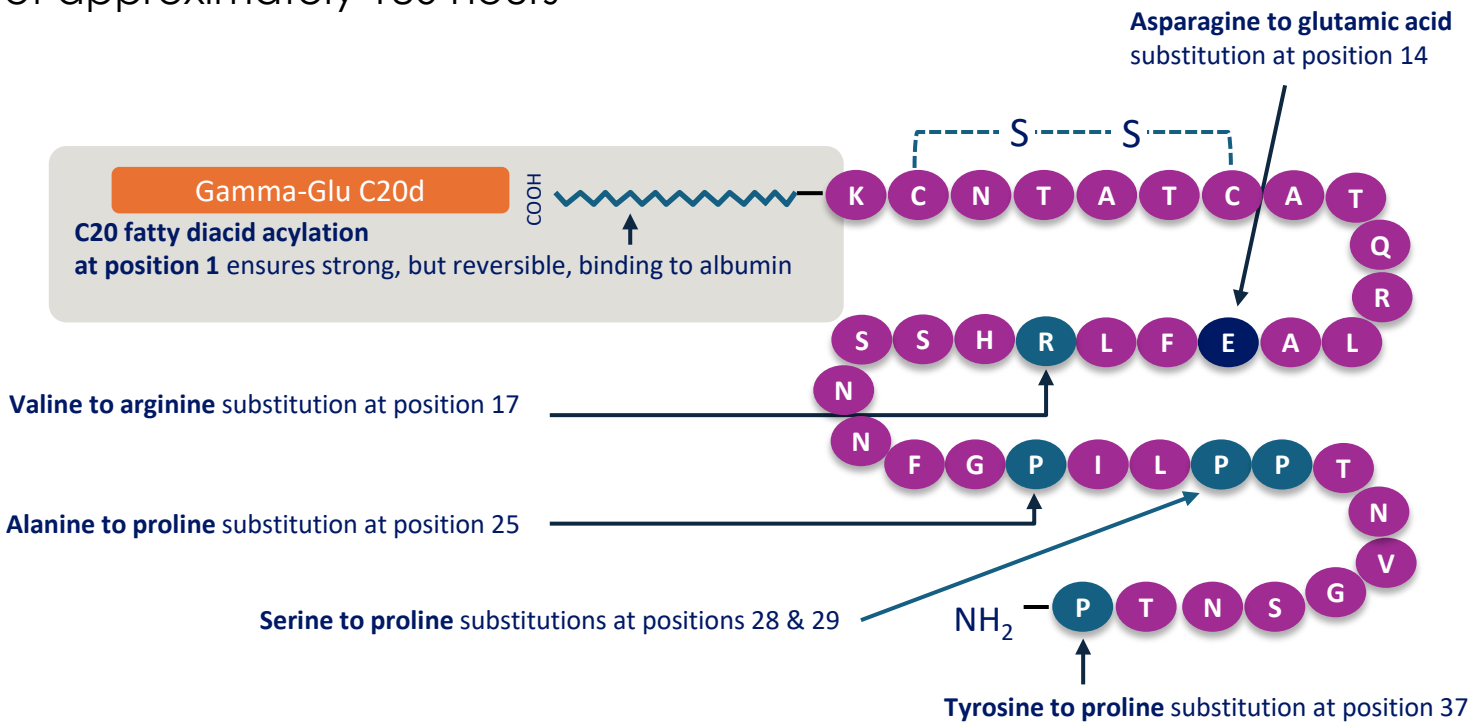
Amylin multiple effects

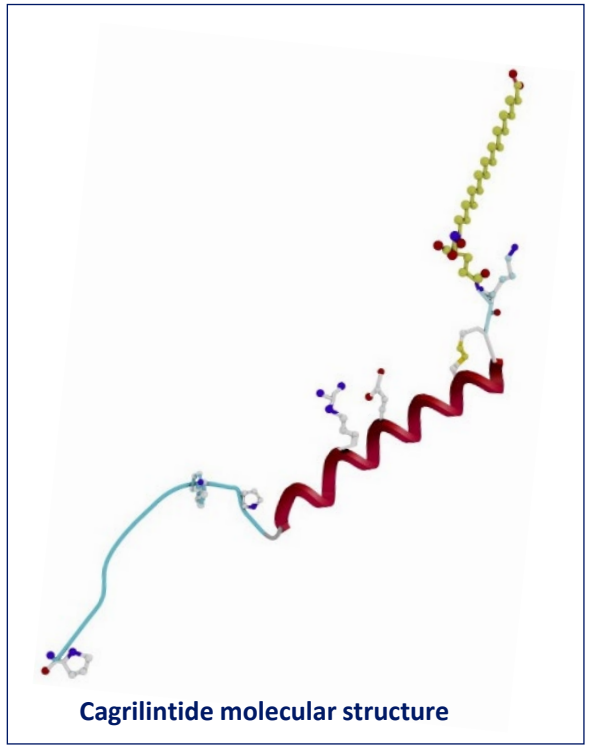


Press M, Mech Ageing Dev. 2019 Jan;177:46-54.

Cagrilintide is a Human Amylin Analogue

- 84% homology to native human amylin
- The purpose of the amino acid substitutions and acylation were primarily to remove the fibrillating properties of human amylin and ensure stability
- $t_{½}$ of approximately 180 hours

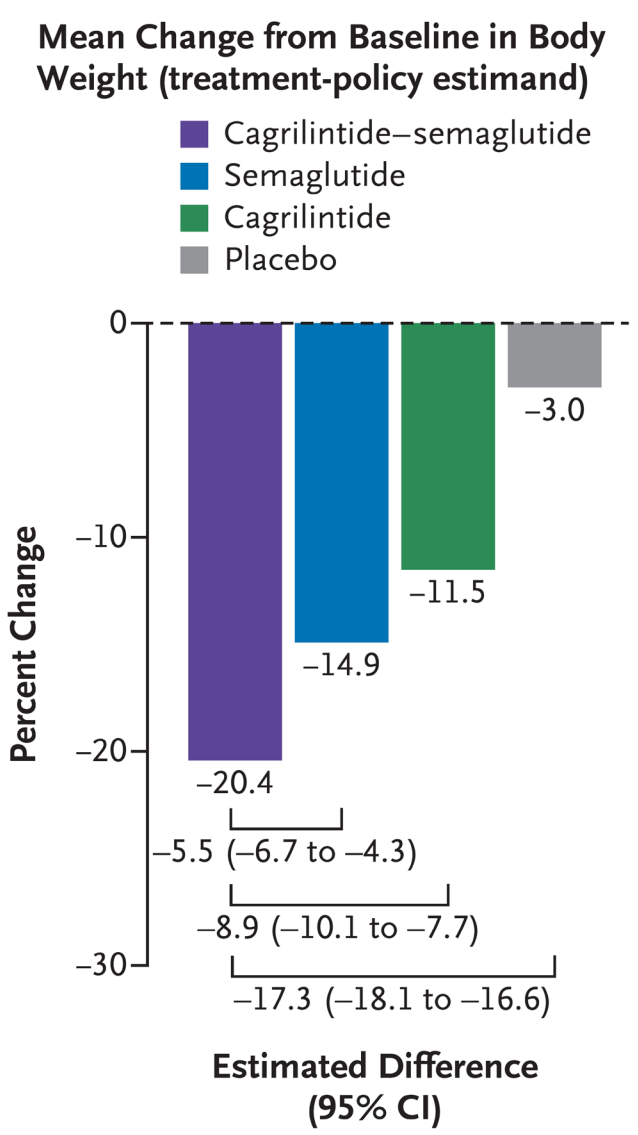


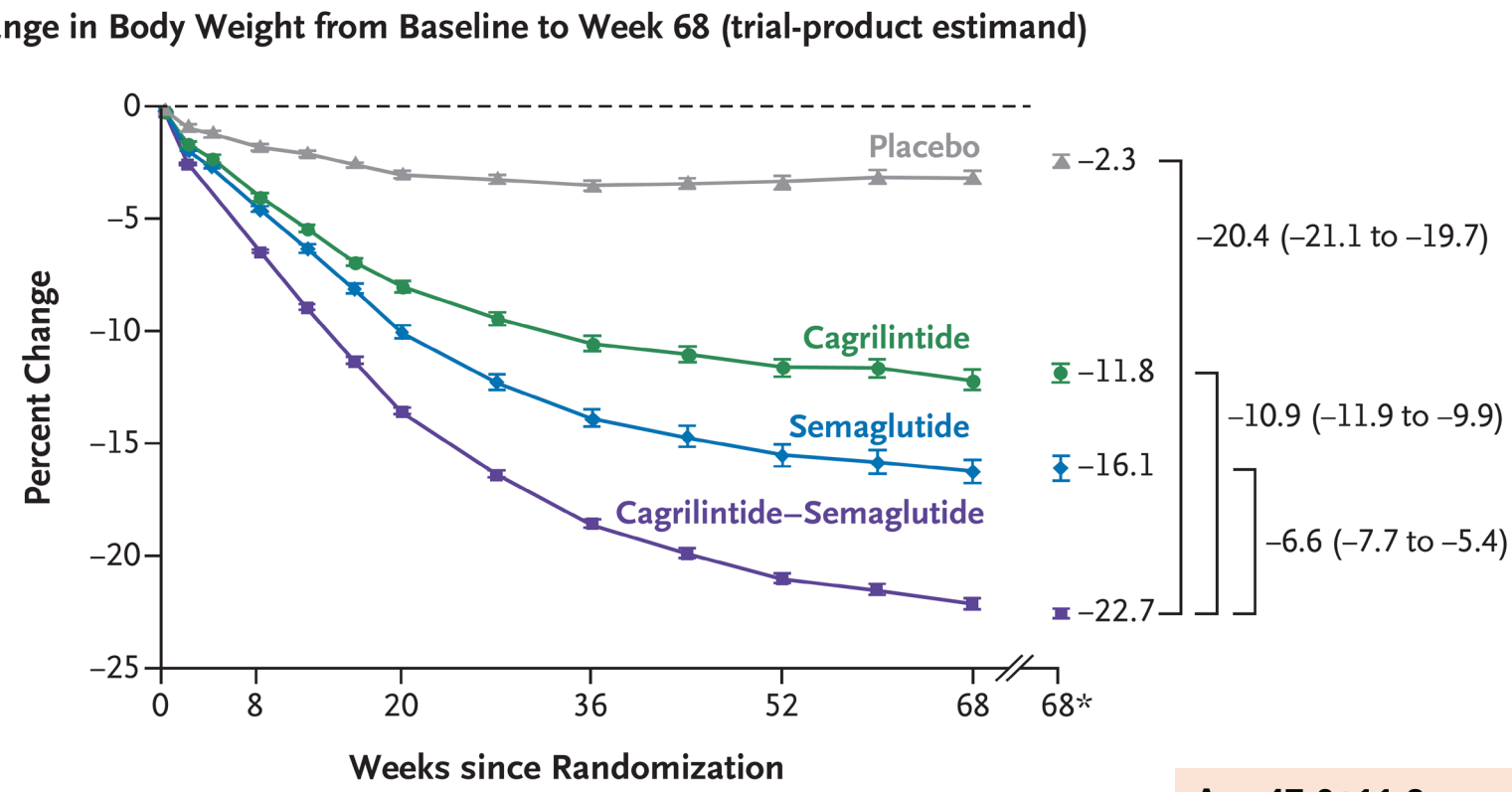


Glu, glutamic acid; NH_2, amino radical.

Kruse T, et al. *J Med Chem.* 2021;64(15):11183–11194.

REDEFINE-1 - Change in Body Weight with Cagrilintide–Semaglutide as Compared with Semaglutide, Cagrilintide, and Placebo





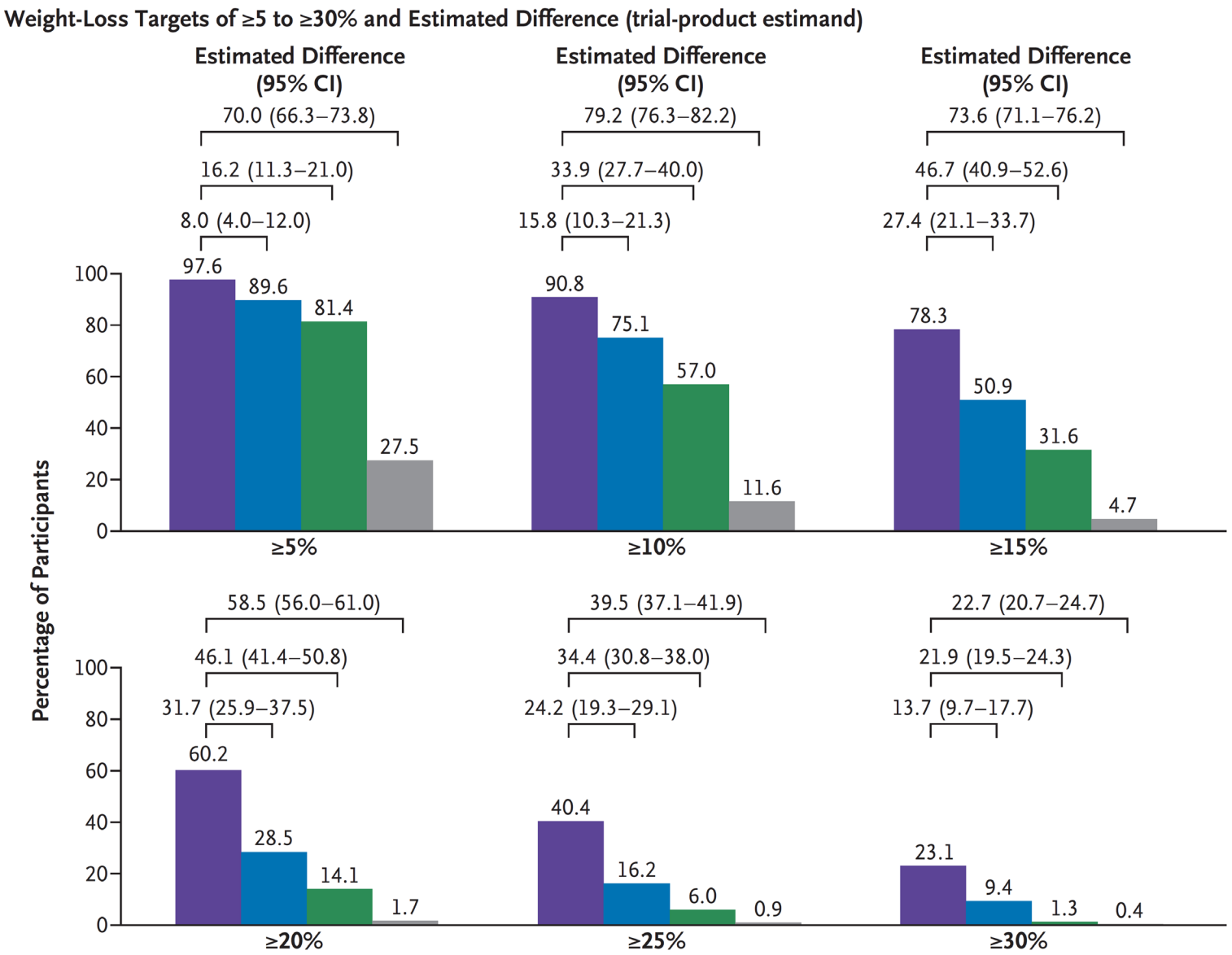
No. at Risk

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

Age 47.0±11.8 yrs
Female 67.6%
BW 106.9±23.1 kg
BMI 37.9±6.7 kg/m²
HbA1c 5.5±0.4%

Garvey WT et al. *N Engl J Med* 2025

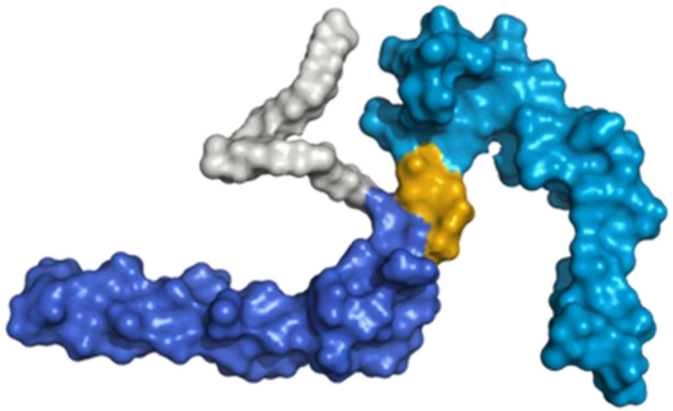
REDEFINE-1 – Weight Loss Targets with Cagrilintide–Semaglutide as Compared with Semaglutide, Cagrilintide, and Placebo



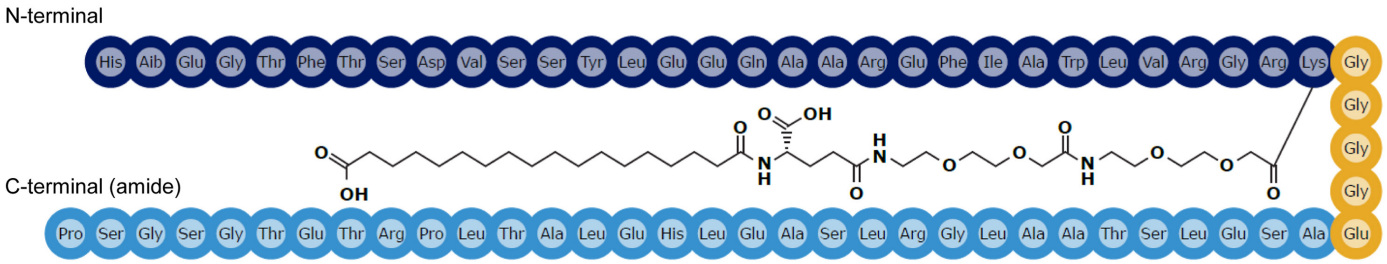
Age 47.0±11.8 yrs
Female 67.6%
BW 106.9±23.1 kg
BMI 37.9±6.7 kg/m²
HbA1c 5.5±0.4%

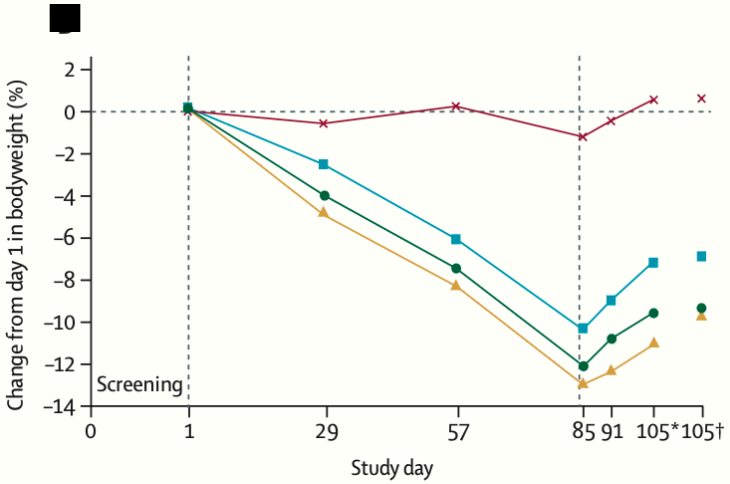
Garvey WT et al. *N Engl J Med* 2025

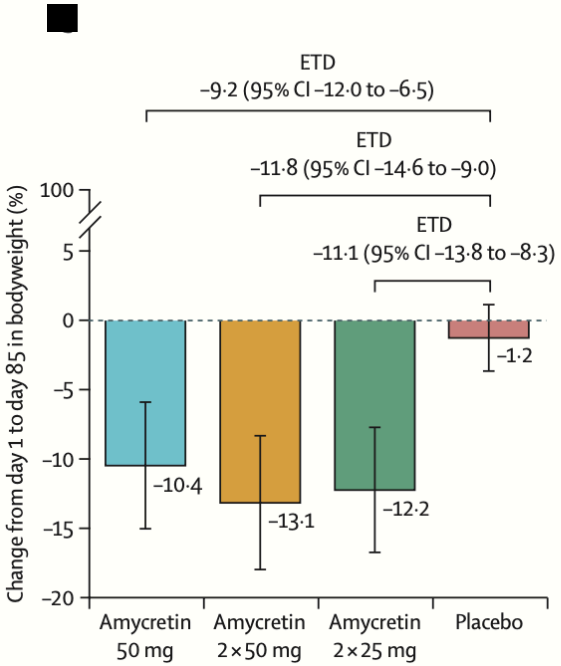
Amycretin is a long-acting, unimolecular amylin receptor and GLP-1 receptor agonist



Amylin receptor agonist
GLP-1 receptor agonist
Linker region
Acylation





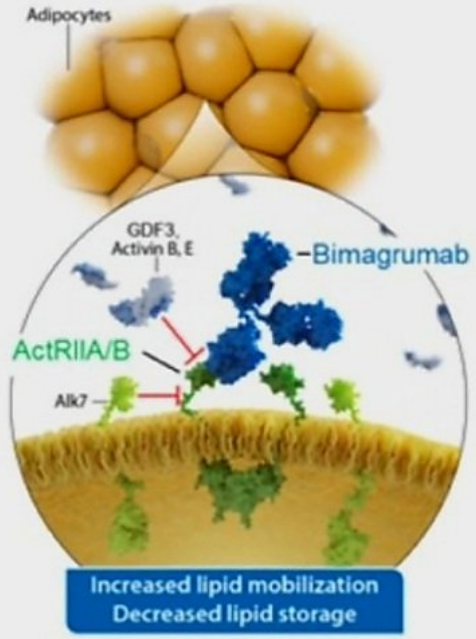


Kuhre, R.E. et al. eBioMedicine, Volume 118, 105862

Gasiorek A. et al., Lancet. 2025 Jul 12;406(10499):135-148.

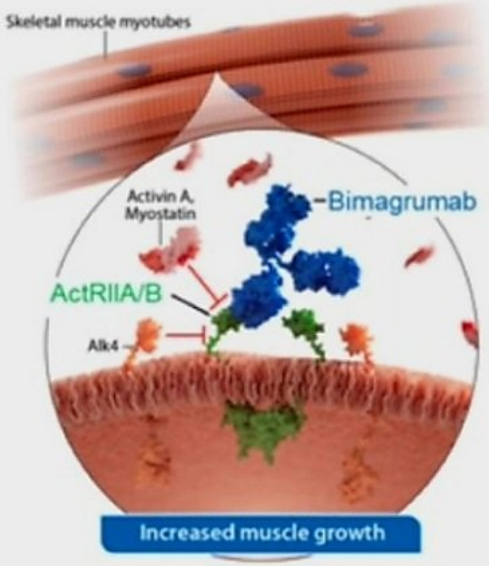
Bimagrumab (also known as BYM338) Is a Human Monoclonal Antibody That Targets Activin Type II Receptors (ACVR2B)

Adipose



Blocks activin E and GDF3 signaling with the goal of decreasing fat mass

Muscle



Blocks activin A and myostatin signaling with the goal of increasing muscle mass

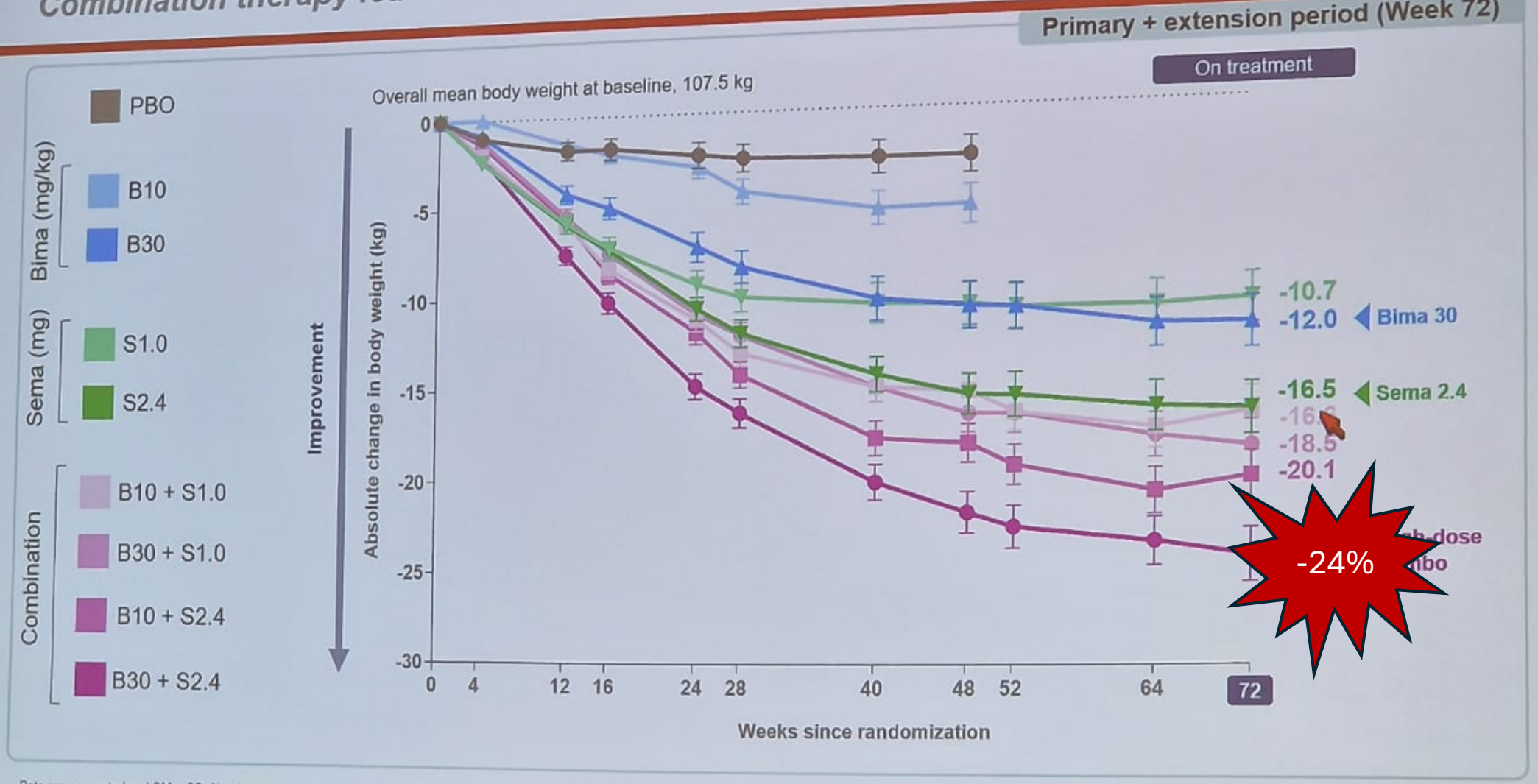
Bimagrumab

- Monoclonal antibody that blocks activin type II receptors
- BELIEVE Phase 2B study evaluated IV bimagrumab dosed quarterly ± semaglutide
- Additional Phase 2 trials evaluating SC bimagrumab dosed weekly ± tirzepatide

1. Heymsfield SB et al, *JAMA Netw Open*. 2021;4(1):e2033457. Published 2021 Jan 4. doi:10.1001/jamanetworkopen.2020.33457
2. Petricoul O et al. *Clin Pharmacokinet*. 2023;62(1):141-155. doi:10.1007/s40262-022-01189-0

Body Weight (kg): Absolute Change from Baseline (Week 72)

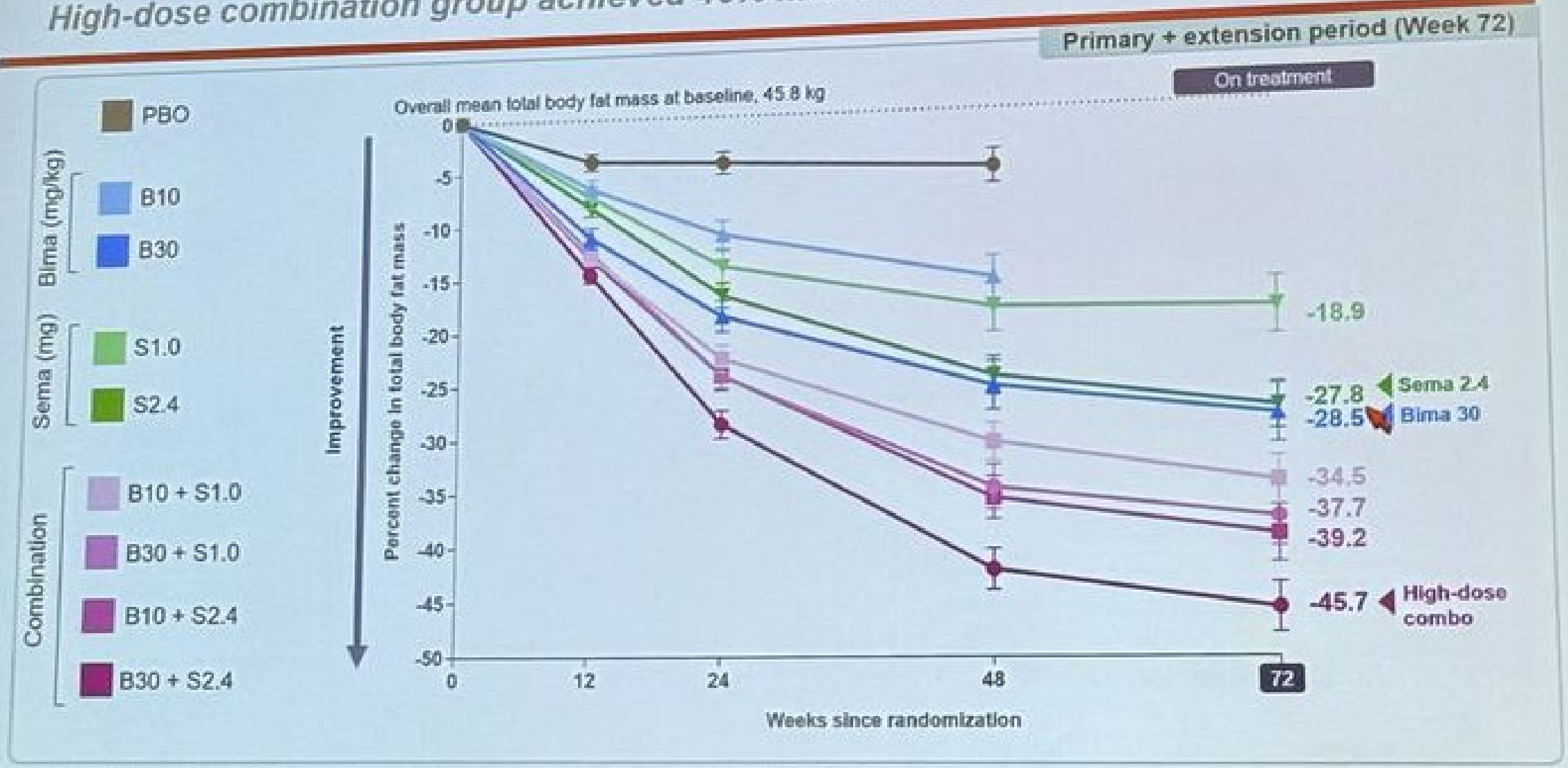
Combination therapy led to similar or greater weight reduction than semaglutide 2.4 mg



Data are presented as LSM ± SE. Absolute changes are based on mixed model for repeated measures for the efficacy estimand.
Abbreviations: Bima, bimagrumab; combo, combination; LSM, least-squares mean; PBO, placebo; SE, standard error; sema, semaglutide.

Total Body Fat Mass: % Change from Baseline (DXA, Week 72)

High-dose combination group achieved 46% mean decrease in total body fat mass

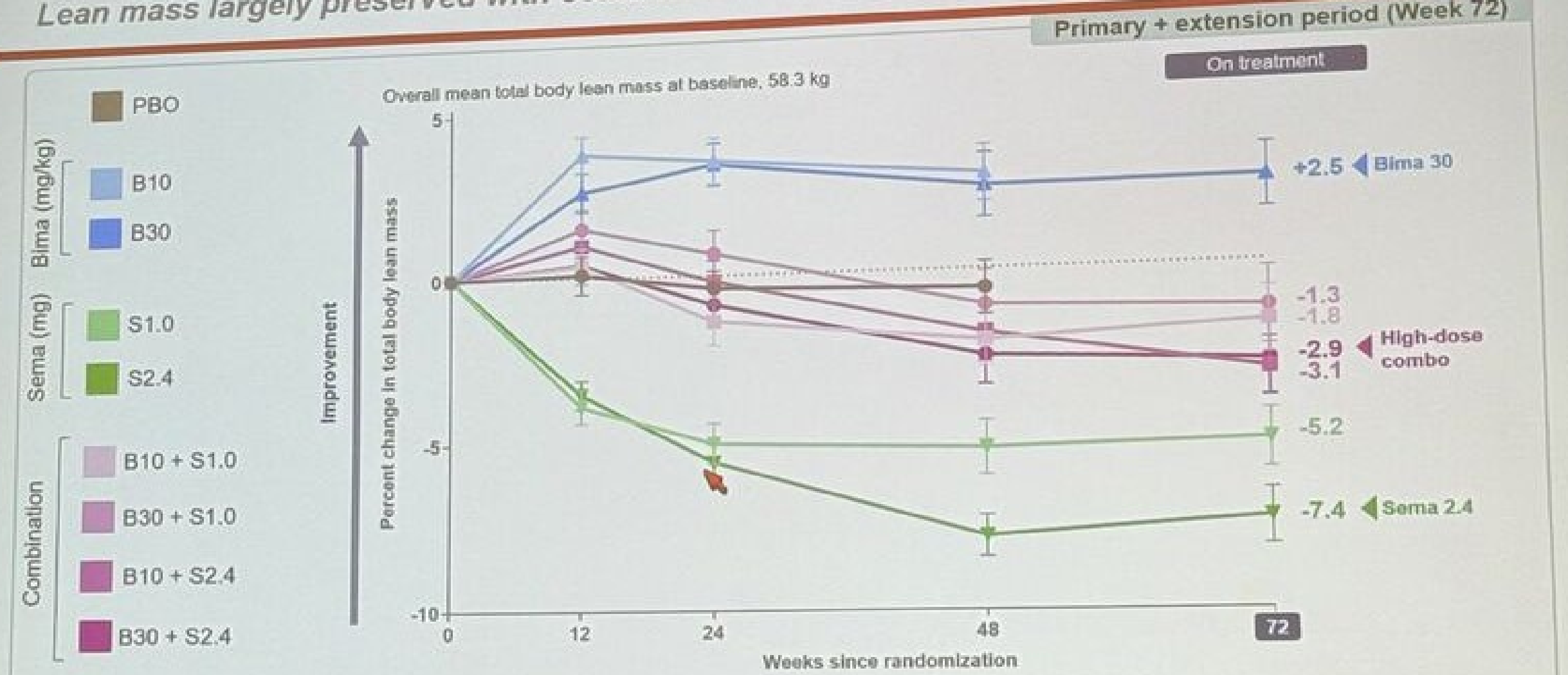


Data are presented as LSM ± SE. Percent changes are based on a mixed model for repeated measures model for the efficacy estimand.

Abbreviations: Bima, bimagrumab; combo, combination; DXA, dual-energy X-ray absorptiometry; LSM, least-squares mean; PBO, placebo; SE, standard error; sema, semaglutide.

Total Body Lean Mass: % Change from Baseline (DXA, Week 72)

Lean mass largely preserved with combination therapy



Appendicular lean mass (Week 72): The LSM percent changes were +2.3% (bimagrumab 30 mg/kg), −9.2% (semaglutide 2.4 mg), and −2.6% (high-dose combination).

Data are presented as LSM ± SE. Percent changes are based on a mixed model for repeated measures model for the efficacy estimand.

Abbreviations: Bima, bimagrumab; combo, combination; DXA, dual-energy X-ray absorptiometry; LSM, least-squares mean; PBO, placebo; SE, standard error; sema, semaglutide.

Metabolic/Comorbidity Reshaping with Multi-Agonist Therapy in Obesity

GLP-1 GIP Glucagon Amylin Activin/Myostatin

Reduced Food Intake
↓
Caloric restriction

Improvement of Insulin Secretion & Insulin sensitivity
↓
Amelioration of Hyperglycemia

Extensive Weight Loss
↓
Amelioration of Mechanical Burden (↓ OSA/Arthritis/HF)

Stimulation of Thermogenesis
↓
↑ Energy Expenditure

Augmentation of Lean Mass
↓
Prevention/Correction of Sarcopenia

Stimulation of Lipolysis
↓
↓ MASLD/MASH

Targeting Inflammation & Atherogenesis/Other
↓
Organ Damage Improvement (↓ CVD/CKD/HF)

CKD, chronic kidney disease; CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HF, heart failure; MASLD/MASH, Metabolic-disease-associated steatotic livel disease/steto-hepatitis; OSA, obstructive sleep apnea

Open questions with Multi-Agonist Therapy in Obesity

GLP-1 GIP Glucagon Amylin Activin/Myostatin

More durable weight loss (following cessation of therapy)?

less frequent administration?

Reduce Nausea/Emesis?

↓

Improved Tolerability
Increased Efficacy

Safety in special populations such as older individuals, in young children and adolescents, and during pregnancy.

cessation of therapy may be associated with a continuing improvements in health?

↓

legacy-like effect