Obesity Management : The notions behind the Numbers

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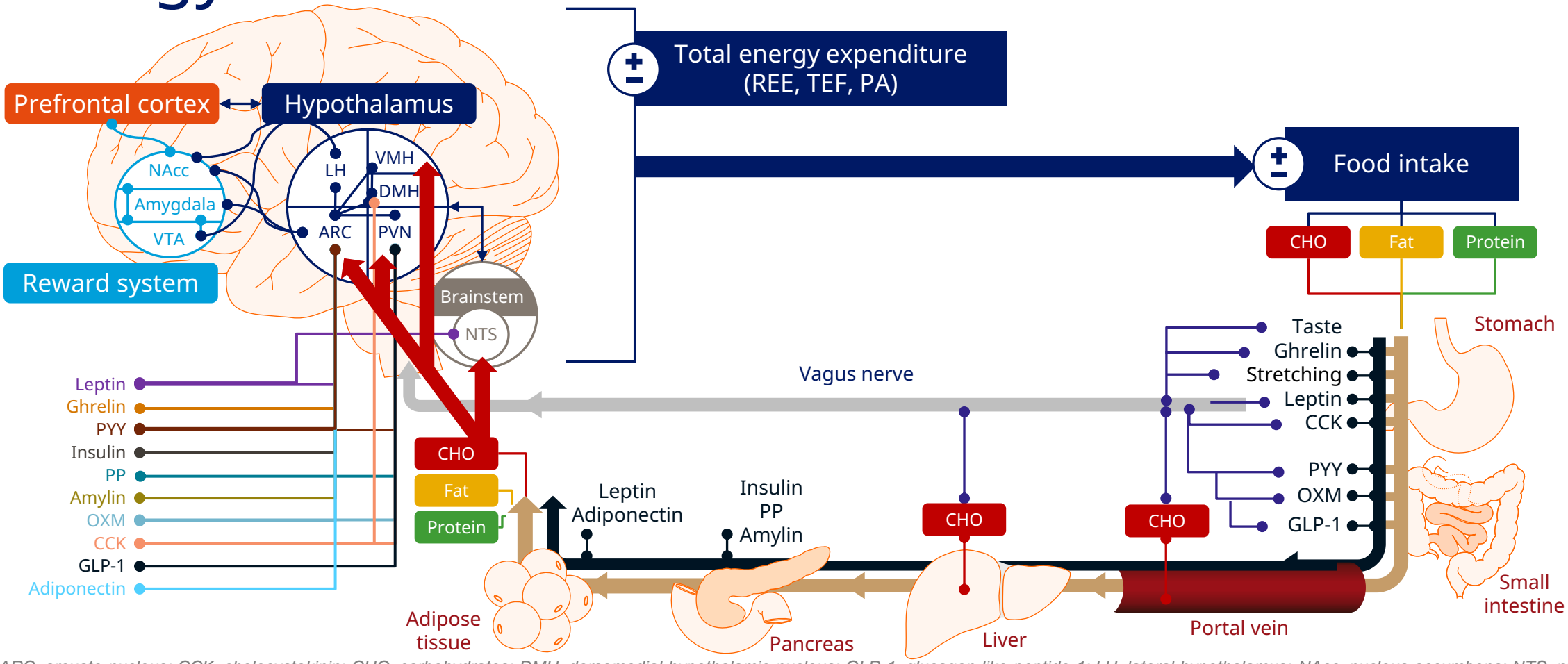
This lecture is sponsored by the Medical Department of Novo Nordisk, Israel

Semaglutide 2.4 mg for weight management was filed for registration in Israel MoH

Semaglutide is not yet approved for weight management in Israel

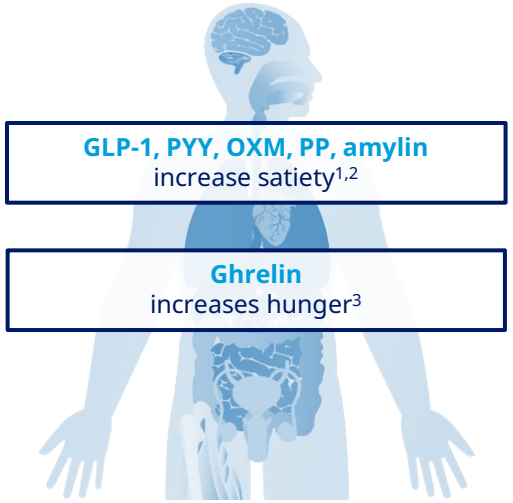
The neuro-hormonal actors involved in energy homeostasis



ARC, arcuate nucleus; CCK, cholecystokinin; CHO, carbohydrates; DMH, dorsomedial hypothalamic nucleus; GLP-1, glucagon-like peptide 1; LH, lateral hypothalamus; NAcc, nucleus accumbens; NTS, nucleus tractus solitarius; OXM, oxyntomodulin; PA, physical activity; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PYY, peptide YY; REE, resting energy expenditure; TEF, thermic effect of food; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

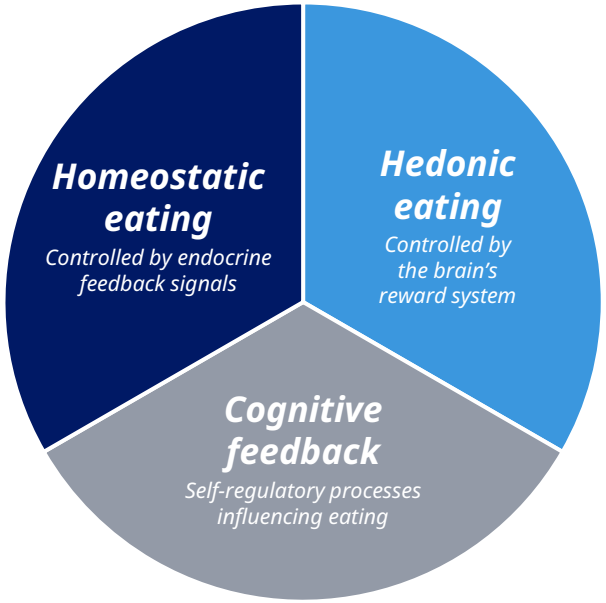
Theilade S et al. Diabetes Obes Metab 2021;Suppl 1:17–35.

The role of the brain in controlling appetite



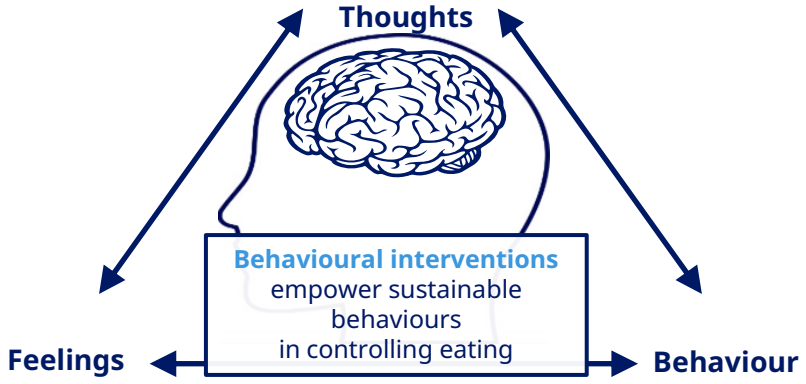
GLP-1, PYY, OXM, PP, amylin
increase satiety[1,2]

Ghrelin
increases hunger[3]



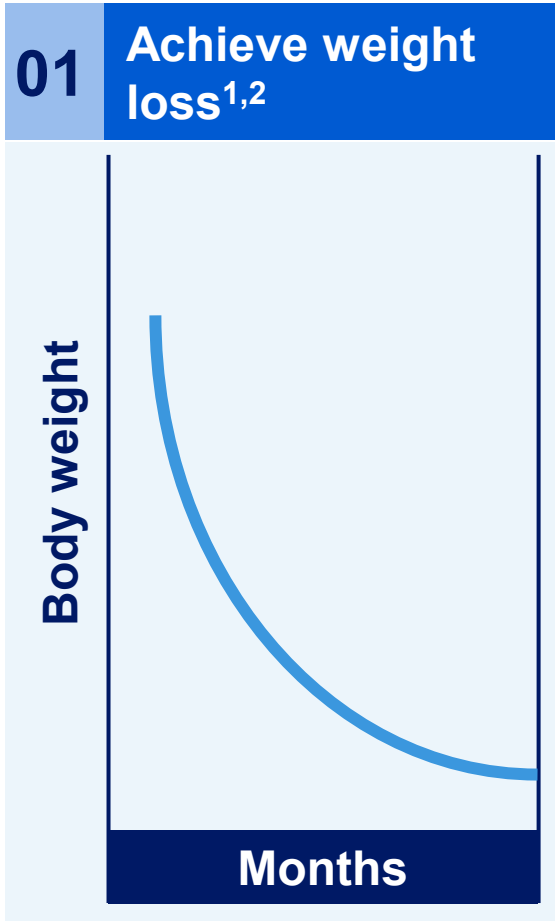
Dopamine controls WANTING,
the motivation/drive to eat

Opioid and cannabinoid receptors control
LIKING, the pleasure associated with food



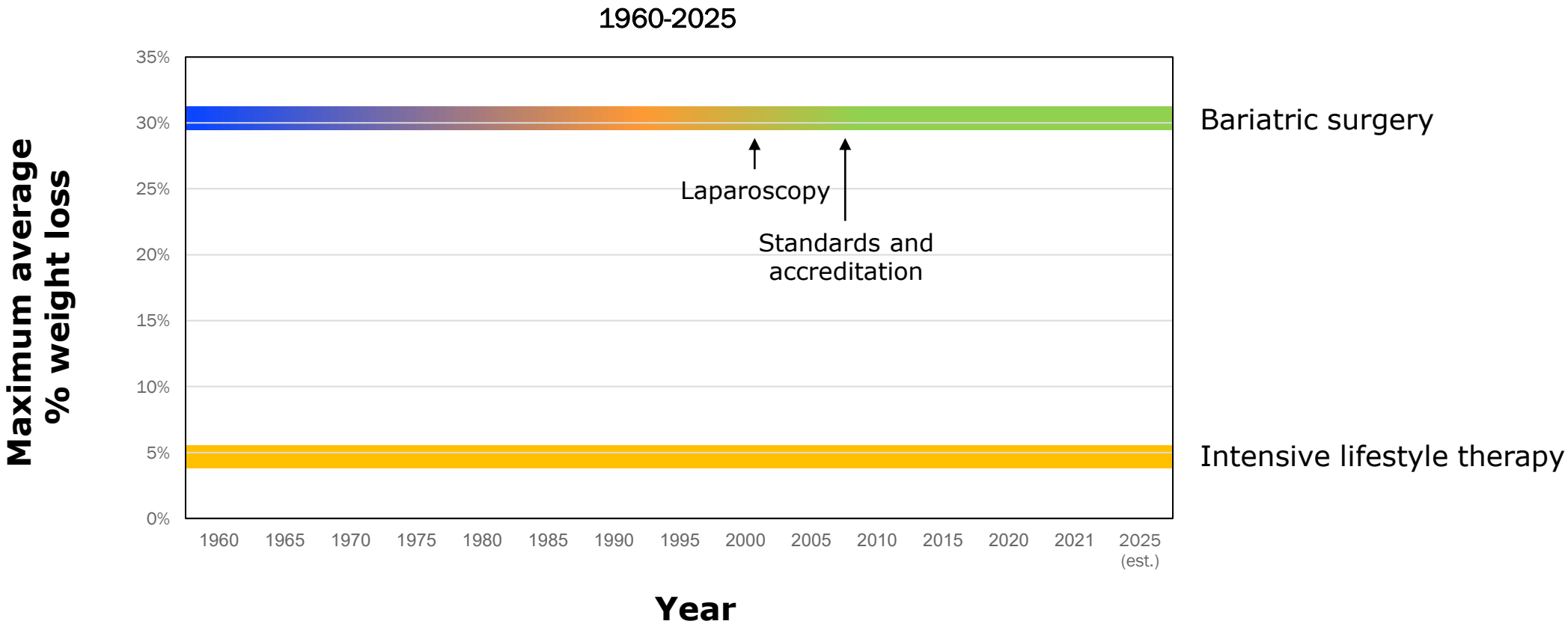
1. Vallis M. Clin Obes 2019;9:e12299; 2. Hall K et al. Am J Public Health 2014;104:1169-75.

Goals and benefits of effective weight management



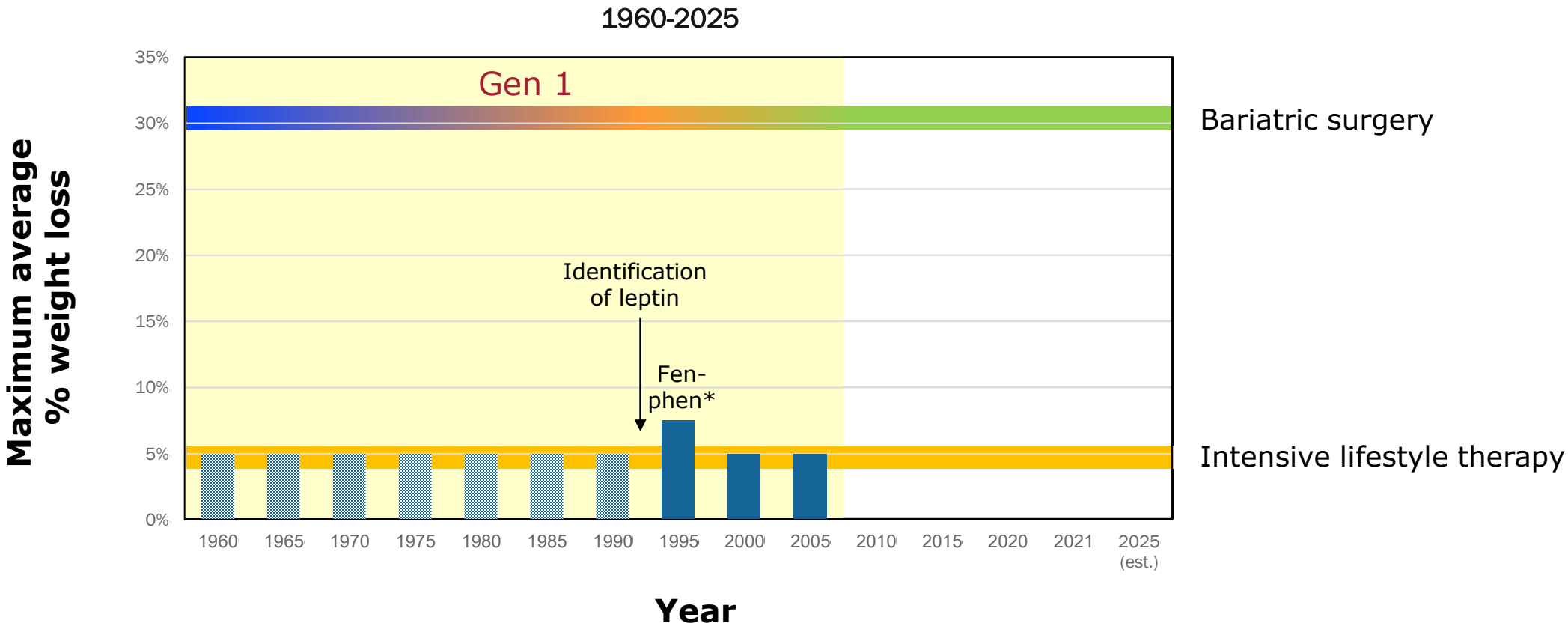
1. Wadden et al. Circulation 2012;125:1157–70; 2. Jensen et al. J Am Coll Cardiol 2014;63(25 Pt B):2985–3023; 3. Purcell et al. Lancet Diabetes Endocrinol 2014;2:954–62; 4. Villareal et al. Am J Clin Nutr 2005;82:923–34.

Obesity therapy since the 1950s



Kaplan LM, 2022

Little progress in anti-obesity pharmacotherapy



*This medication combination is not approved for the treatment of obesity

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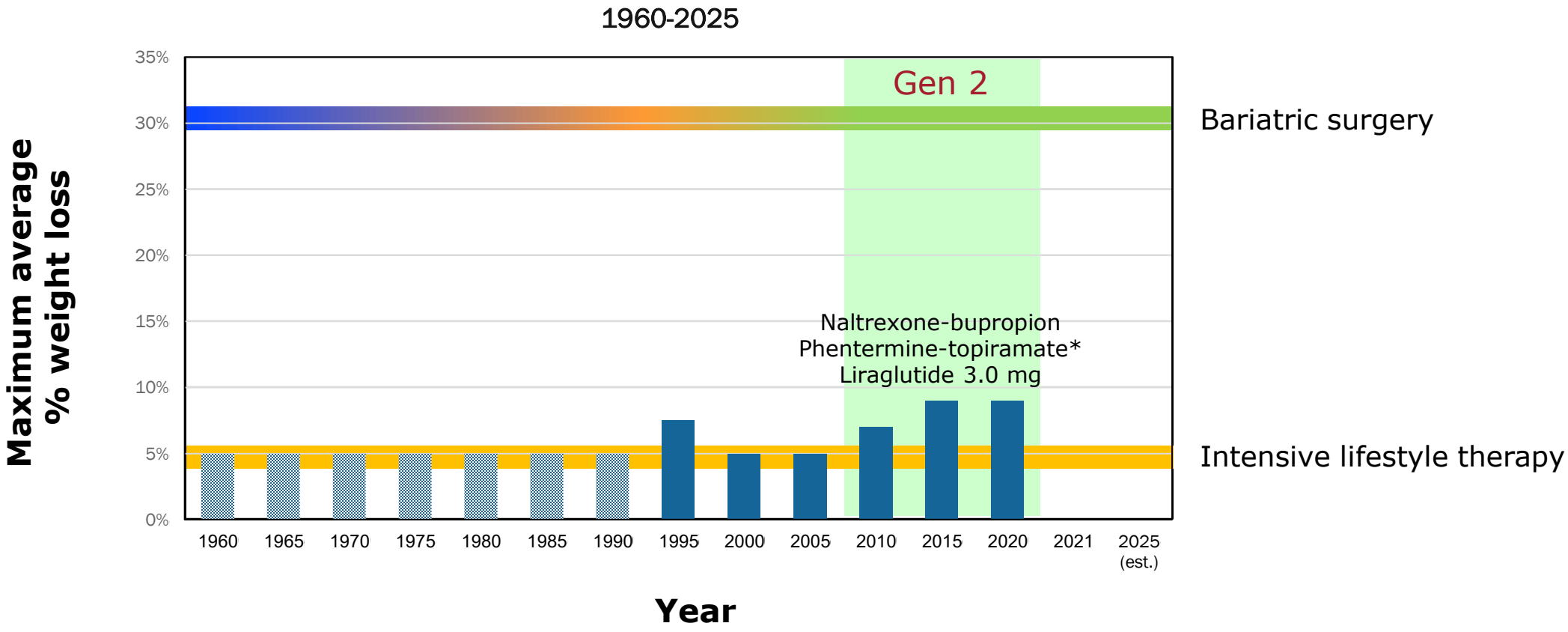
Incremental improvements in anti-obesity medications



*Phentermine-topiramate has not been approved by the EMA for the treatment of obesity

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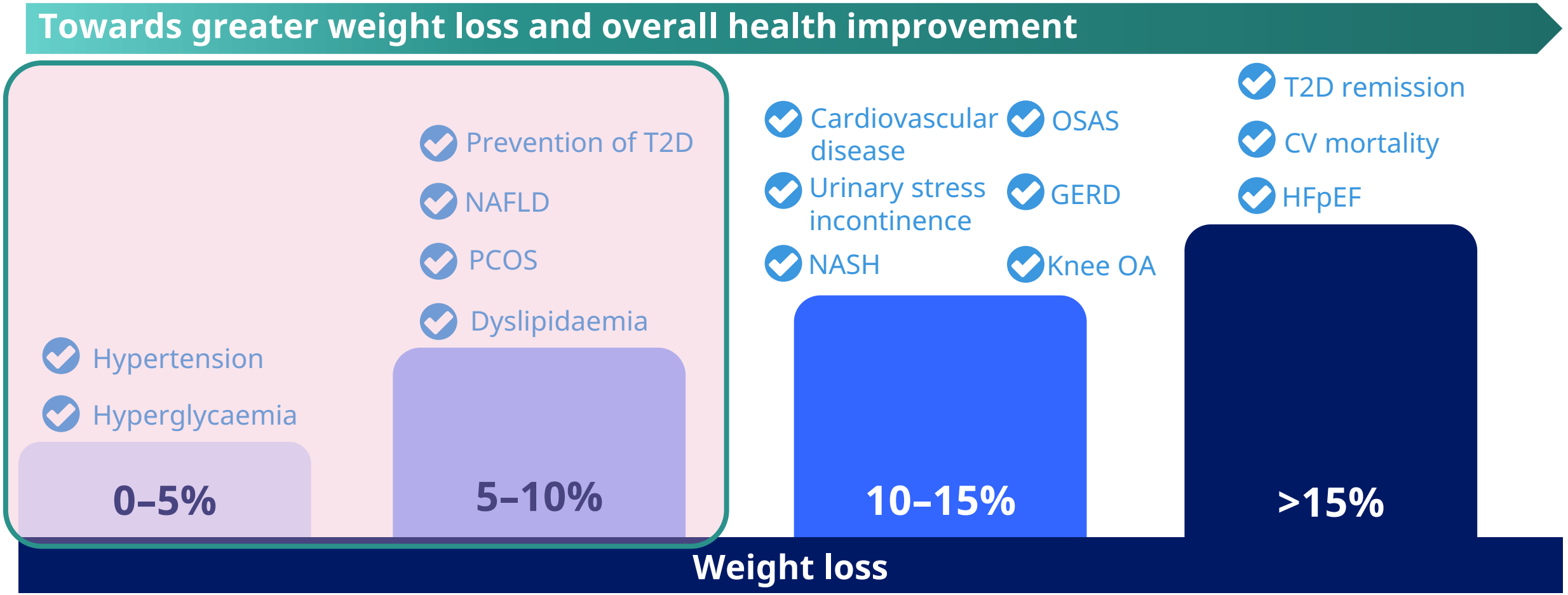
Efficacy of previous AOMs with diet and lifestyle therapy



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.

Physician and patient expectations on weight loss

Weight-loss goal

Set by a person with obesity for themselves

16%

Received from healthcare professional

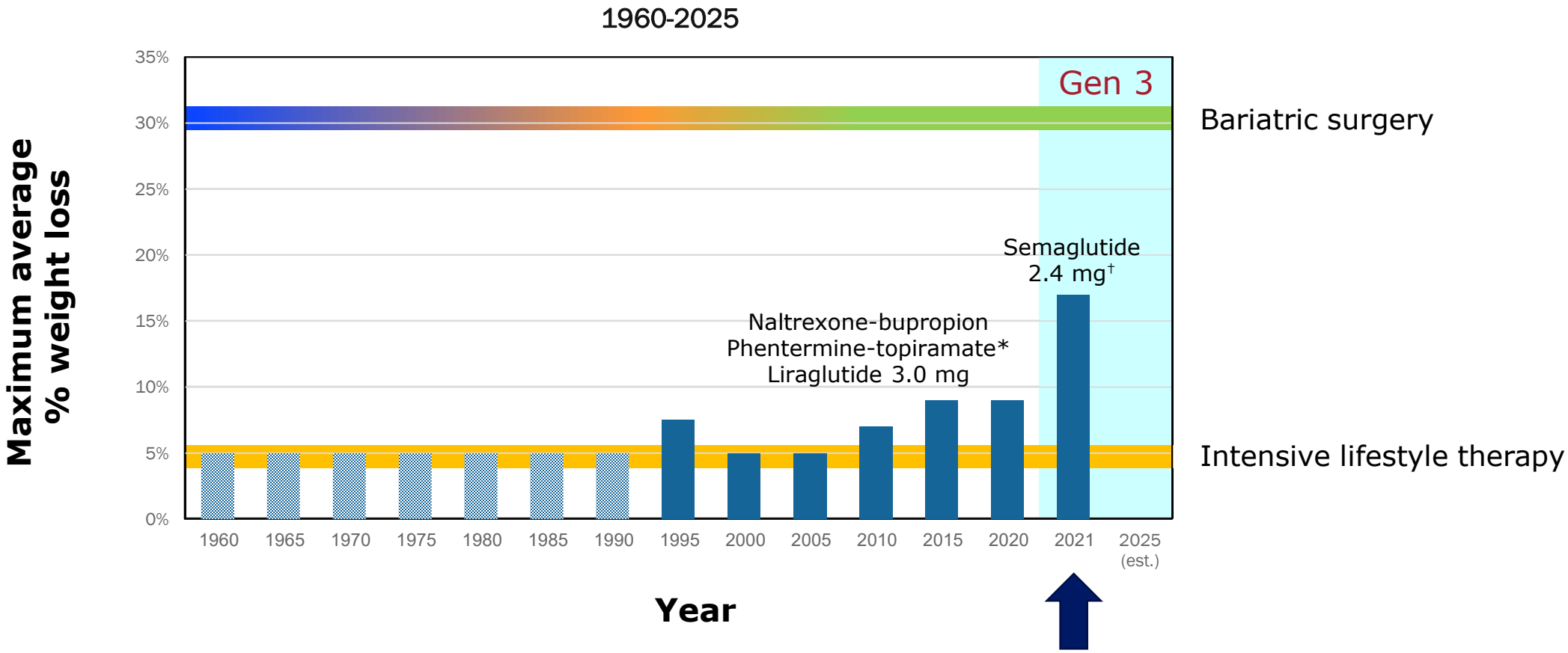
17%

Caterson et al. Diabetes Obes Metab 2019;21:1914–24.

ACTION IO
AWARENESS, CARE & TREATMENT IN OBESITY MANAGEMENT - AN INTERNATIONAL OBSERVATION

Semaglutide is not yet approved for weight management in Israel

The emergence of truly effective anti-obesity medications



*Phentermine-topiramate has not been approved by the EMA for the treatment of obesity

†Trial product estimand

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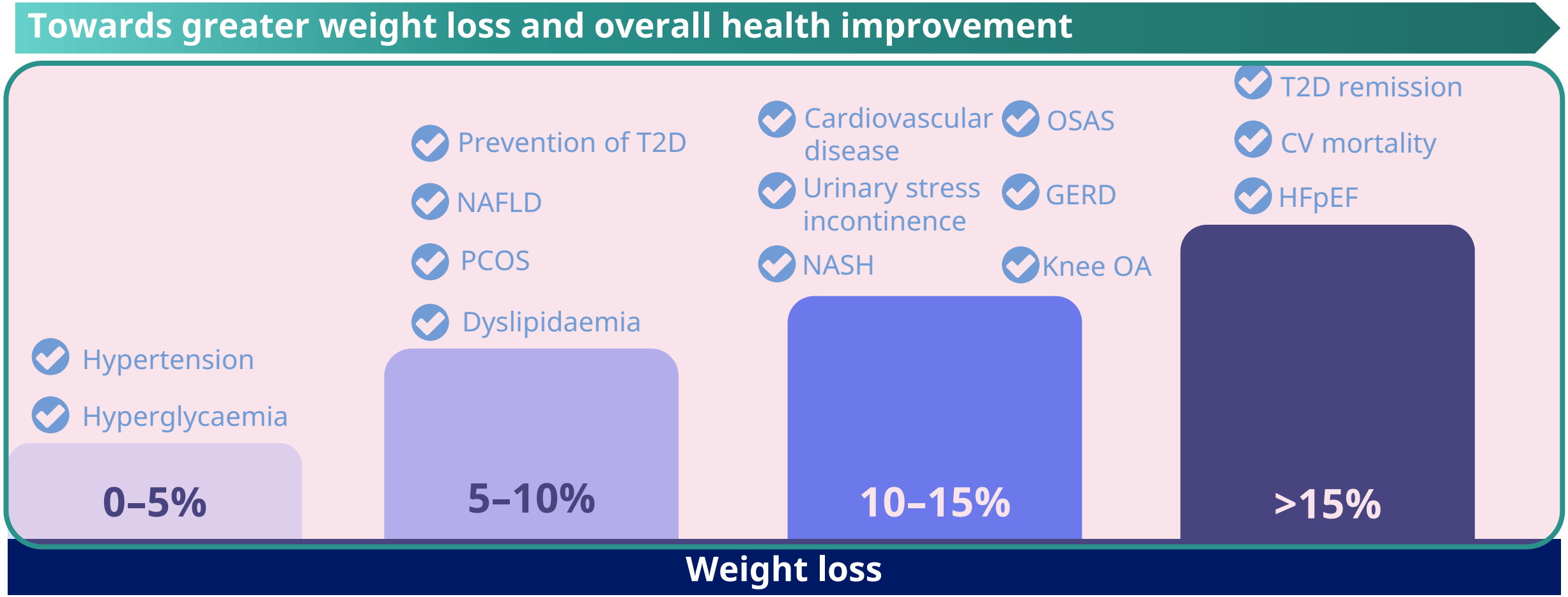
Efficacy of newer AOMs with diet and lifestyle therapy



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.

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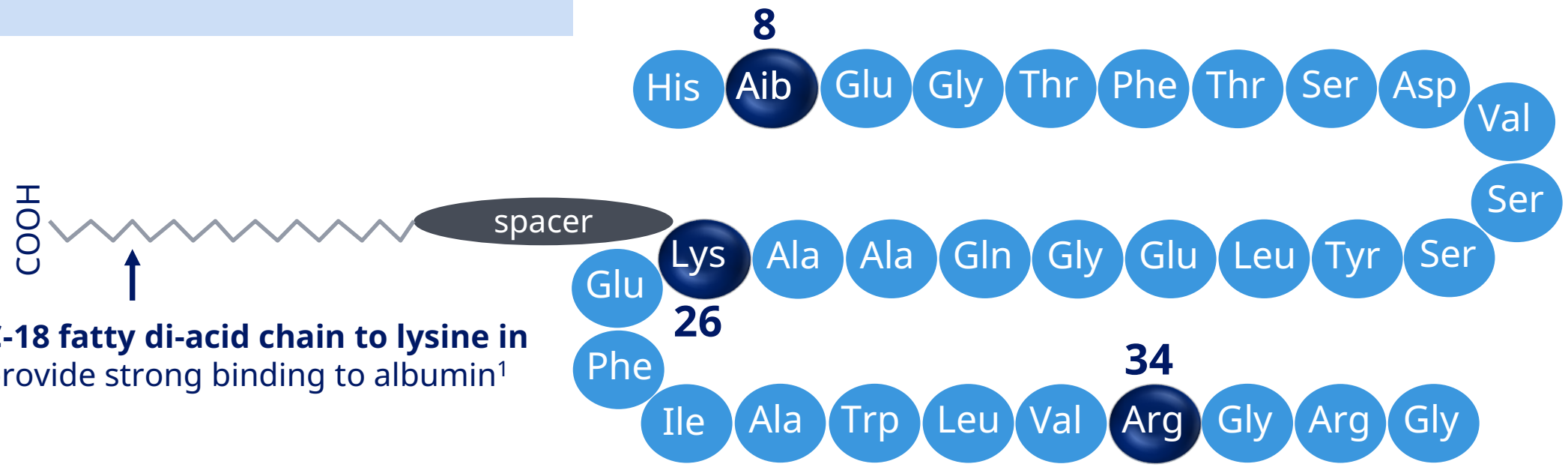
Semaglutide is a human GLP-1 analogue

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2,3]

Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation[1]



Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin[1]

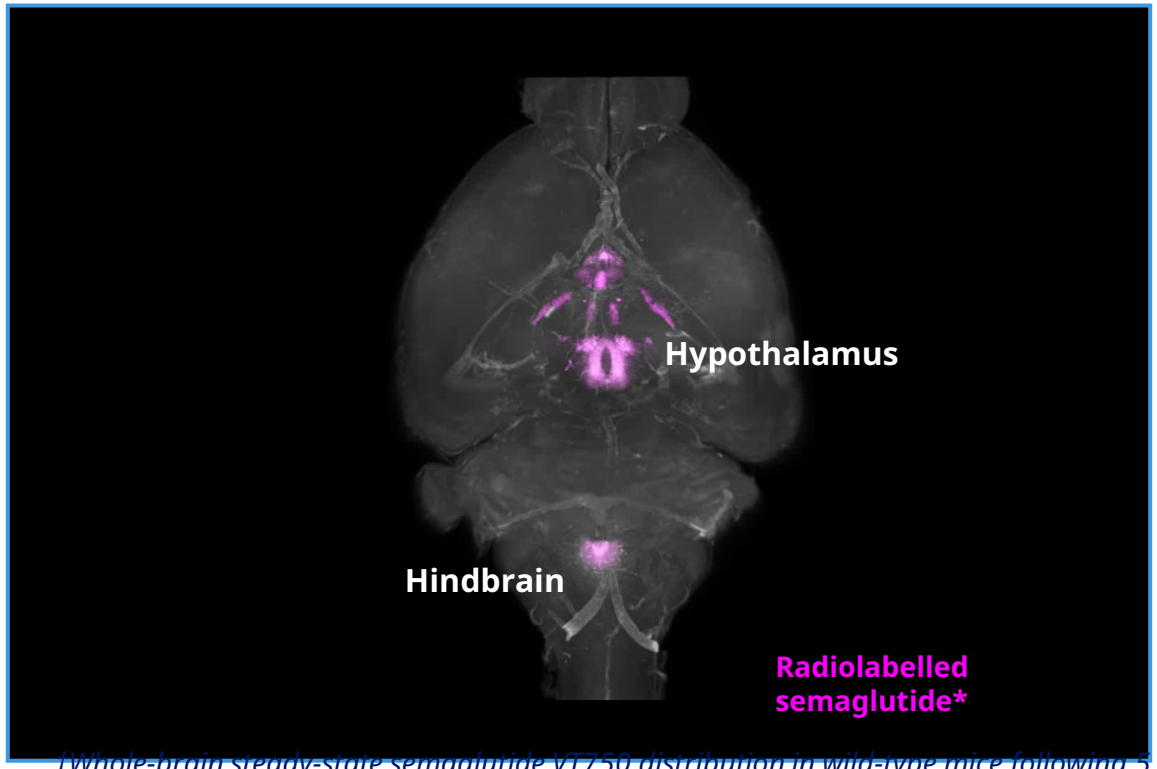
Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site[1]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life.

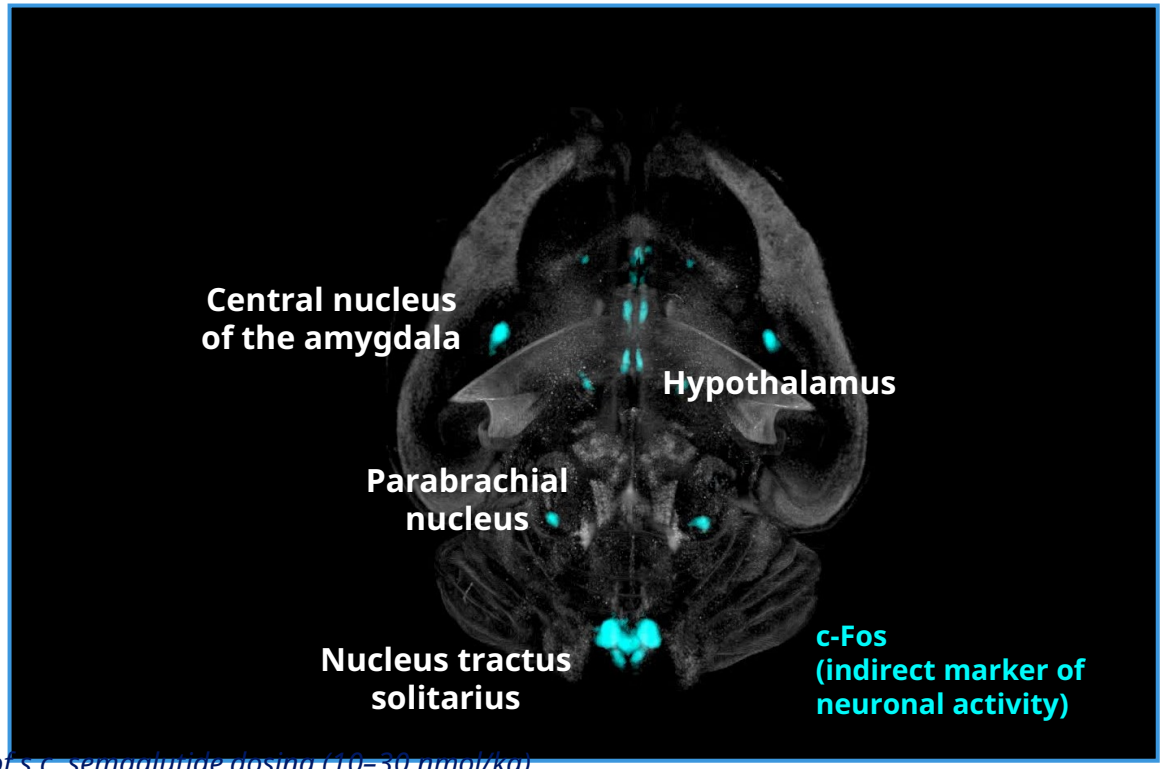
1. Lau J et al. J Med Chem 2015;58:7370–80; 2. Kapitza C et al. J Clin Pharmacol 2015;55:497–504; 3. Marbury TC et al. Clin Pharmacokinet 2017;56:1381–90.

Several brain regions are activated by semaglutide In rodents

Semaglutide distribution in the hypothalamus and hindbrain†



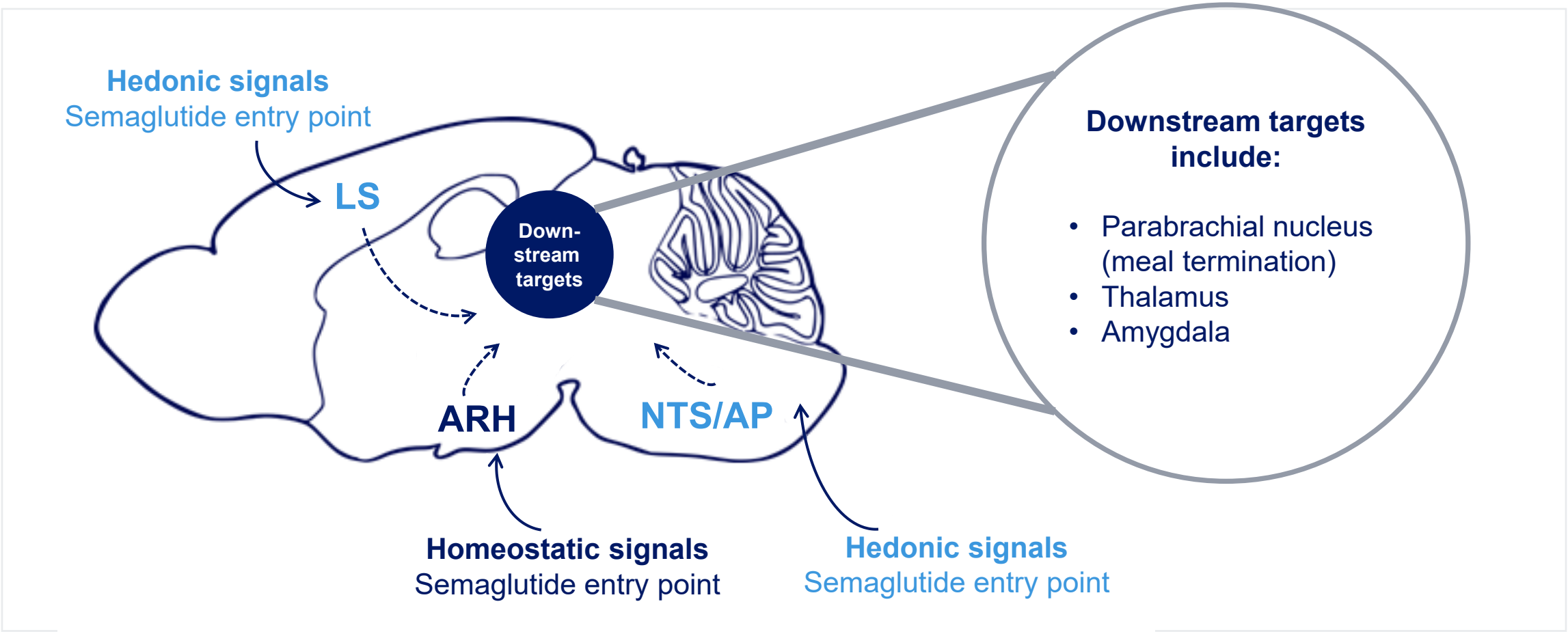
Secondary activation in regions associated with control of food intake‡



†Whole-brain steady-state semaglutide VT750 distribution in wild-type mice following 3 days of s.c. semaglutide dosing (10–30 nmol/kg).
**SemaglutidecVT750. ‡Whole-brain c-Fos expression in DIO mice following a single s.c. dose of semaglutide (0.01 mg/kg).*
GLP-1R, glucagon-like peptide-1 receptor; semaglutideVT750, VivoTag750-S-labelled semaglutide.
Gabery et al. JCI Insight 2020;5:e133429; Novo Nordisk. Data on file.

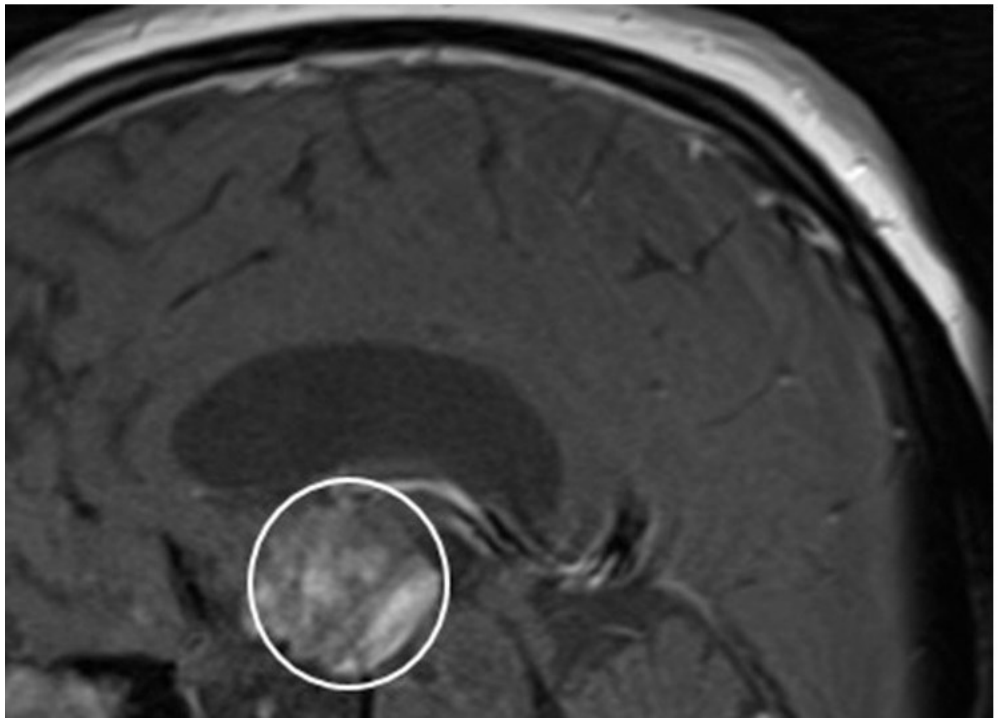
Semaglutide entry points and activation circuits

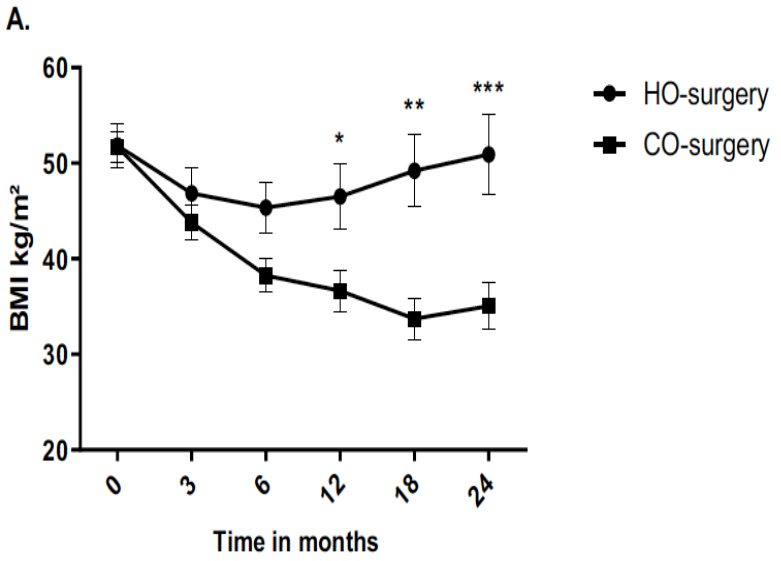
Appetite regulation in rodents

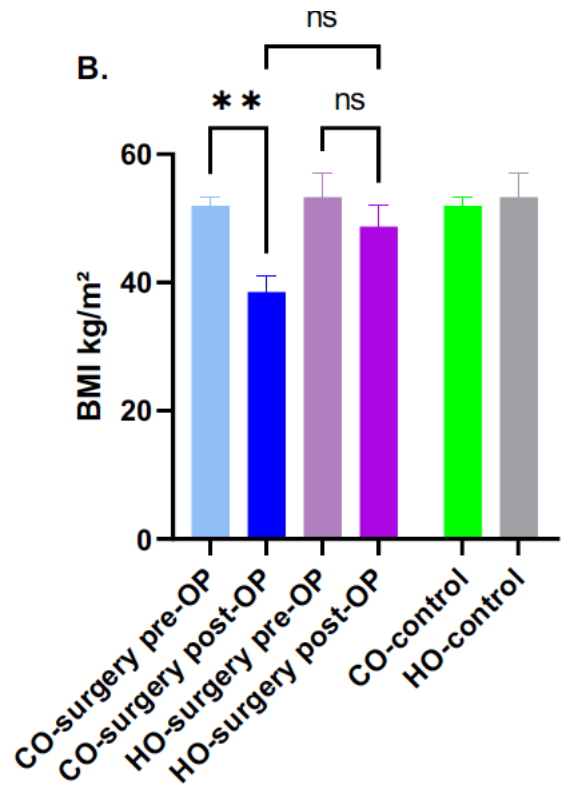


AP, area postrema; ARH, arcuate nucleus; LS, lateral septal nucleus; NTS, nucleus of the solitary tract;
Modified from Campos et al. Cell metabolism 2016;23(5):811-820

Mean concentrations of plasma GLP-1 after the test meal in HO-surgery and CO-surgery individuals.







Dischinger, Metabolism, 2023

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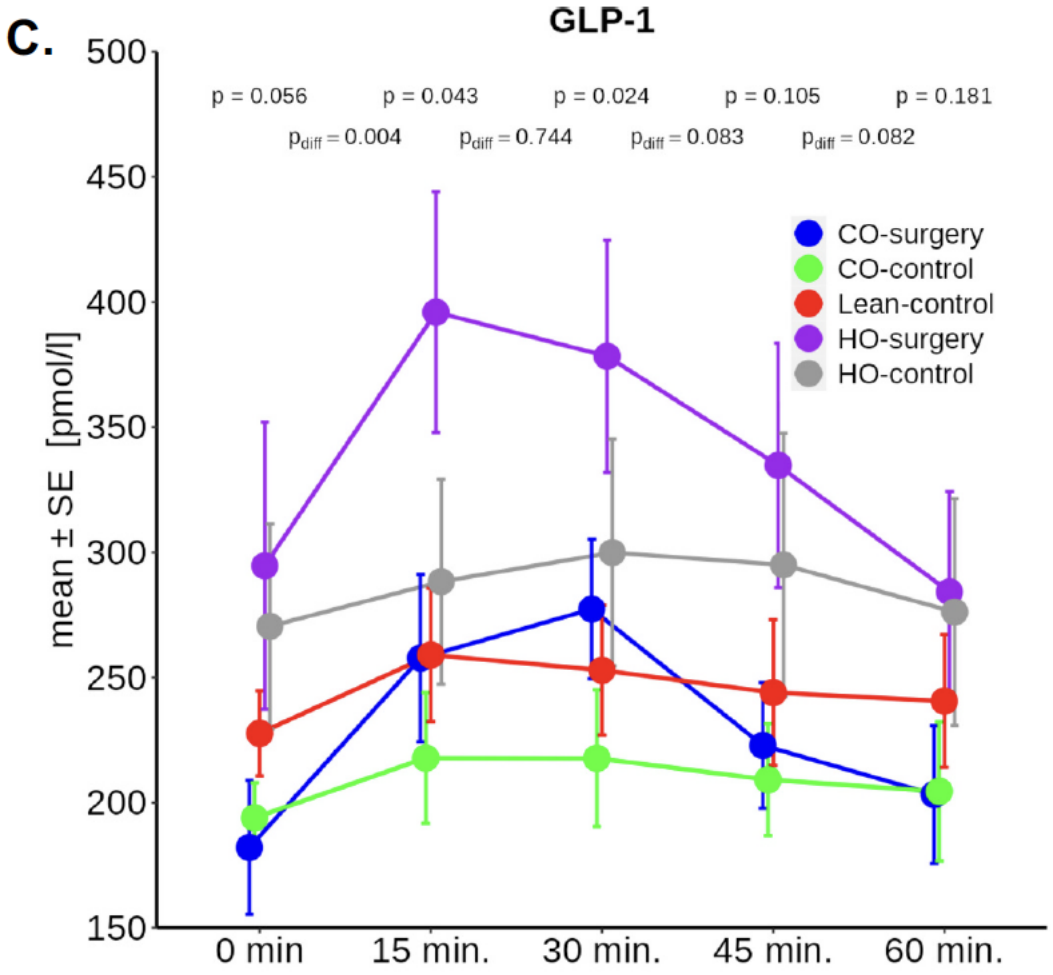
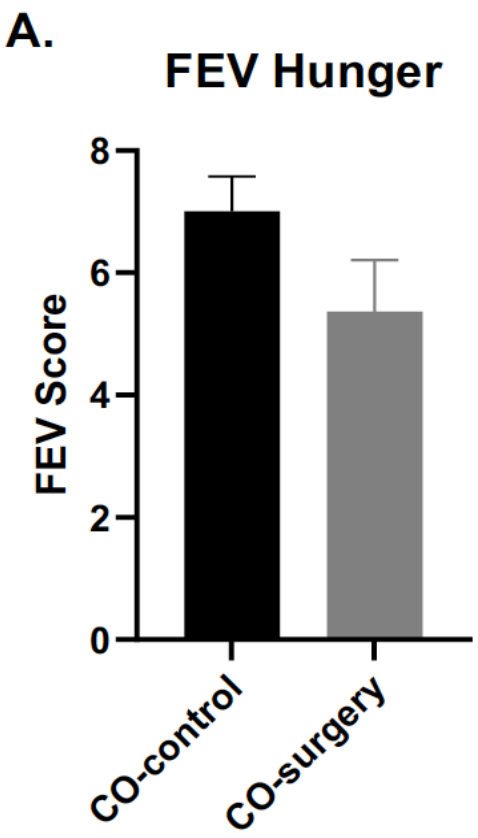
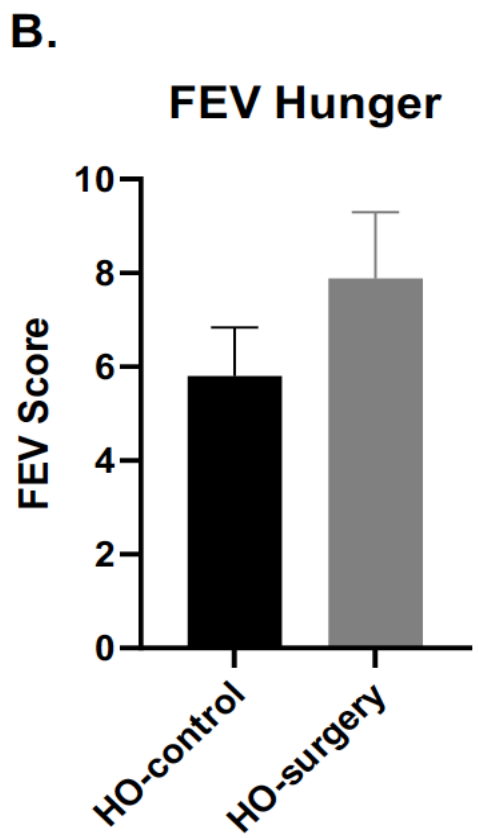




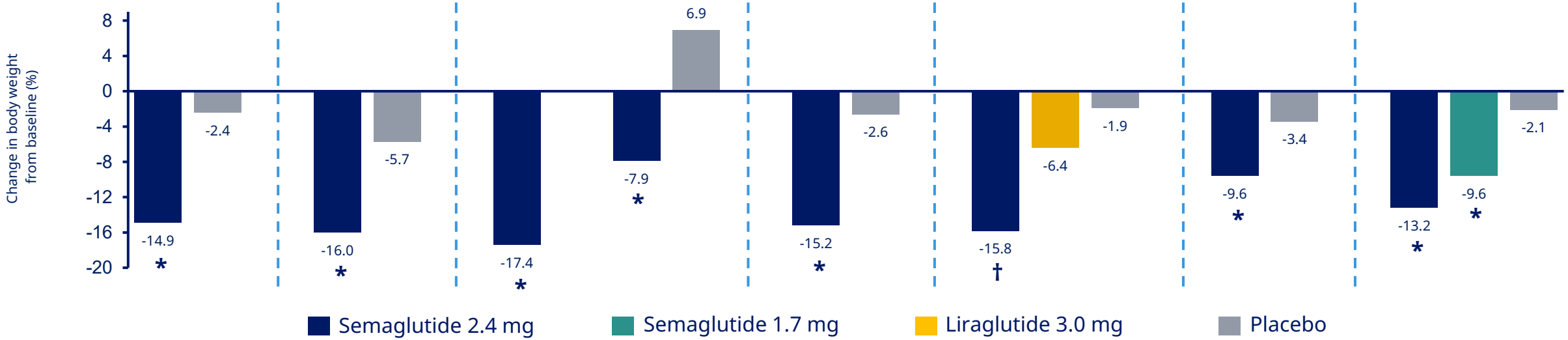


Dischinger, Metabolism, 2023

Weight loss across STEP trials

Semaglutide 2.4 mg once-weekly in participants with overweight or obesity

	STEP 1[1]	STEP 3[3]	STEP 4[4]		STEP 5[5]	STEP 8[7]	STEP 2[2]	STEP 6[6]
	Weight management	Weight management with IBT	Sustained weight management		Long term weight management	Head to head vs. liraglutide 3.0 mg	Weight management in T2D	Weight management in East Asian population
Baseline BW	105.3 kg	105.8 kg	107.2 kg	96.1 kg	106.0 kg	104.5 kg	99.8 kg	87.5 kg
	After 68 weeks	After 68 weeks	After 68 weeks	20–68 weeks	104 weeks	After 68 weeks	After 68 weeks	After 68 weeks



Treatment policy estimand: Evaluates the treatment effect regardless of trial product discontinuation and use of rescue medication

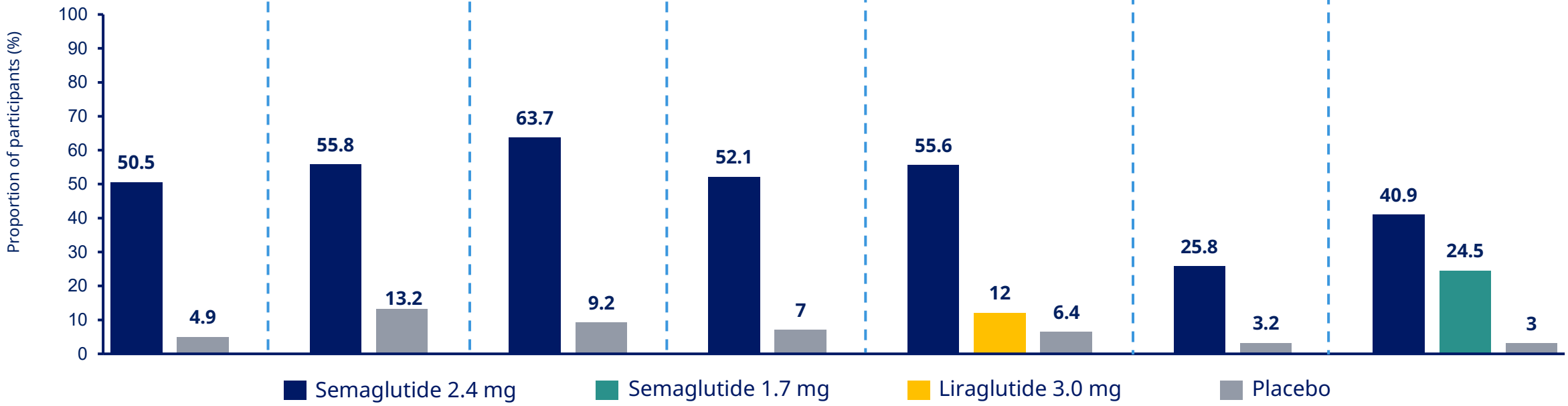
**Statistically significant vs placebo.† Statistically significant vs. liraglutide 3.0 mg*
BW, body weight; IBT, intensive behavioural therapy.

1. Wilding et al. N Engl J Med 2021; doi:10.1056/NEJMoa2032183; 2. Davies et al. Lancet, 2021; doi.org/10.1016/S0140-6736(21)00213-0: 3. Wadden et al. JAMA. doi:10.1001/jama.2021.1831; 4. Rubino et al. JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. 5. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 6. Kadowaki et al. Presented at the International Congress on Metabolic Syndrome hybrid meeting .September 2-4, 2021; 7. Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

≥15% weight loss across STEP trials

Semaglutide 2.4 mg once-weekly in participants with overweight or obesity

	STEP 1[1]	STEP 3[3]	STEP 4[4]	STEP 5[5]	STEP 8[7]	STEP 2[2]	STEP 6[6]
	Weight management	Weight management with IBT	Sustained weight management	2-year effect of sema 2.4 mg	Weight management (vs. liraglutide 3.0 mg^)	Weight management in T2D	East Asian trial
Baseline BW	105.3 kg	105.8 kg	107.2 kg	106.0 kg	104.5 kg	99.8 kg	87.5 kg
	After 68 weeks	After 68 weeks	After 68 weeks	104 weeks	After 68 weeks	After 68 weeks	After 68 weeks

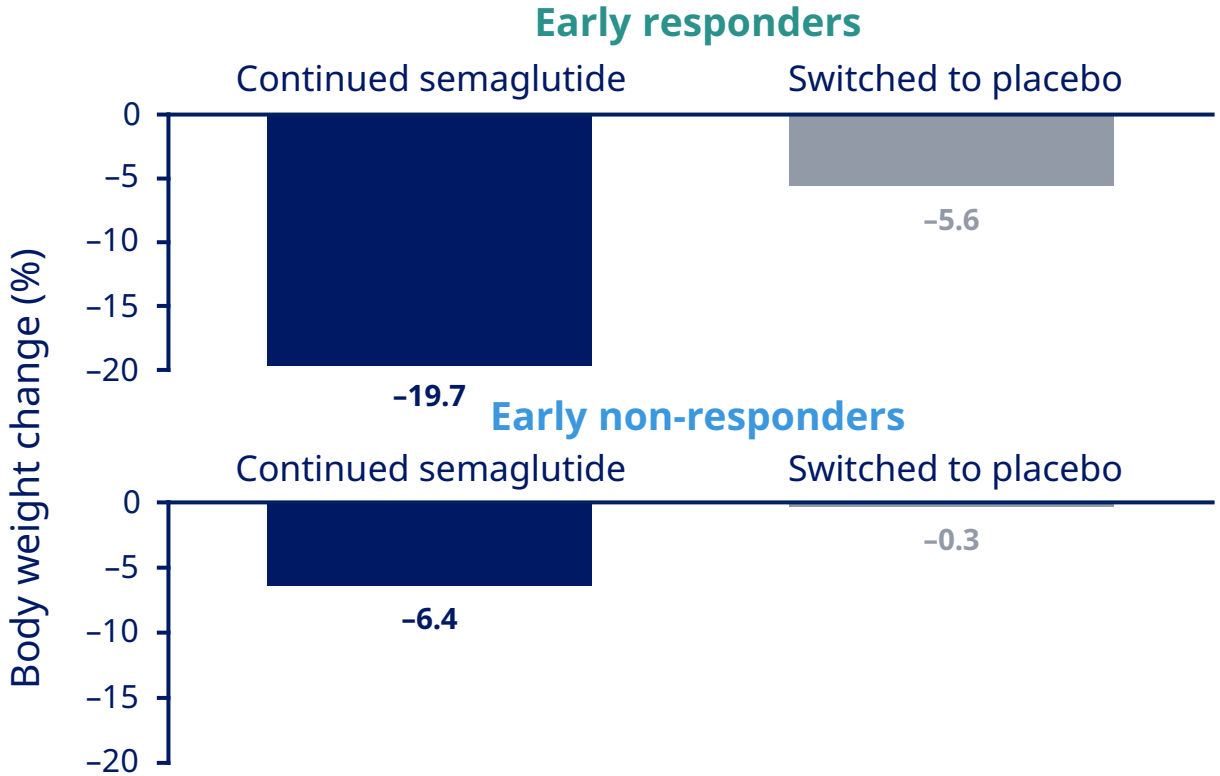


Data are for the in-trial period. BW, body weight; IBT, intensive behavioural therapy.

1. Wilding et al. N Engl J Med 2021; doi:10.1056/NEJMoa2032183; 2. Davies et al. Lancet, 2021; doi.org/10.1016/S0140-6736(21)00213-0: 3. Wadden et al. JAMA. doi:10.1001/jama.2021.1831; 4. Rubino et al. JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. 5. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 6. Kadowaki et al. Presented at the International Congress on Metabolic Syndrome hybrid meeting .September 2-4, 2021; 7. Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

STEP 4: Mean weight loss from week 0 to 68 by week 20 responder status (≥ or <5% weight loss)

Mean weight loss at week 68 with continued semaglutide vs switched to placebo

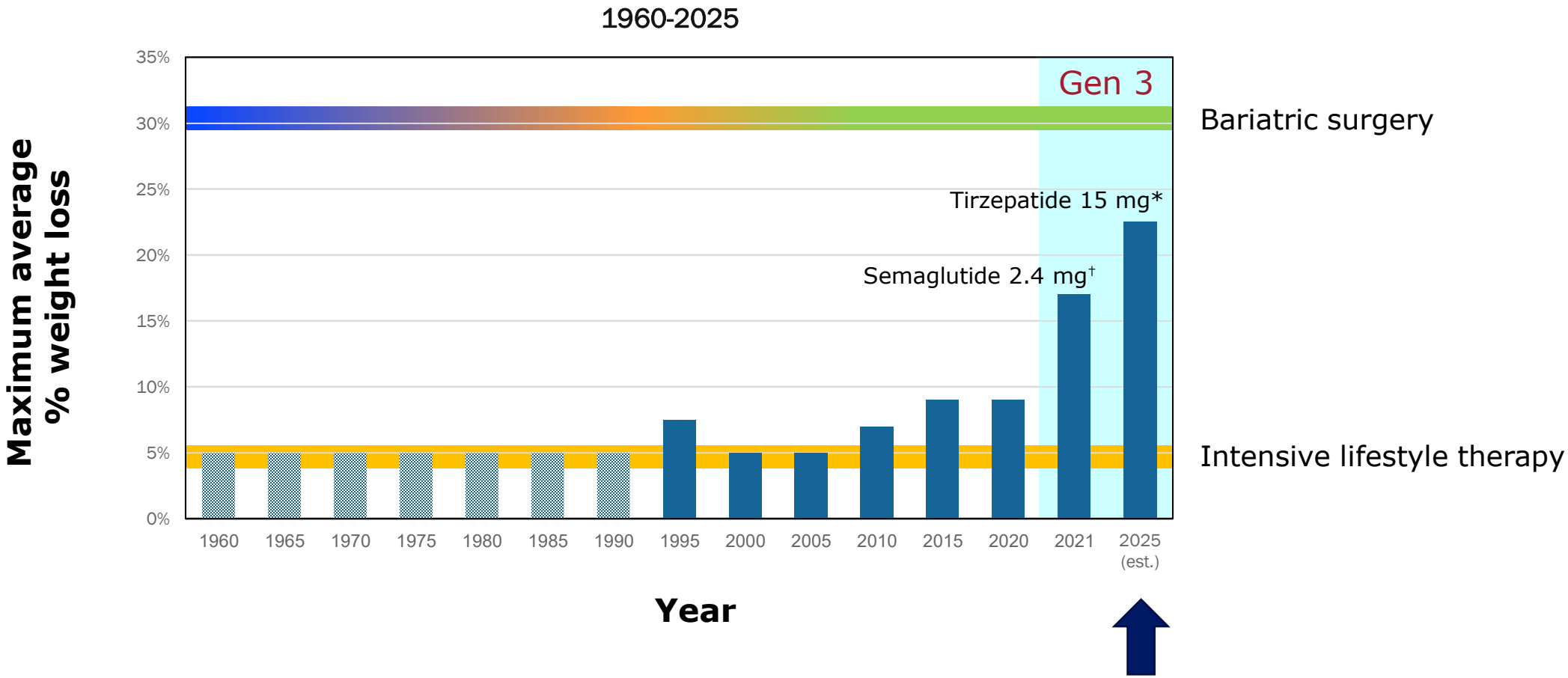


- **Early response** was associated with **greater mean weight loss** by week 68 with continued semaglutide vs early non-response
- **Early non-responders** still achieved **clinically-relevant weight loss** by week 68 with continued semaglutide, compared with the switch to placebo

Analysed in all participants using a mixed model for repeated measurements analysis with treatment, responder status and the interaction of these as factors, and baseline body weight as a covariate, all nested within visit. The analysis assumed all participants were treatment adherent (the trial product estimand).
Mosenzon et al. Presented at the Endocrine Society (ENDO) virtual meeting, March 20–23, 2021.

The emergence of truly effective anti-obesity medications

… mimic the action of native GI and CNS peptides



*Efficacy estimand; tirzepatide is not approved for treatment of obesity

†Trial product estimand

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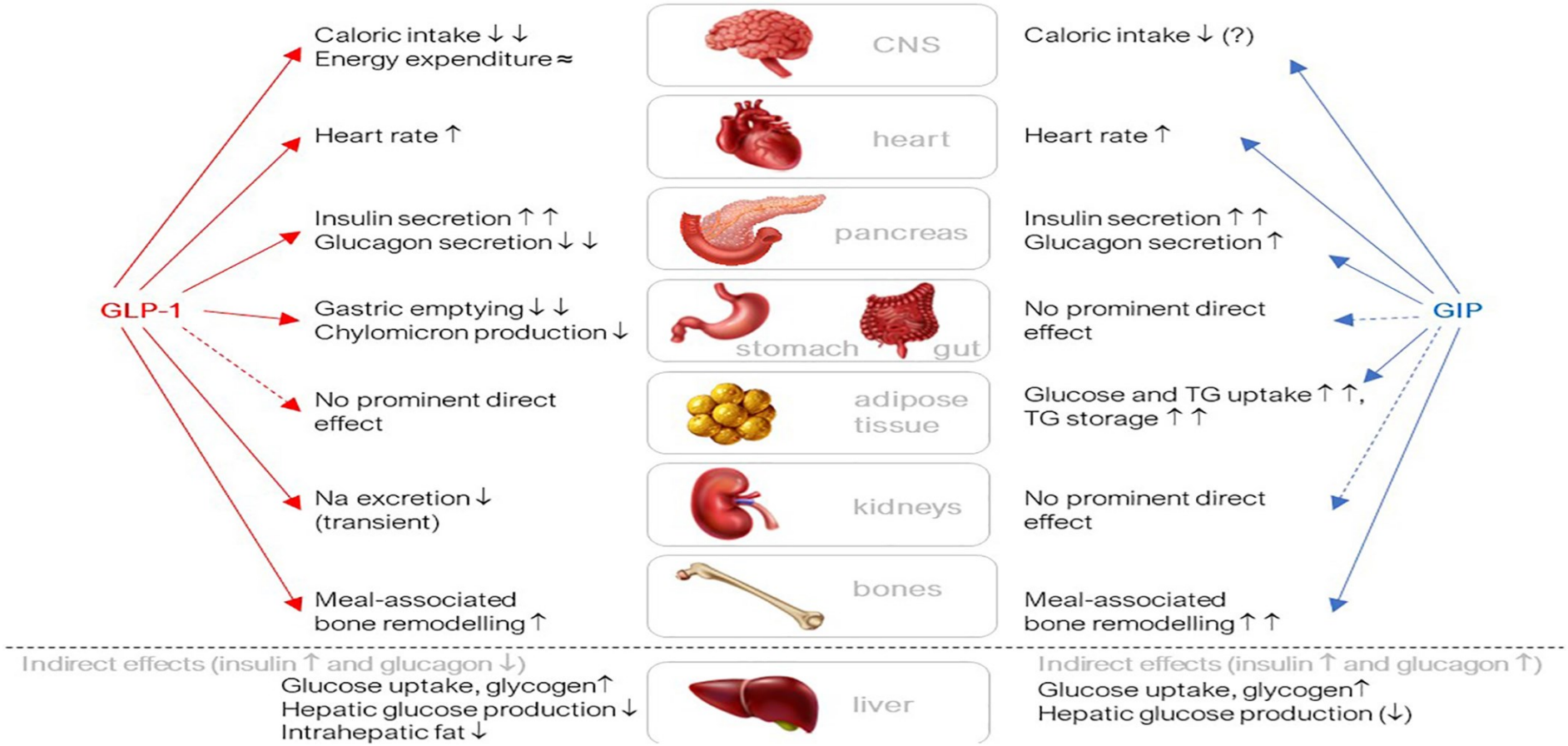
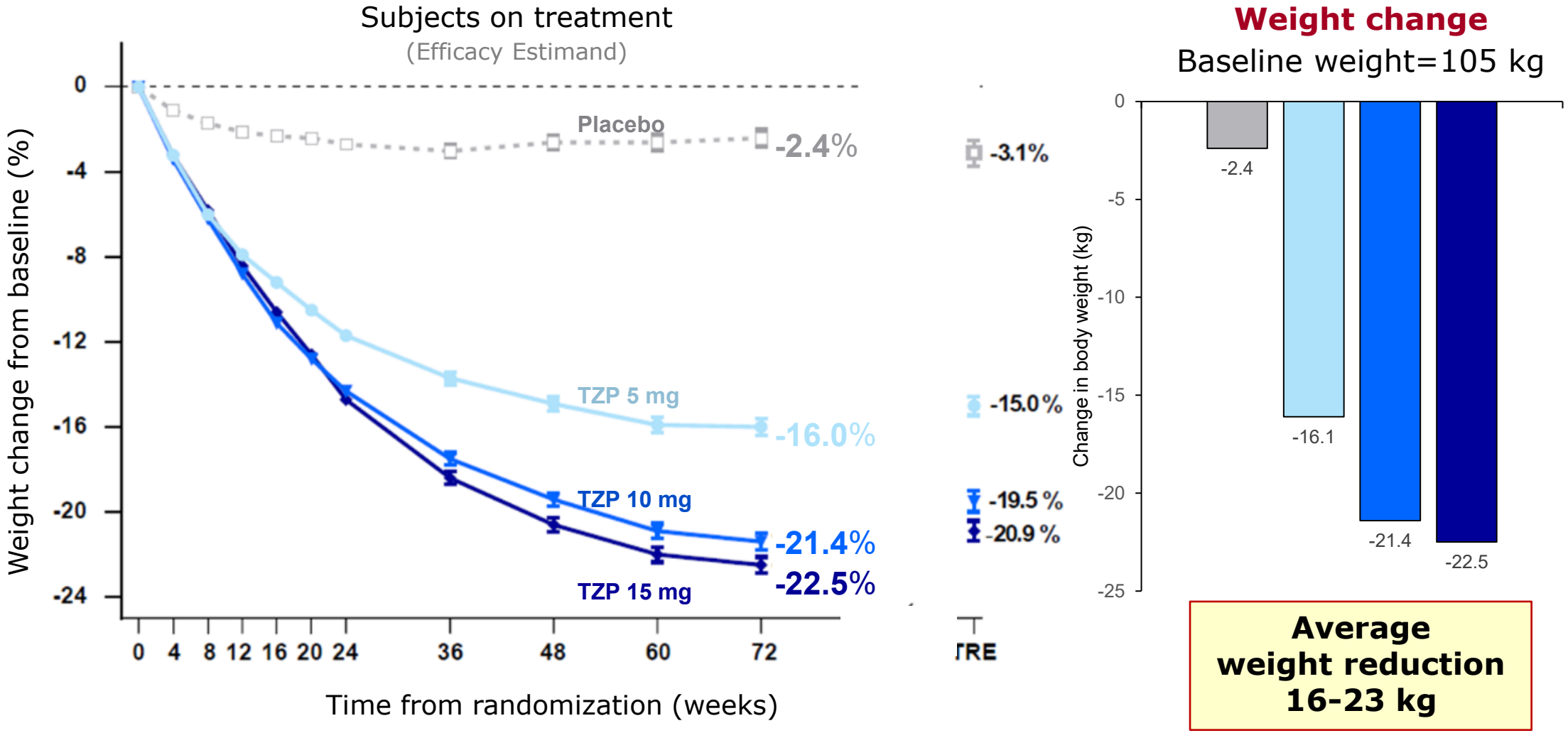
Overview on biological glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) effects at the organ/tissue level



Nauck MA, Diabetes Obes Metab. 2021

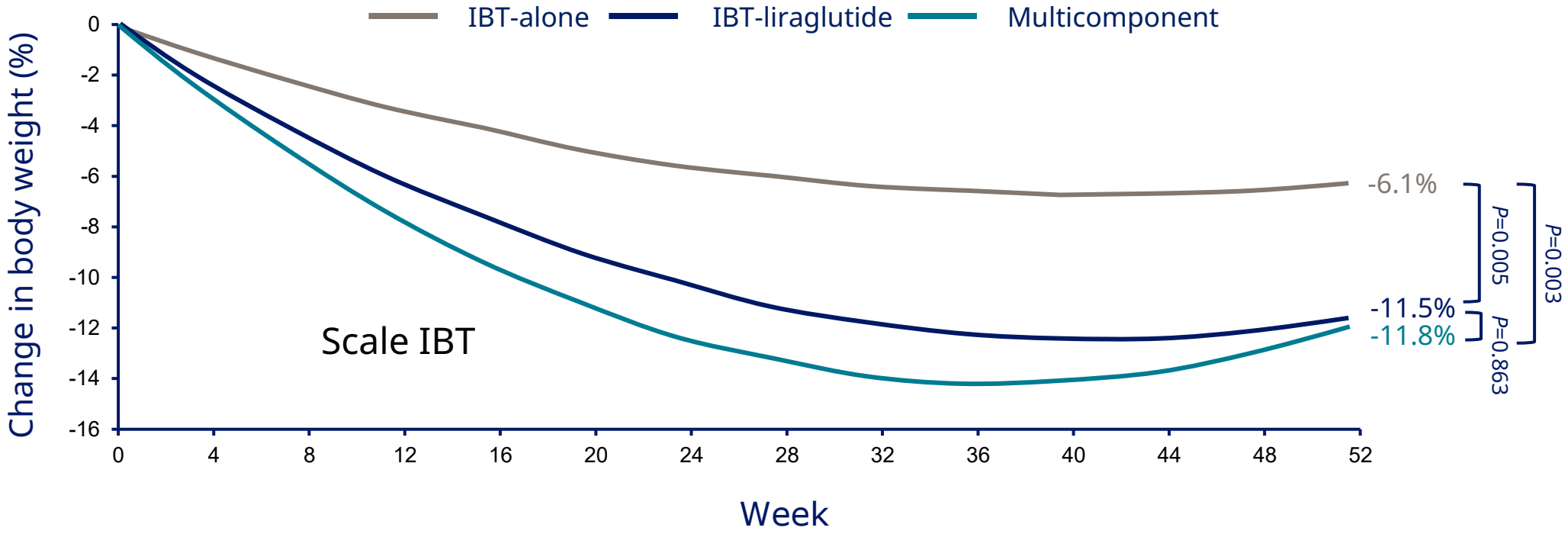
Weight reduction on tirzepatide* – subjects without diabetes



Notion 1 : We should aim for 15-20% weight loss

Does IBT add much to Pharmacotherapy weight loss?

SCALE IBT

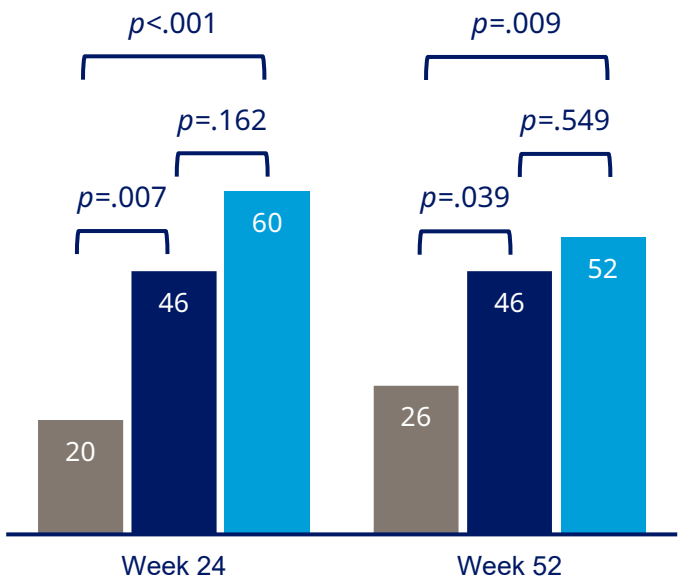


IBT (IBT-alone), providing 21 counselling visits; IBT combined with liraglutide (IBT-liraglutide); or IBT-liraglutide combined for 12 weeks with a 1,000- to 1,200-kcal/d meal-replacement diet (Multicomponent).

Data are estimated mean percentage reduction in the ITT population. ITT, intention to treat
Wadden, T.A., et al., Obesity (Silver Spring), 2019; 27(1): 75-86.

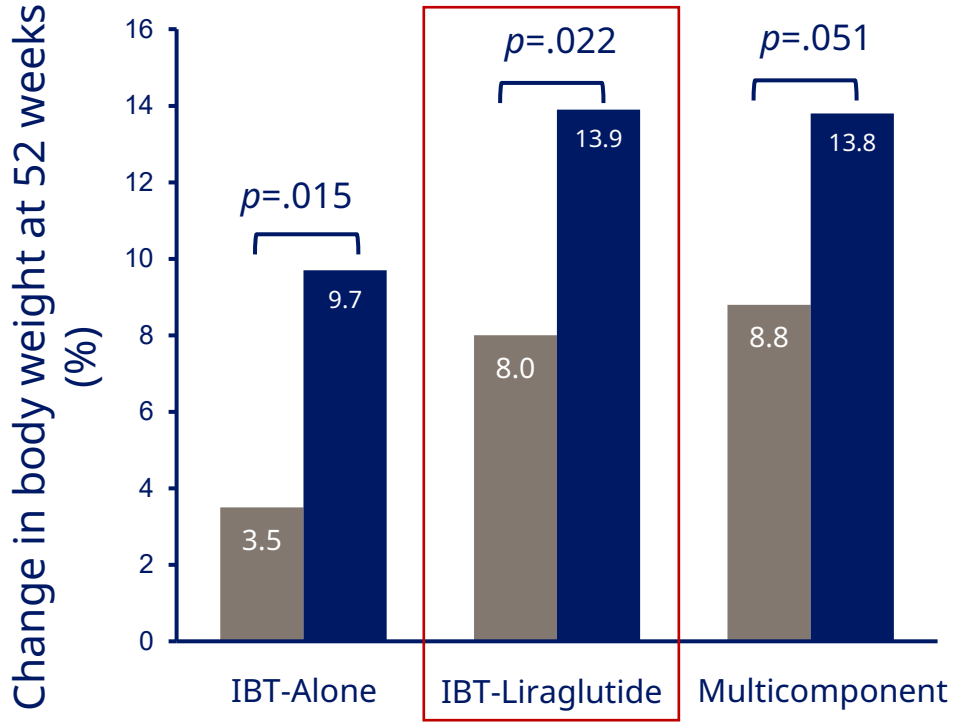
SCALE IBT

Percentages of participants who lost ≥ 10%



IBT-alone IBT-liraglutide Multicomponent

Mean weight losses based on attendance of IBT visits*



Less attendance Full attendance

Wadden, T.A., et al., *Obesity (Silver Spring),* 2019; 27(1): 75-86.

STEP 3: Principles of intensive behavioural therapy (IBT)

30 IBT sessions, delivered by a registered dietitian

Physical activity

100 minutes per week (prescribed at randomisation)

Moderate intensity exercise

Increase by **25 minutes** every 4 weeks

200 minutes per week (target duration)

Caloric intake

Week 0–8:

Low-calorie diet (LCD)

1,000–1,200 kcal/day
(meal replacements/portion-controlled meals)

Week 8 onwards:

Hypo-caloric diet (conventional food)

Weight at randomisation	Prescribed daily caloric intake
<200 lb (90.7 kg)	1,200 kcal
200–300 lb	Body weight (lb) x 6 (kcal/lb)
>300 lb (136.1 kg)	1,800 kcal

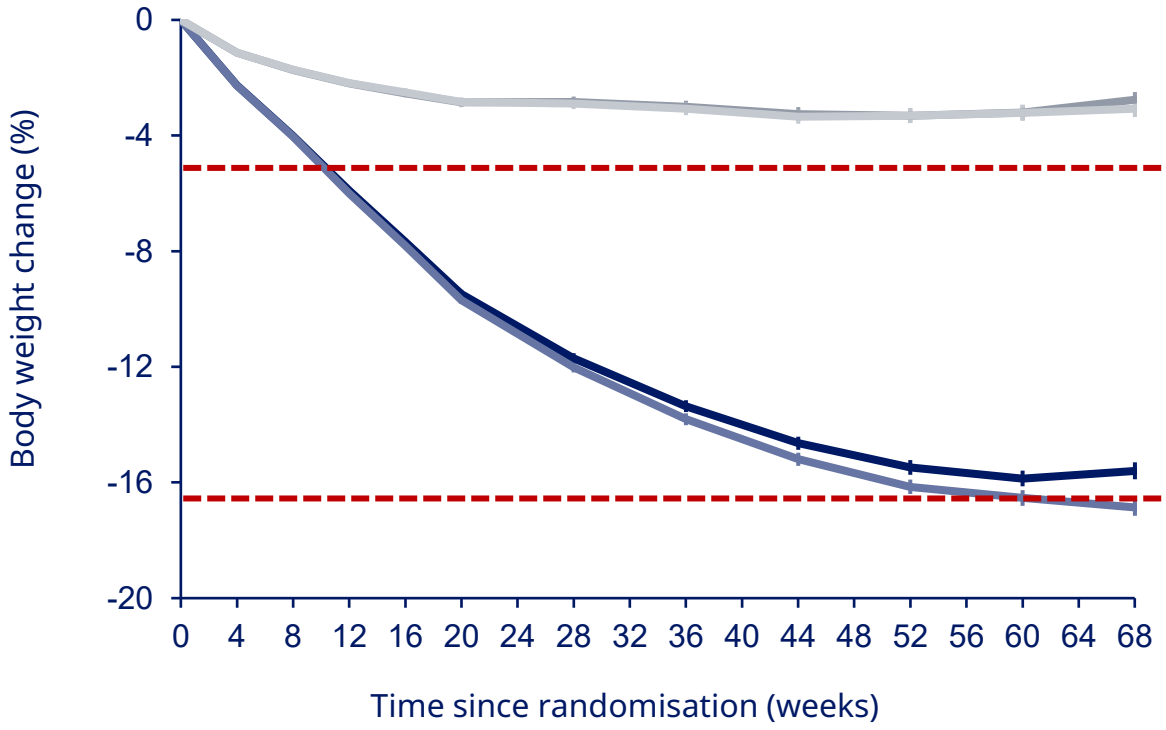
IBT based on an abbreviated version of Diabetes Prevention Program (DPP), adapted by Wadden TA, et al. Obesity 2019;27:1562-1566. IBT, intensive behavioural therapy.

Wadden TA, et al. Presented at the 38th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, November 2–6, 2020 [Oral 084].

STEP 1and 3: Body weight change comparison

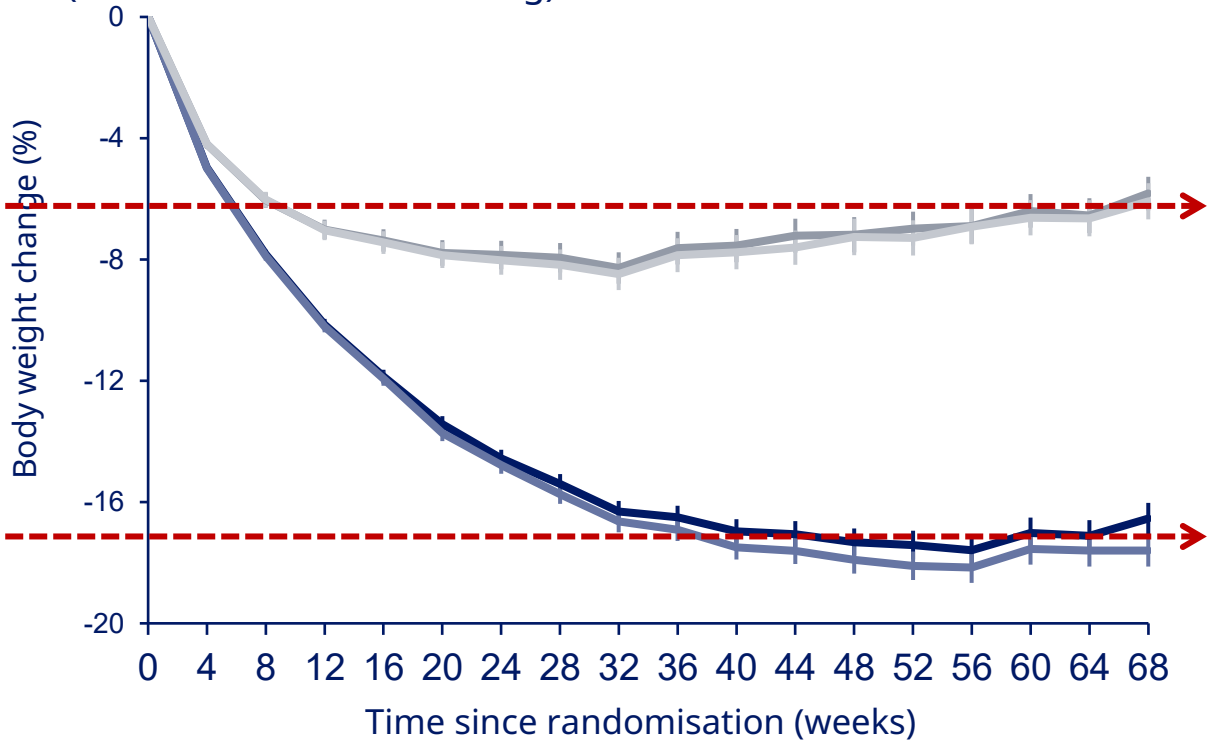
Observed body weight change over time (STEP 1)

(Mean at baseline: 105.3 kg)



Observed body weight change over time (STEP 3)

(Mean at baseline: 105.8 kg)



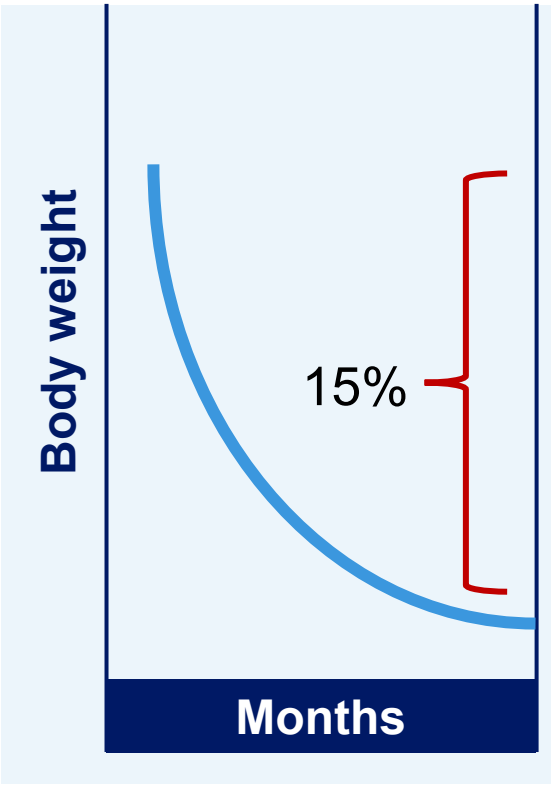
- Error bars are +/- standard error of the mean.
  CI, confidence interval; ETD, estimated treatment difference.
  Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print.

*This is an indirect trial comparison

Notion 2 : In 15-20% weight loss IBT doesn’t add much to the Pharmacotherapy weight loss.

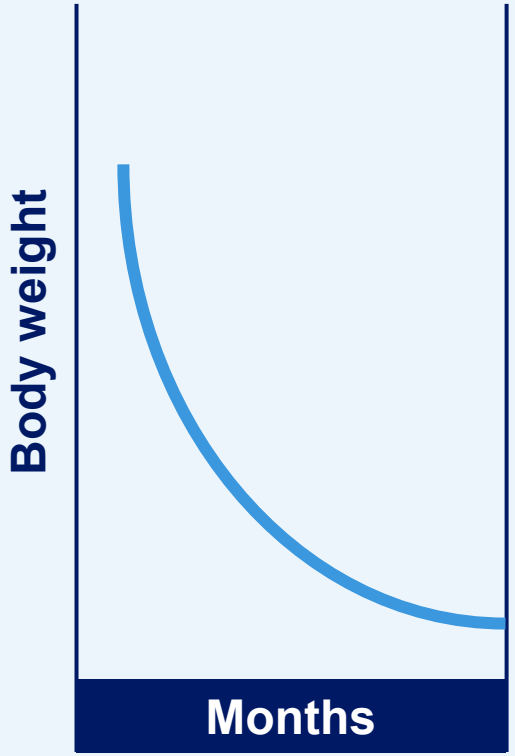
Goals and benefits of effective weight management

01 **Achieve weight loss[1,2]**



Goals and benefits of effective weight management

01 Achieve weight loss[1,2]



03 Provide clinically meaningful benefits[1]

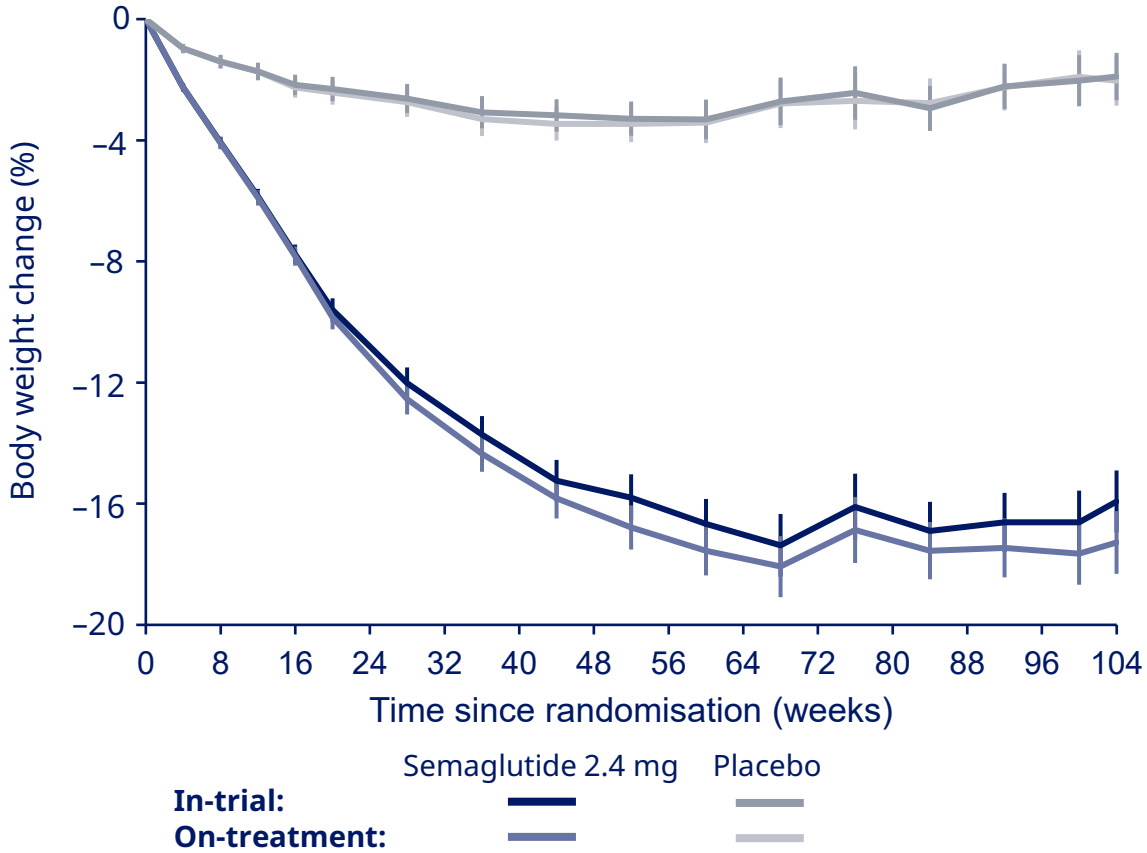
- Reduce diabetes risk[1]

Body weight change

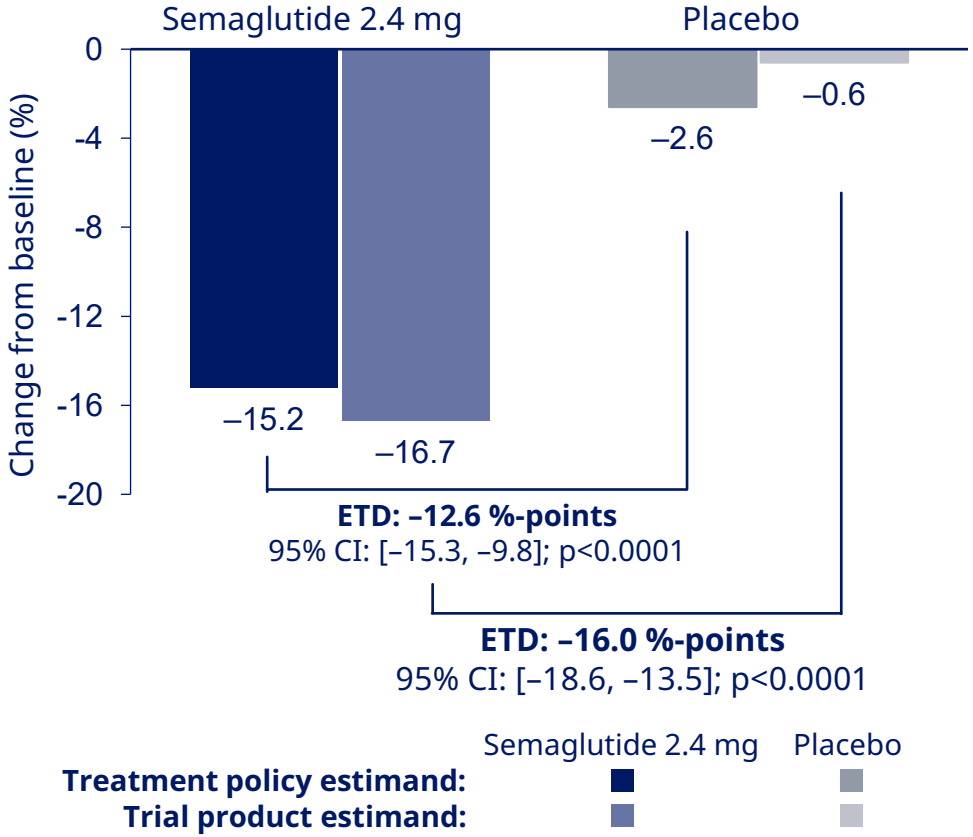
STEP 5

Observed mean change over time

(Mean at baseline: 106.0 kg)



Estimated mean change from baseline to week 104



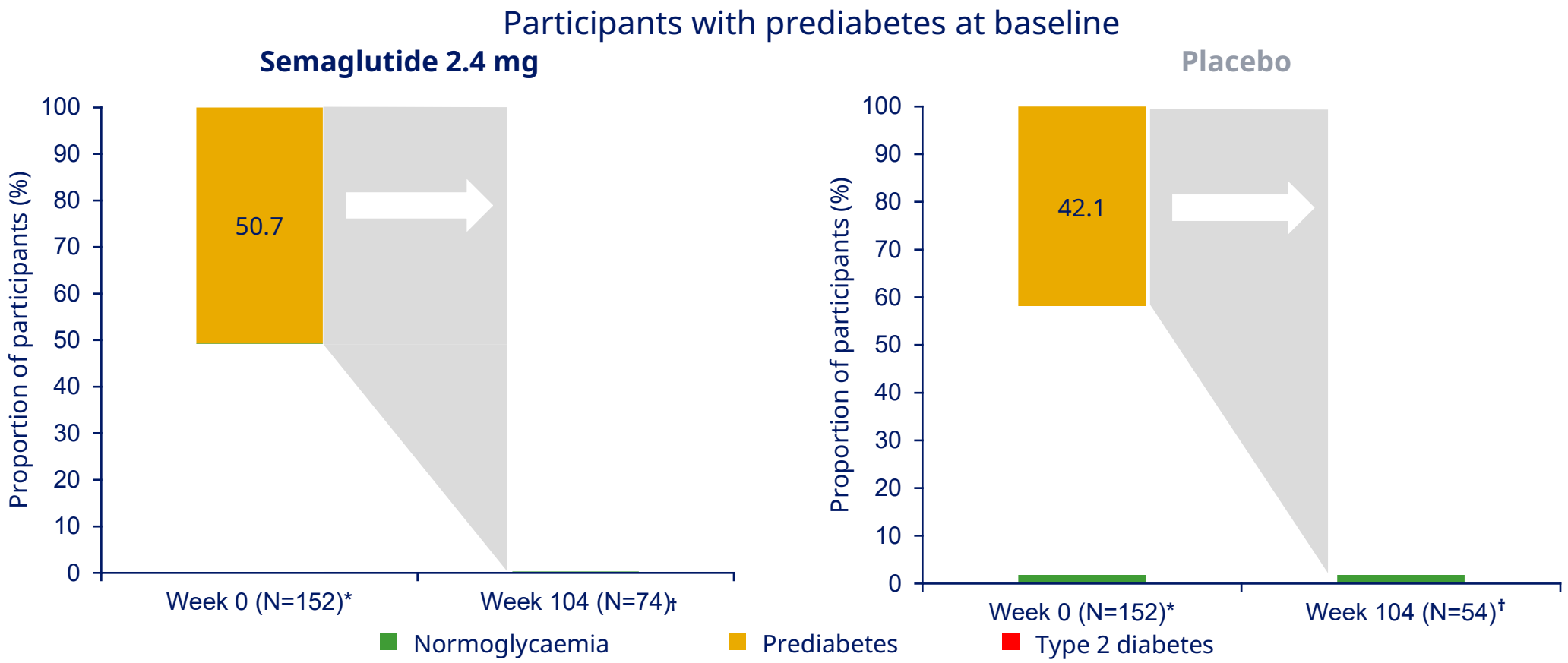
Treatment policy estimand assesses treatment effect regardless of treatment discontinuation or rescue intervention); Trial product estimand assesses treatment effect if trial product was taken as intended.

CI, confidence interval; ETD, estimated treatment difference.

Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Shift from baseline to week 104 in glycaemic status

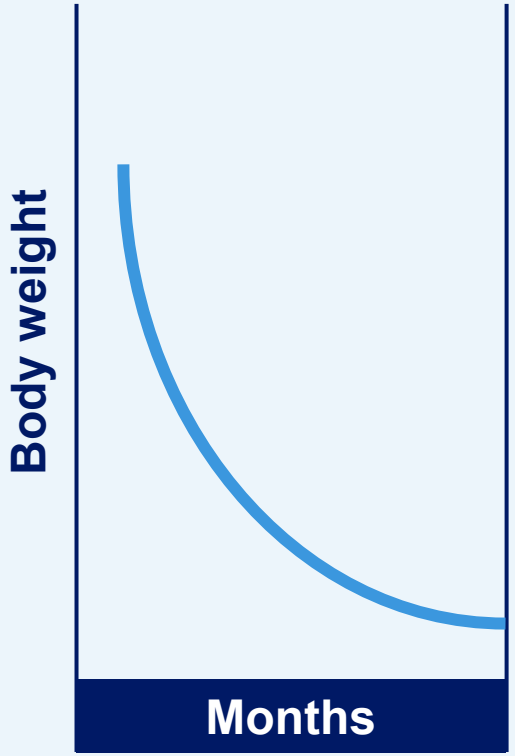
STEP 5



Data are observed data during the in-trial period (regardless of treatment discontinuation or rescue intervention). glycaemic category was evaluated by the investigator based on all available relevant information (e.g. concomitant medication, medical records, and blood glucose parameters) in accordance with American Diabetes Association definitions.
**Number of participants in overall population; †Number of participants with prediabetes at baseline and evaluable data at week 104.*
Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Goals and benefits of effective weight management

01 Achieve weight loss[1,2]

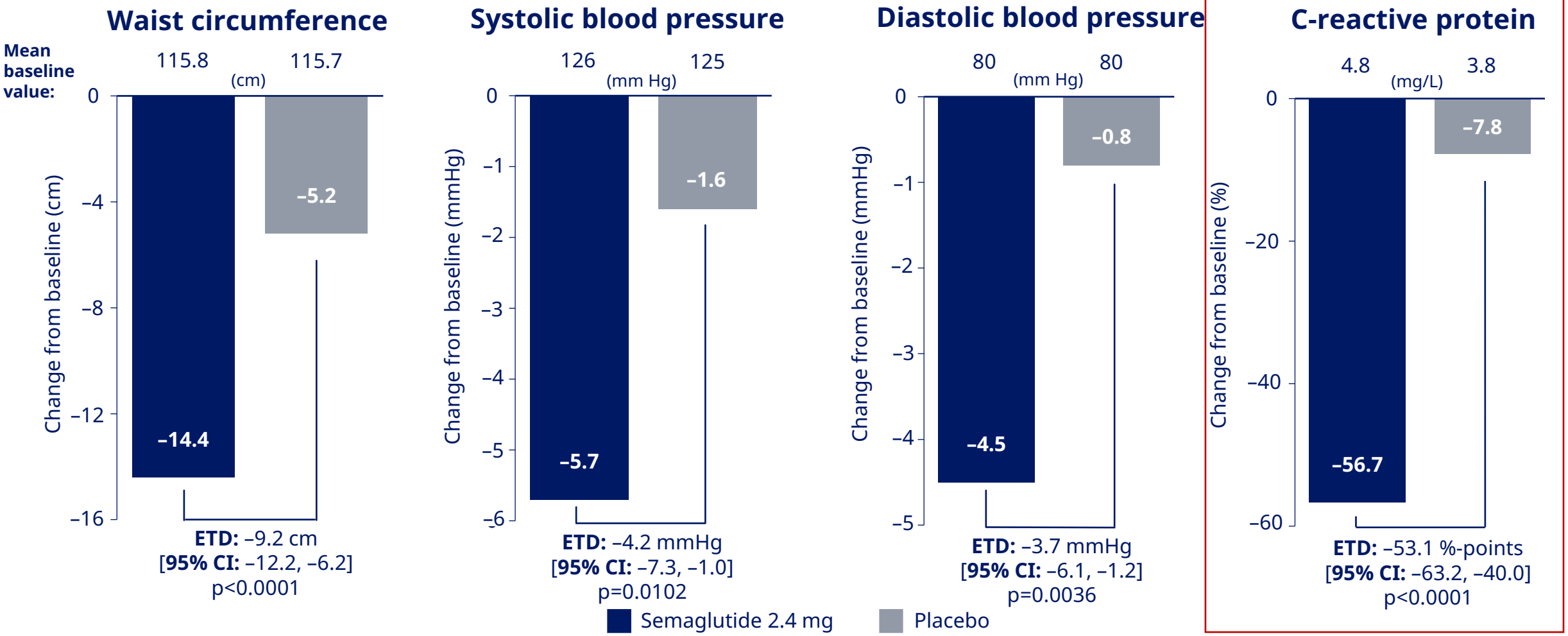


03 Provide clinically meaningful benefits[1]

- Reduce diabetes risk[1]
- Improve markers of cardiovascular risk[1]

Cardiovascular risk factors

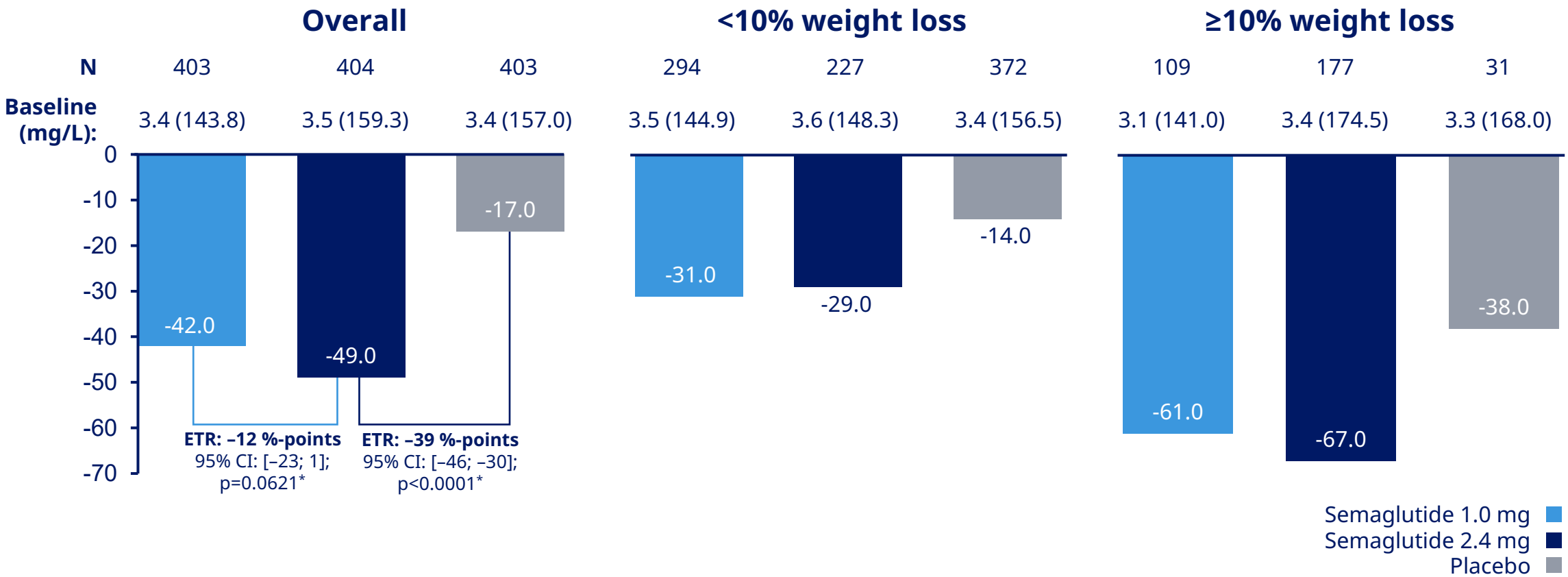
STEP 5



Change from baseline to week 104 based on the treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention). CI, confidence interval; ETD, estimated treatment difference. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Change in C-reactive protein (%)

STEP 2*: Baseline to week 68



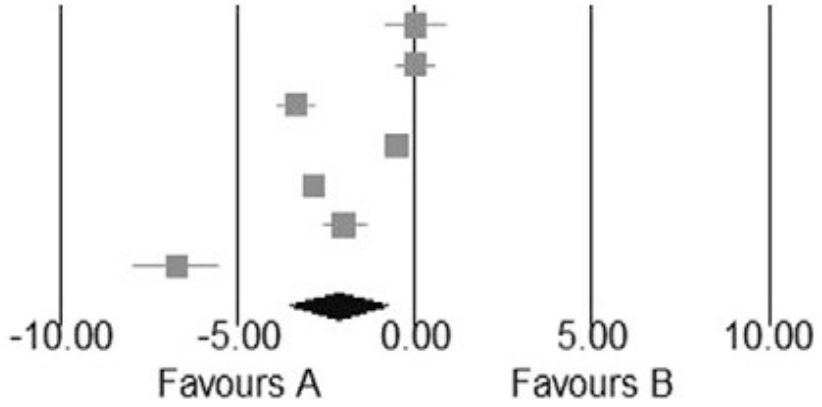
STEP 2 is a Randomised, double-blind, multicentre, double dummy, placebo-controlled trial – the trial enrolled 1210 adult T2D subjects with BMI: ≥27 kg/m2 treated with Diet and exercise alone or up to 3 OADs with a (1:1:1) randomization to placebo, semaglutide 1.0 mg, semaglutide 2.4 mg for a duration of 68 weeks.

*Results are presented for effect regardless of treatment discontinuation or use of other anti-obesity therapies. Baseline values are mean ± standard deviation. *Not adjusted for multiplicity.*
CI, confidence interval; ETD, estimated treatment difference.
Kushner et al. Presented at the American Diabetes Association (ADA) 81st Scientific Sessions virtual meeting, June 25–29, 2021.

Plot to display weighted mean difference and 95% confidence intervals for the impact of glucagon-like peptide-1 therapy on C-reactive protein.

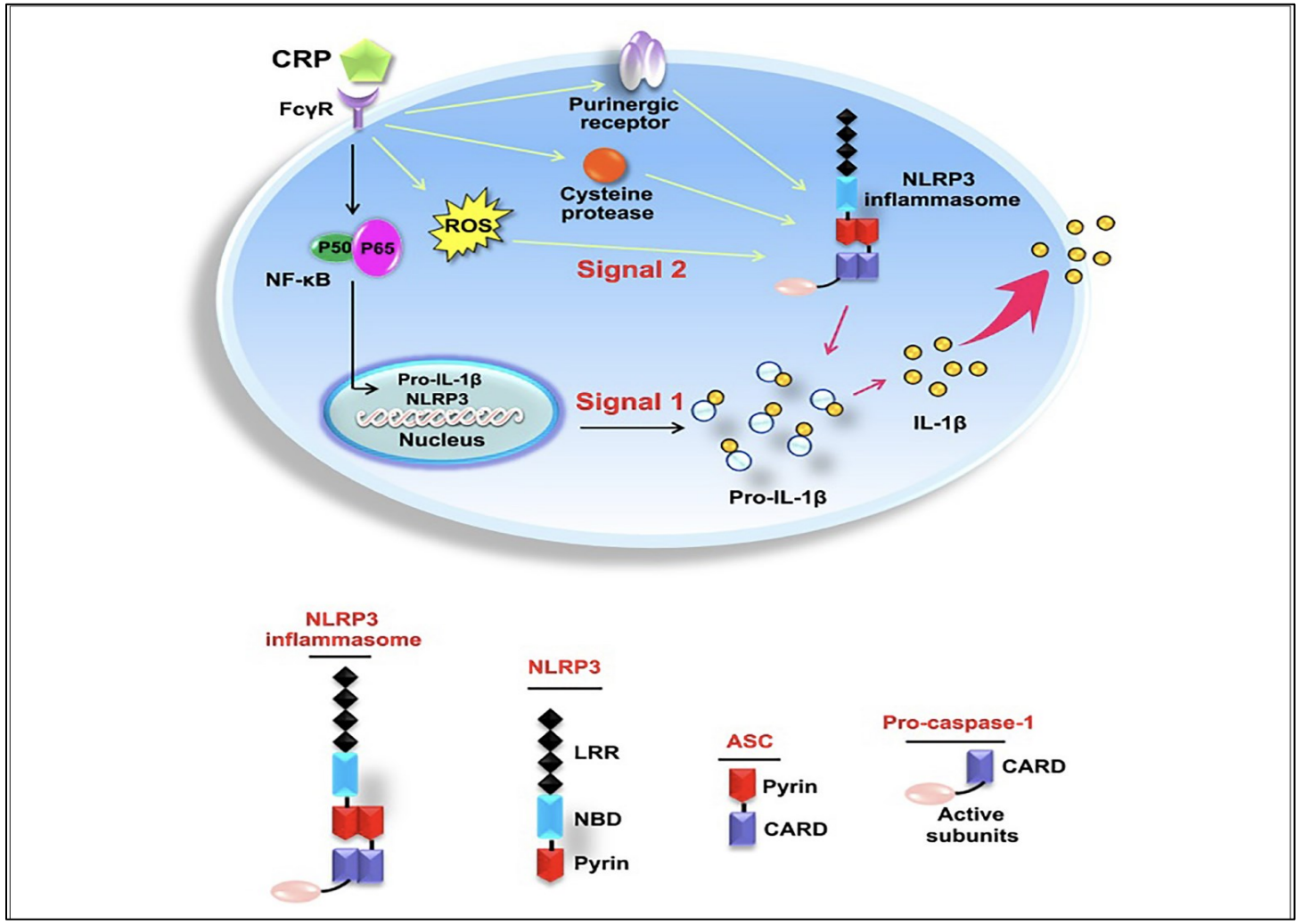
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
A. Faurschou	-0.006	0.449	0.202	-0.887	0.875	-0.013	0.990
Aaron S Kelly	0.000	0.283	0.080	-0.554	0.554	0.000	1.000
G. Derosa	-3.333	0.287	0.082	-3.896	-2.771	-11.613	0.000
Hui Fan	-0.499	0.190	0.036	-0.872	-0.126	-2.622	0.009
Jin-dan Wu	-2.837	0.591	0.349	-3.995	-1.678	-4.800	0.000
MATHIJS C. BUNCK	-2.000	0.319	0.102	-2.625	-1.375	-6.271	0.000
Ziwen Liang	-6.743	0.618	0.382	-7.954	-5.531	-10.910	0.000
	-2.148	0.696	0.484	-3.512	-0.784	-3.086	0.002

Statistics for each study



M. Mazidi et al. / Journal of Diabetes and Its Complications 31 (2017)

Schematic diagram of CRP-induced NLRP3 inflammasome activation



- CRP increased the expression of pro-IL-1b and NLRP3 via the FcgRs/NF-kB pathway.
- CRP Promots NLRP3 inflammasome activation and IL-1b maturation by upregulation of reactive oxygen species (ROS) levels, purinergic receptor signaling, and activation of cysteine proteases.
- NLRP3 inflammasome activation was shown to be involved in CRP-mediated LDL transcytosis across ECs.

Bian F, Frontiers in Pharmacology

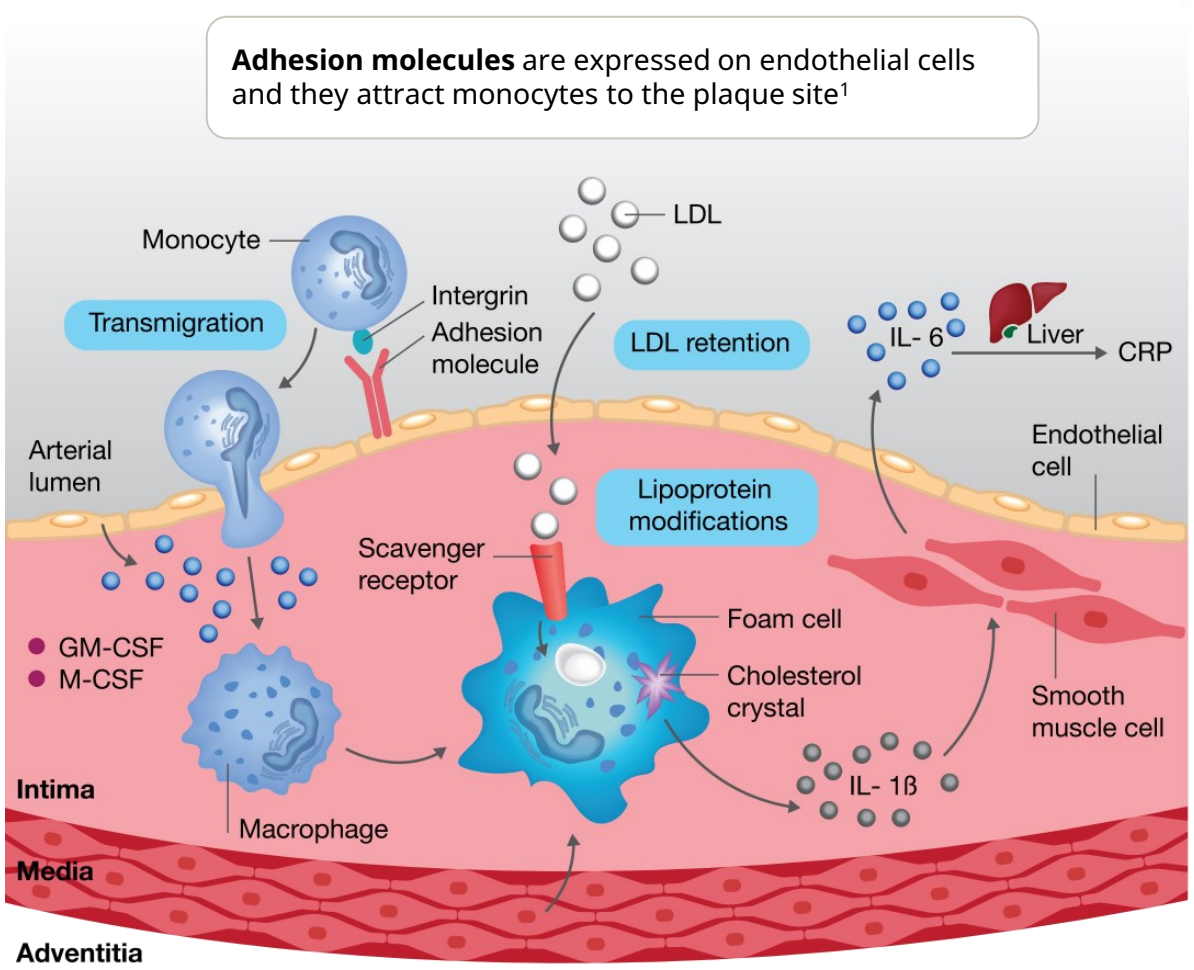
Both the innate and adaptive immune system are involved in atherosclerosis

Innate immune system

Monocytes are the most abundant inflammatory cell type in atherosclerotic plaques. They transform into macrophages within the intima[1]

Macrophages gather lipoproteins and express pro-inflammatory molecules[1]

Adhesion molecules are expressed on endothelial cells and they attract monocytes to the plaque site[1]

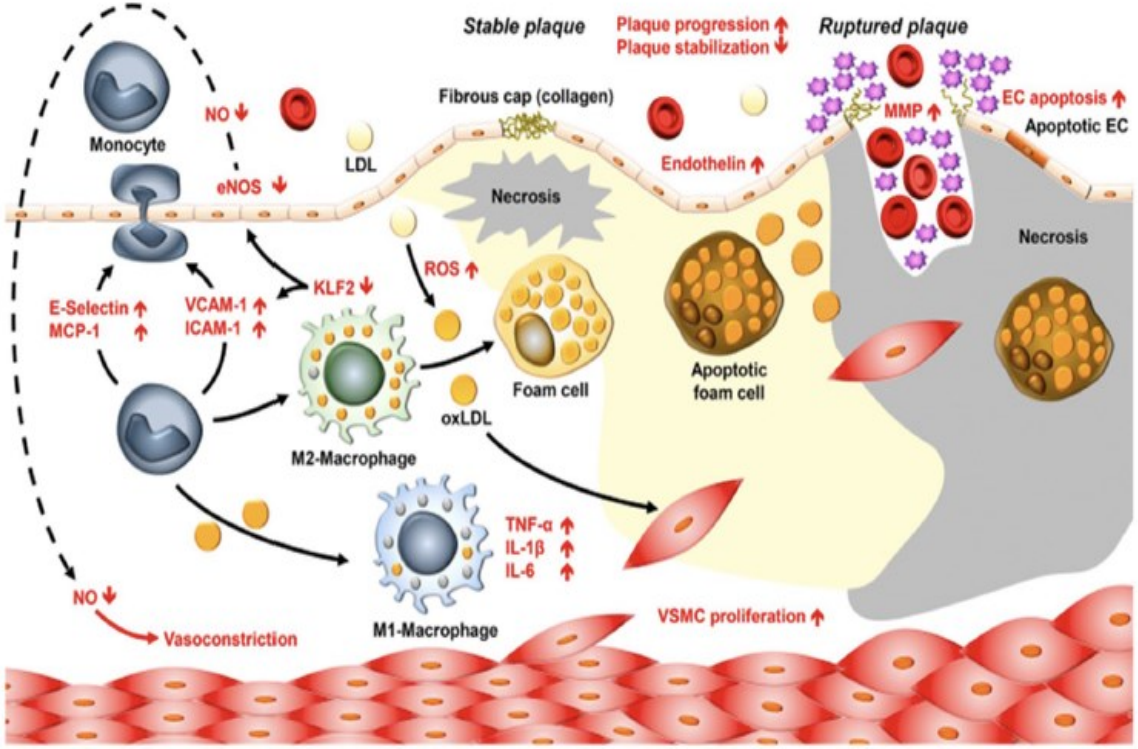


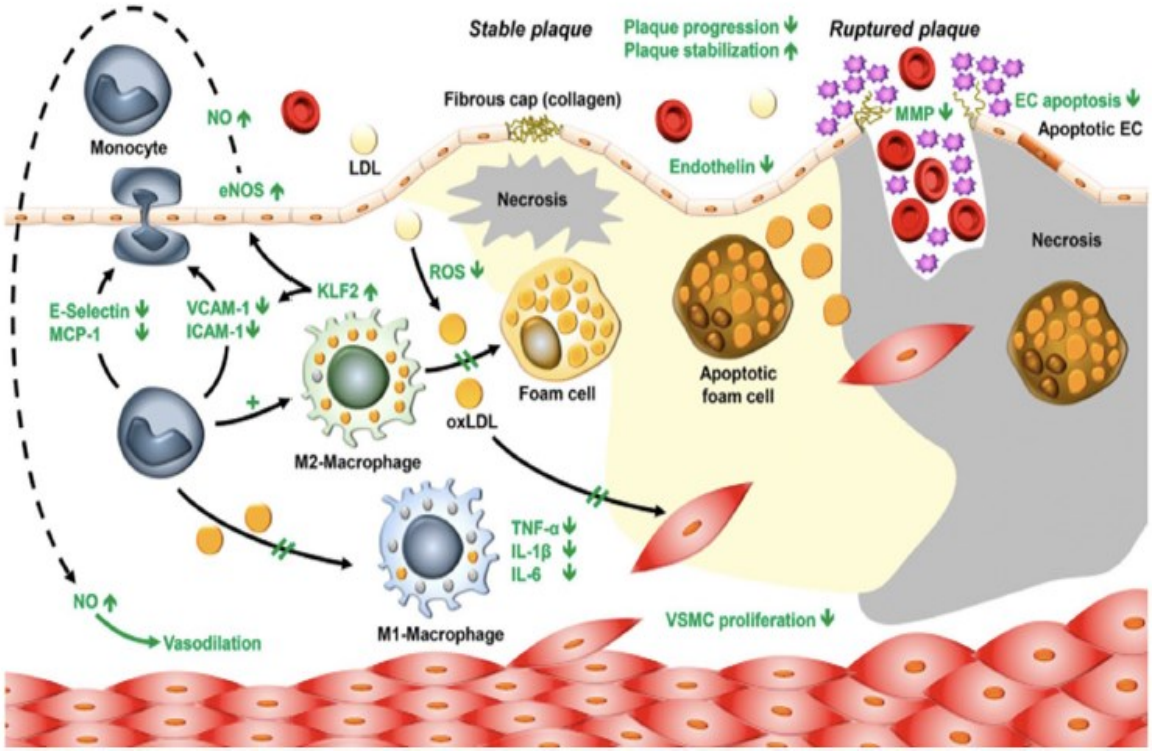
IL-6 is also a pro-inflammatory cytokine. It may lead to systemic inflammation by causing the liver to produce CRP, which is a biomarker for CV risk prediction[2]

IL-1β is a pro-inflammatory cytokine released by foam cells which has a number of different roles including promoting endothelial activation, adhesion molecule expression, LDL metabolism, VSCM proliferation, matrix degradation by MMPs and platelet activation.[3] It is activated as a result of the NLRP3 inflammasome[4]

Grebe A et al. *Circ Res* 2018;122(12):1722–1740.

The protective effects of GLP-1RA on atherosclerosis

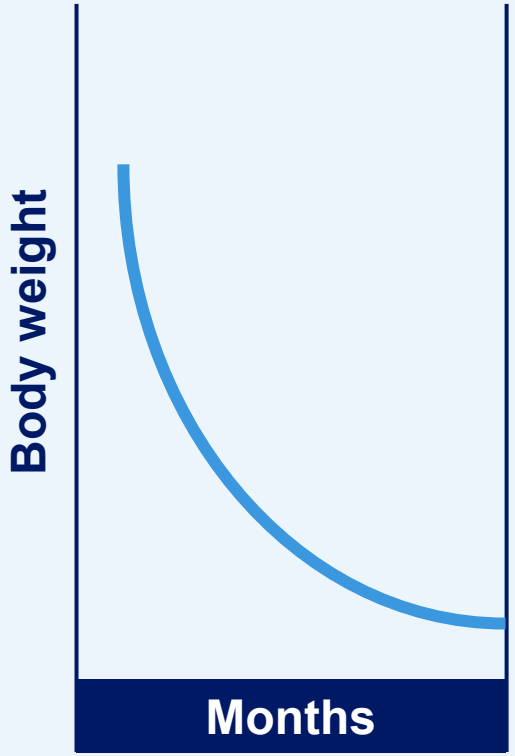




Pedrosa MR et al. Current Atherosclerosis Reports (2022)

Goals and benefits of effective weight management

01 Achieve weight loss[1,2]

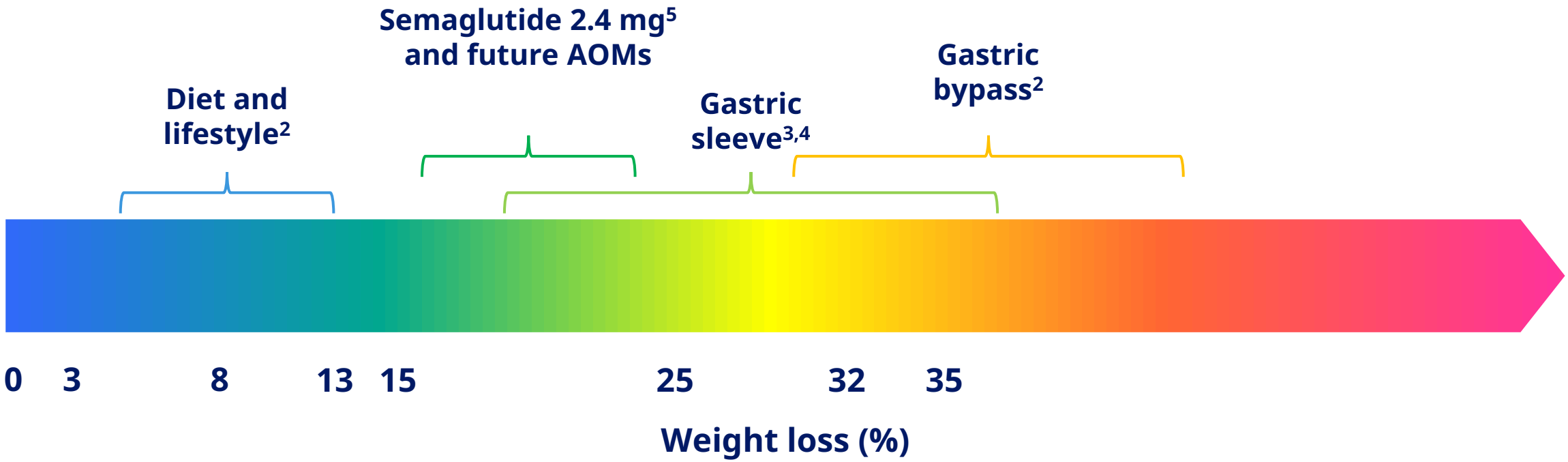


03 Provide clinically meaningful benefits[1]

- Reduce diabetes risk[1]
- Improve markers of cardiovascular risk[1]
- Reduce functional impairment[4]
- Improve quality of life[4]

Third generation AOMs are closing the gap between lifestyle modifications and bariatric surgery

Pharmacotherapy combined with lifestyle intervention can provide >15% weight loss[1]



AOMs, Anti-obesity medications;

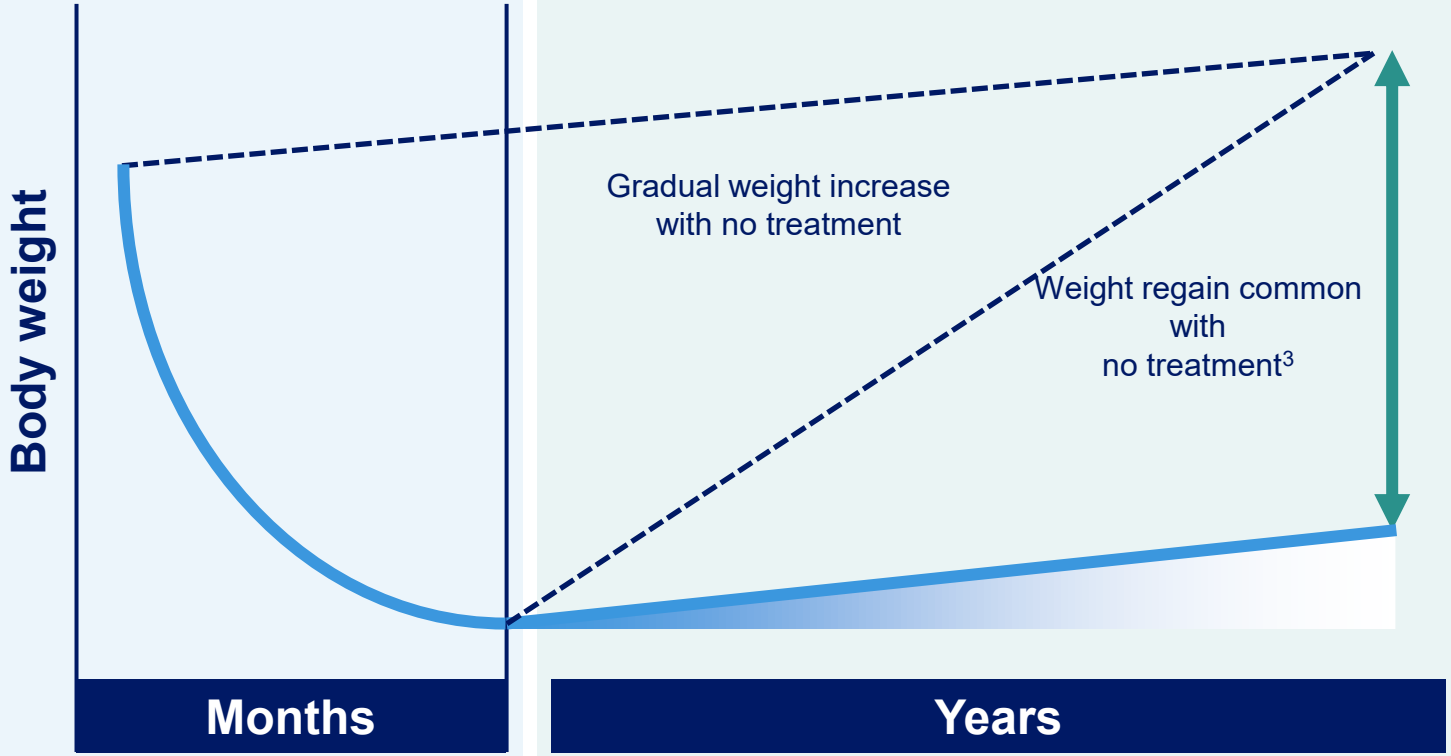
1. George Washington University School of Public Health and Health Services. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. Accessed September 2021;
2. Jensen et al. Circulation 2014;129:S102–38; 3. Salminen et al. JAMA 2018;319:241–54; 4. Berry et al. Obes Surg 2018;28:649–55; 5. Wilding et al. N Engl J Med 2021;384:989−1002

Can we maintain Weight Loss effectively ?

Goals and benefits of effective weight management

01 Achieve weight loss[1,2]

02 Maintain weight loss and prevent regain[1,2]



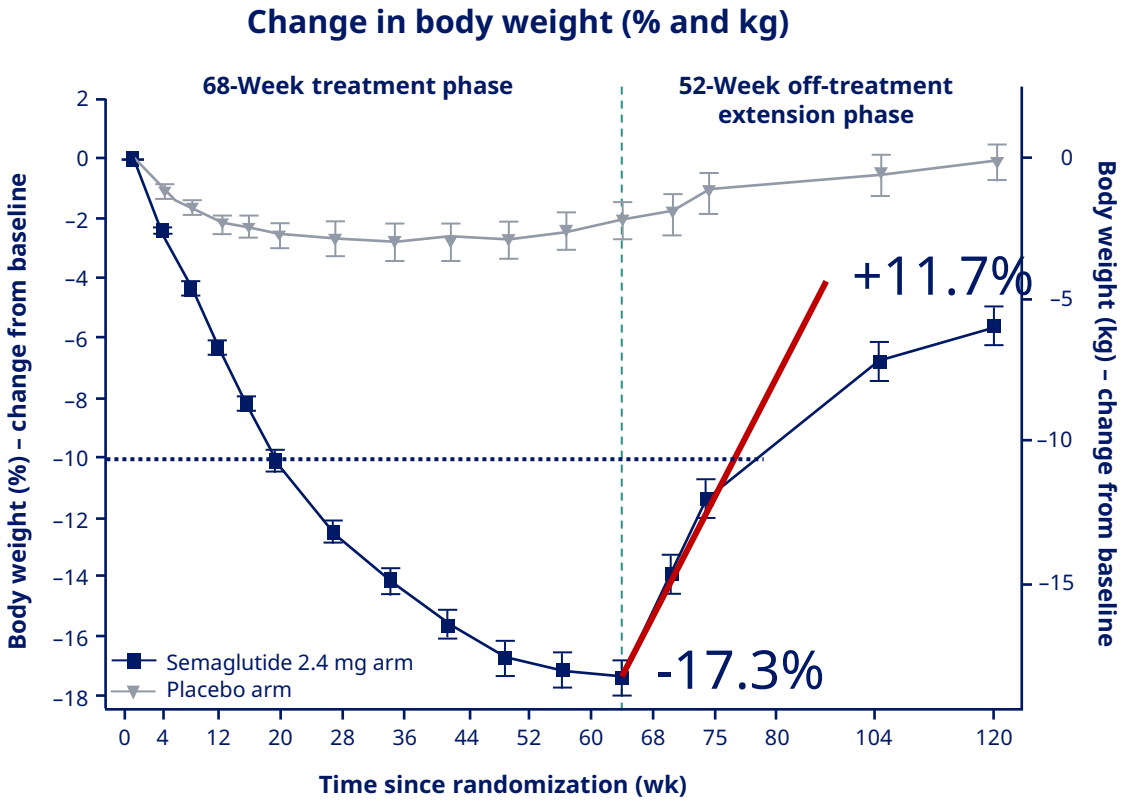
03 Provide clinically meaningful benefits[1]

- Reduce diabetes risk[1]
- Improve markers of cardiovascular risk[1]
- Reduce functional impairment[4]
- Improve quality of life[4]

1. Wadden et al. Circulation 2012;125:1157–70; 2. Jensen et al. J Am Coll Cardiol 2014;63(25 Pt B):2985–3023; 3. Purcell et al. Lancet Diabetes Endocrinol 2014;2:954–62; 4. Villareal et al. Am J Clin Nutr 2005;82:923–34.

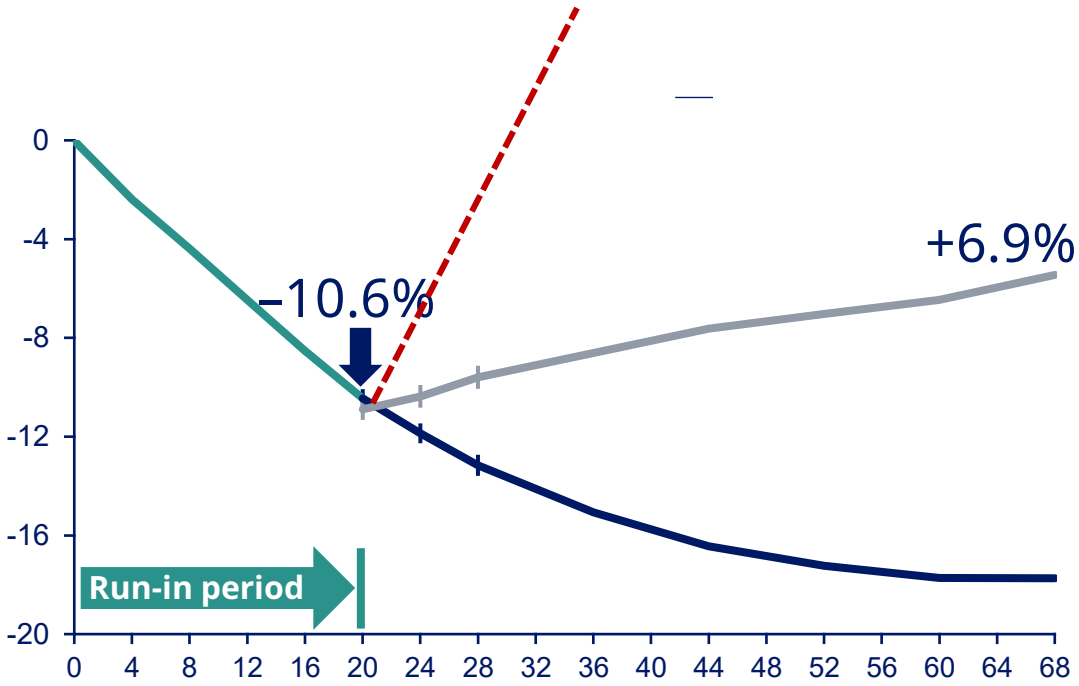
Change in body weight

STEP 1 extension Vs. STEP 4



Semaglutide 2.4 mg arm	228	226	228	228	228	228	228	228	227	228	209	174	171	197
Placebo arm	99	99	99	98	99	99	99	99	99	99	93	79	80	93

STEP 4

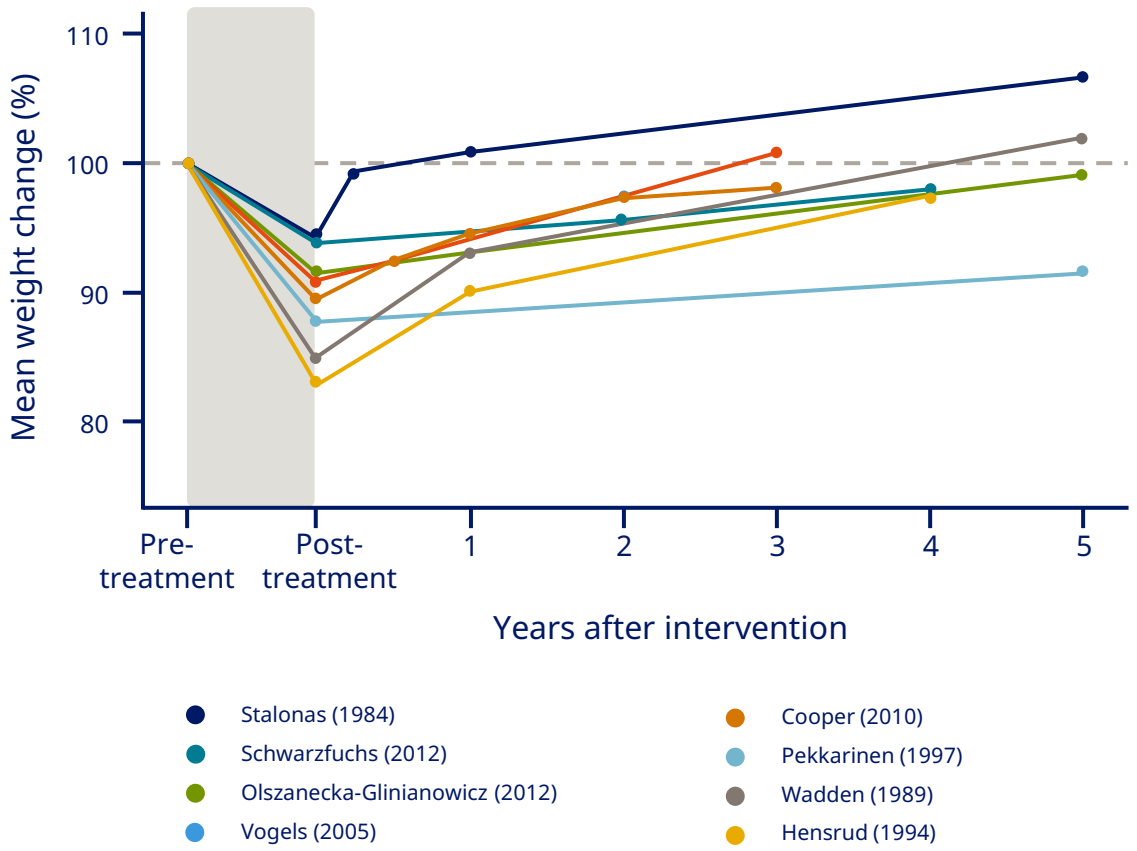


Wilding et al. Diabetes Obes Metab. 2022 Apr 19. doi: 10.1111/dom.14725. Online ahead of print

*This is an indirect trial comparison

Long-term weight loss is challenging

Maintenance of weight loss



Metabolic adaptation following weight loss

Weight loss

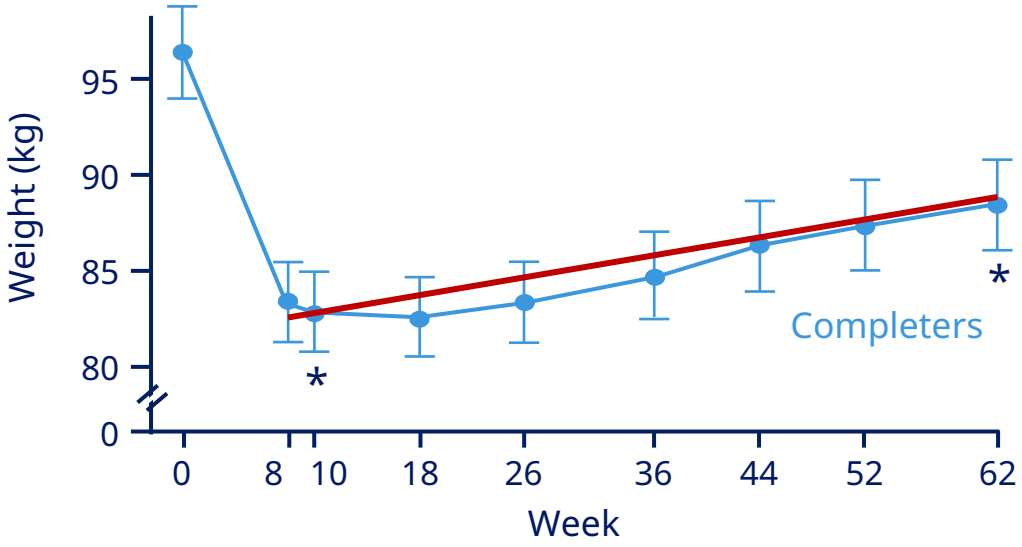
Adaptations that resist weight loss:

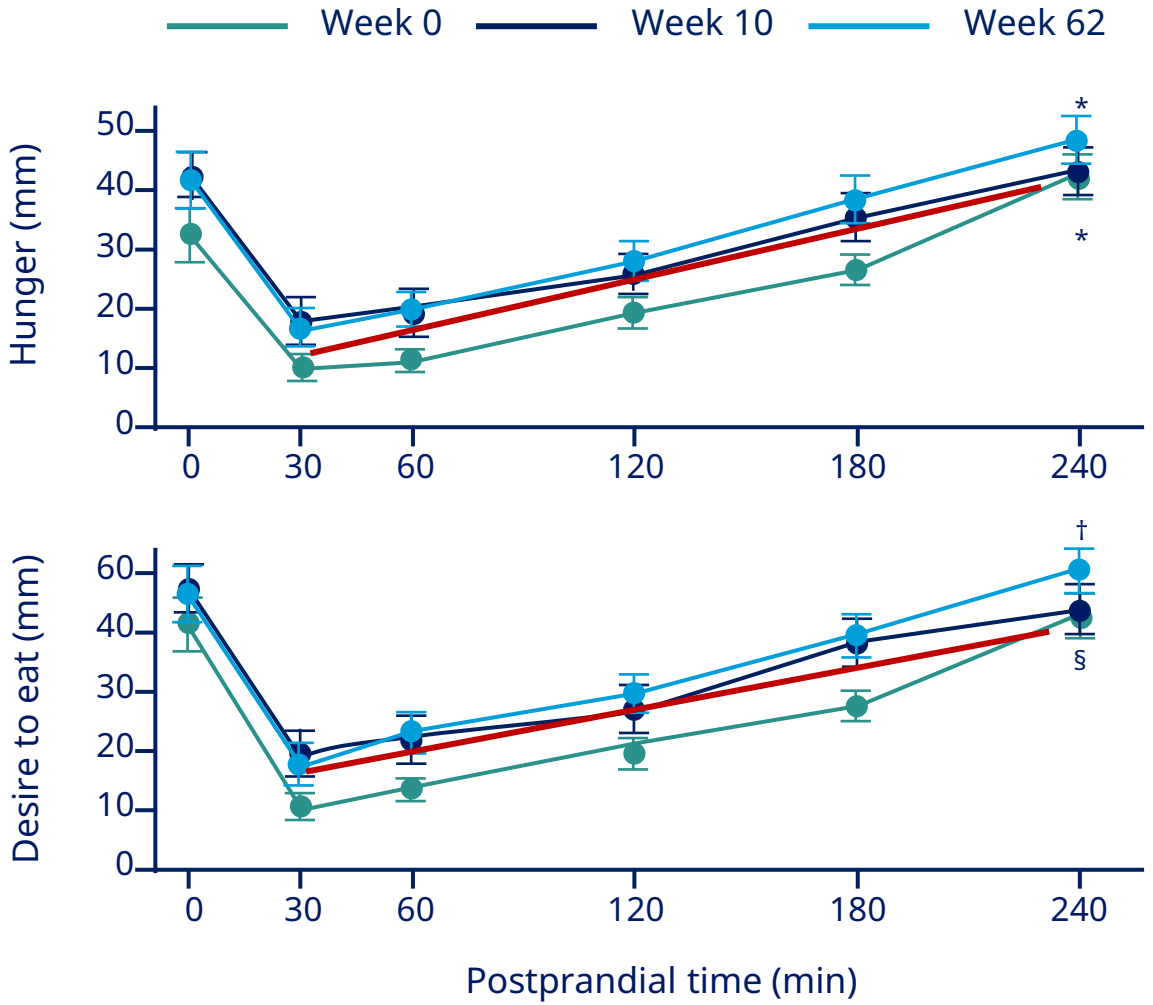
- **Hormone levels**
  ↓ satiety hormones
  ↑ hunger hormones
- **Metabolism**
  ↓ energy expenditure

Weight regain

Hunger increases in response to weight loss

- 50 individuals with overweight/obesity lost weight on a 10-week very low energy diet
- Appetite was measured using VAS scores at 0, 10 and 62 weeks

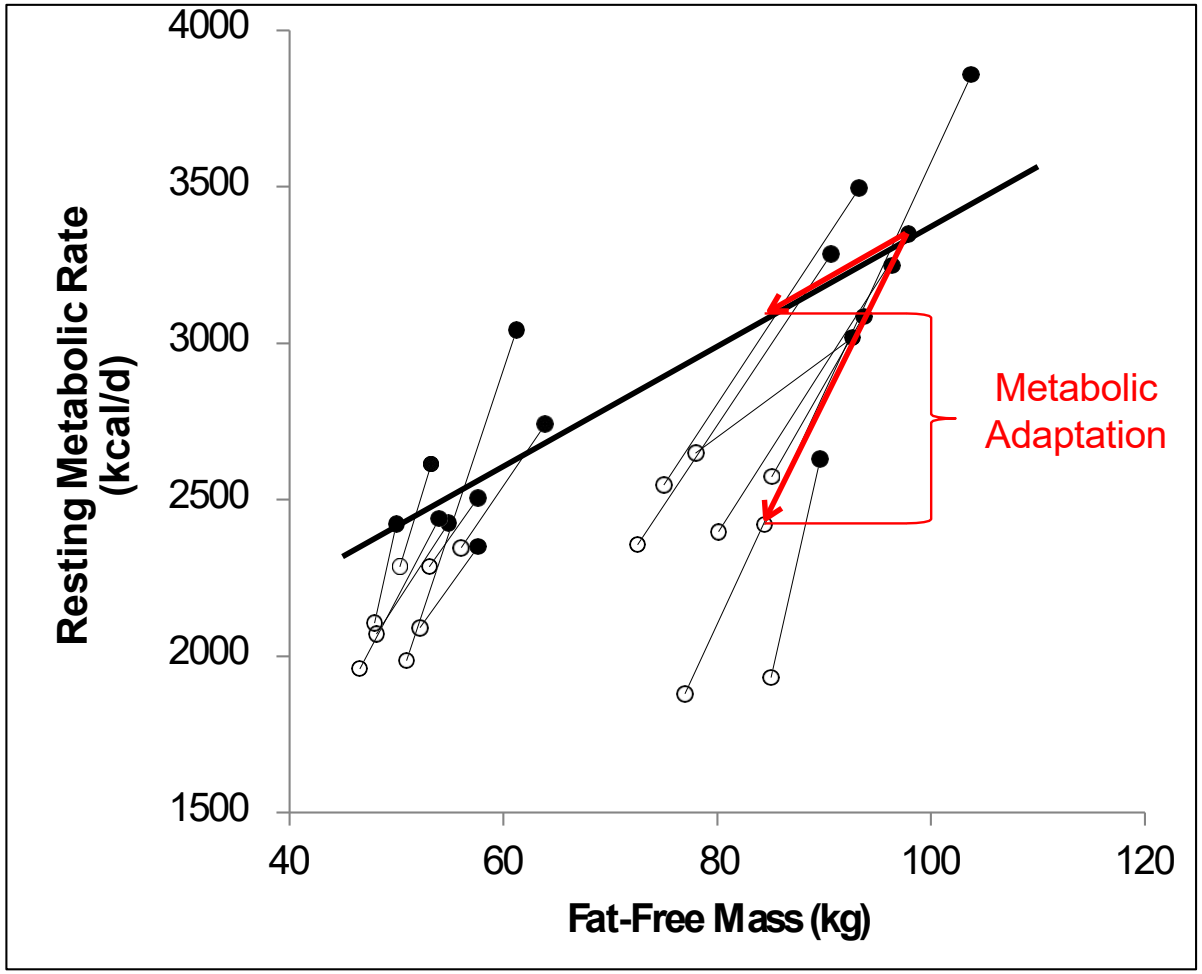




**p<0.001, §p=0.008, †p=0.09 vs mean at baseline (week 0).*
ITT, intention to treat; VAS, visual analogue scale.
Sumithran P et al. N Engl J Med 2011;365:1597–604.

Energy expenditure is reduced with reduced caloric intake and body weight loss

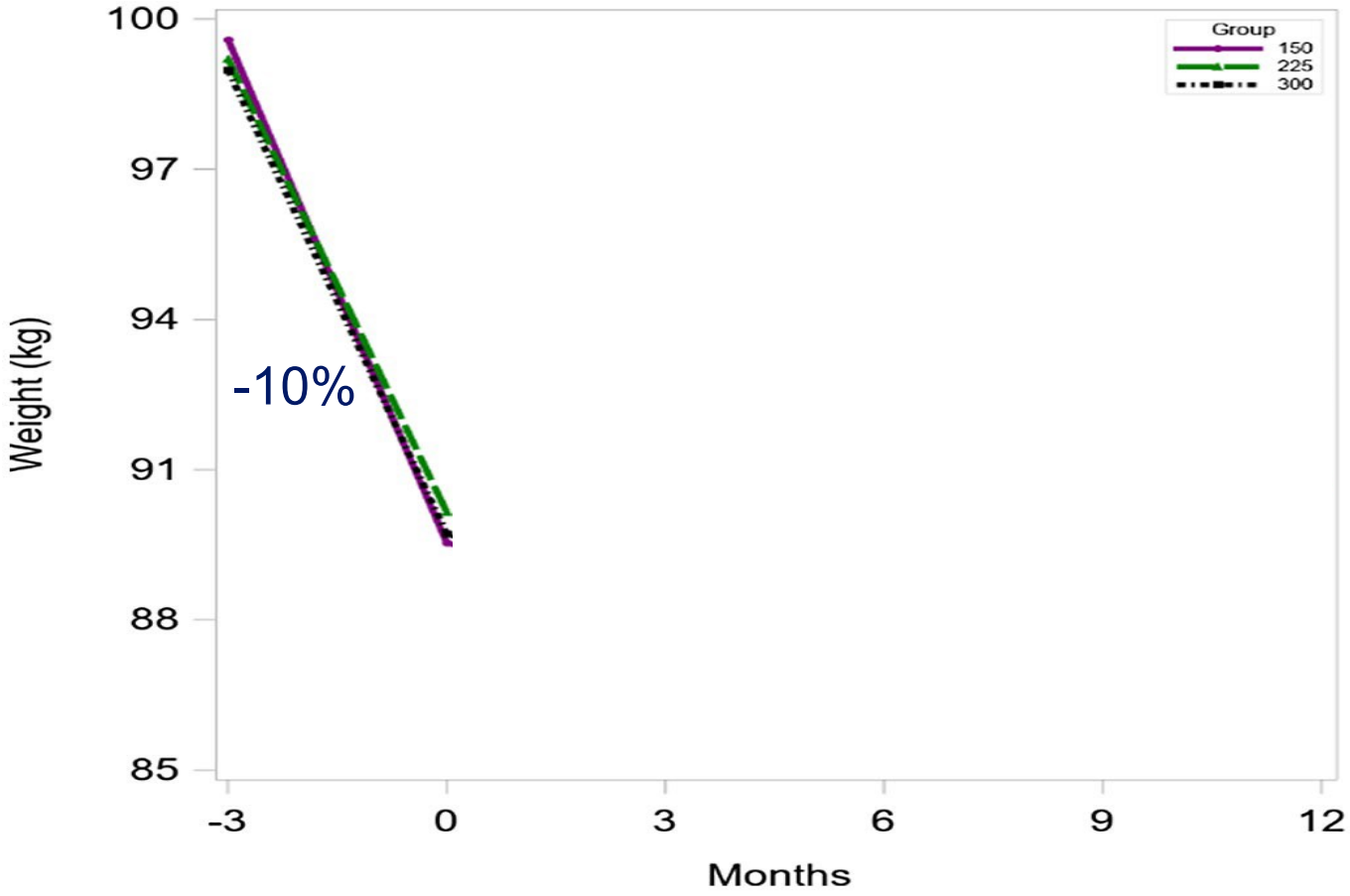
- Reduction in caloric intake and reduced body mass results in reduced energy expenditure
- Metabolic adaptation might counter interventions aimed at reducing body weight and limit efficacy and potentially durability



DL Johannsen et al. JCEM 97(7):2489–2496 (2012)
Ravussin, 2022 PBRC Symposium

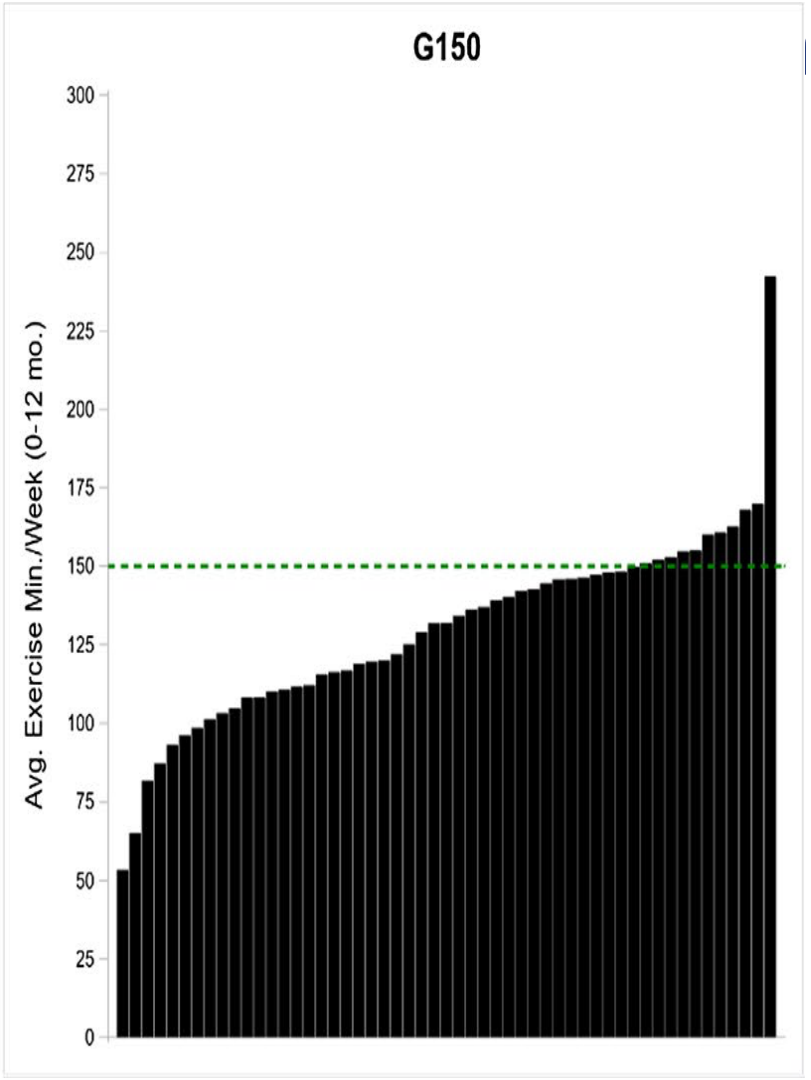
Body weight at −3 to 12 months by randomized group. 150 min/wk;, 225 min/wk; 300 min/wk.

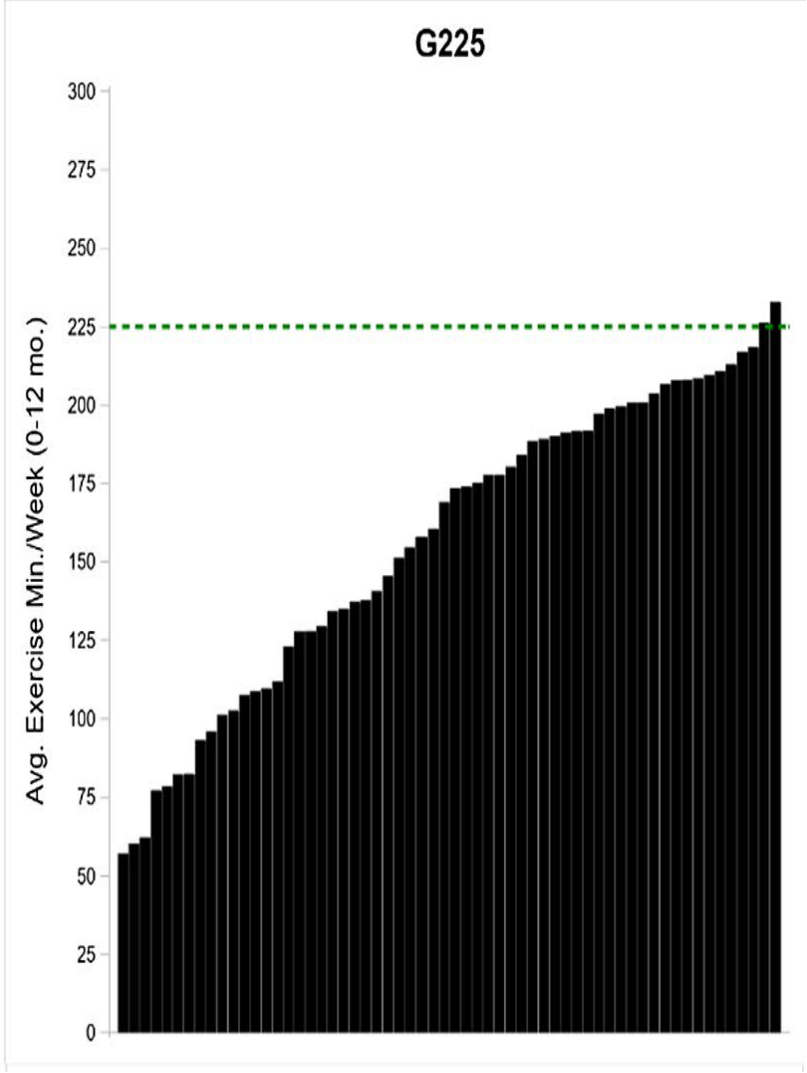
- **Energy intake** was reduced to 1,200 to 1,500 kcal/d for women and 1,500 to 1,800 kcal/d for men.
- Participants attended weekly 60-minute **in-person sessions**.
- **Exercise** progressed from 10 min/d and 5 d/wk at 65% of the age-predicted maximal heart rate (HRmax = 220 − age in years) to the goal of 20 min/d and 5 d/wk at 70% of the HRmax

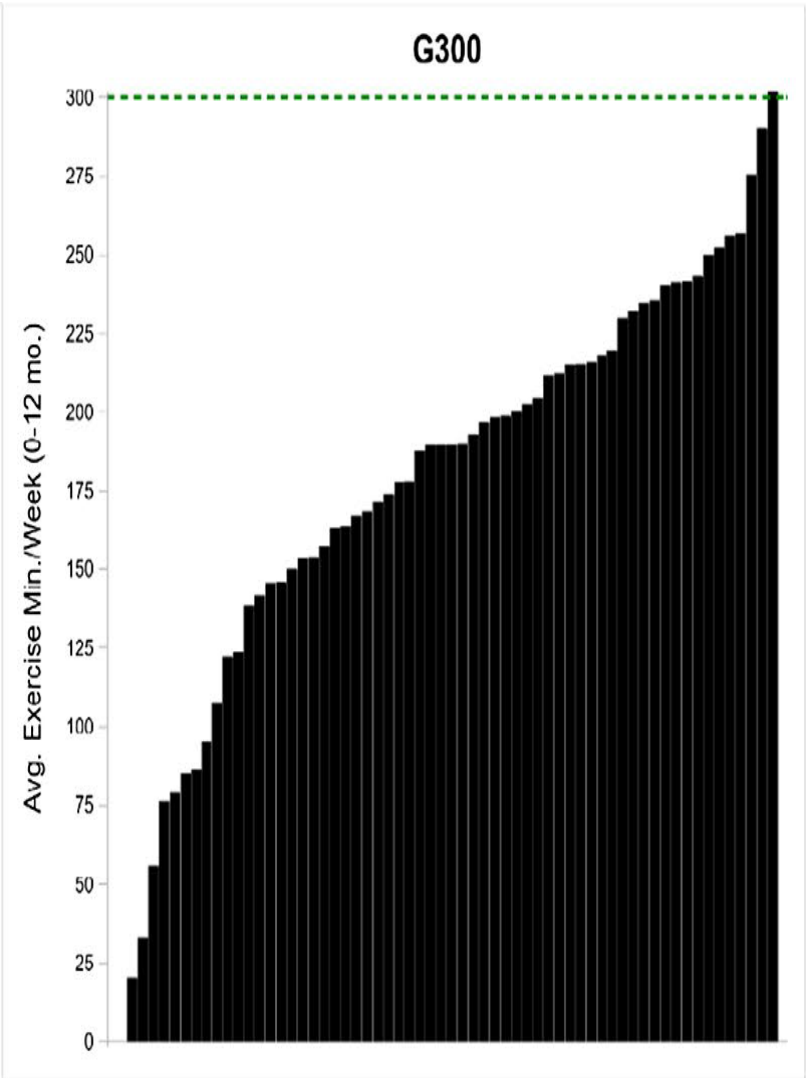


Washburn RA, Obesity 2021

Individual average weekly minutes of exercise across the 12-month

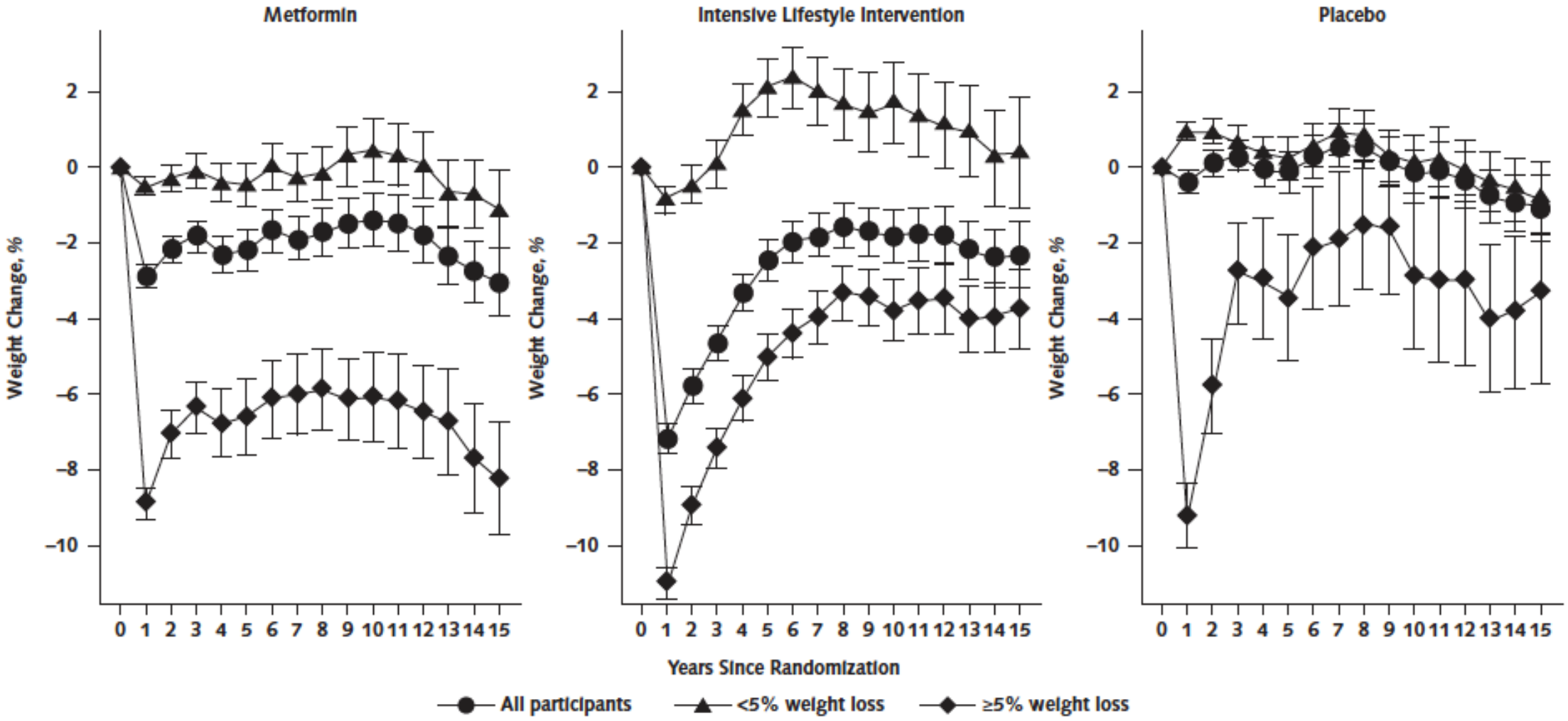






Washburn RA, Obesity 2021

Wight Loss maintenances

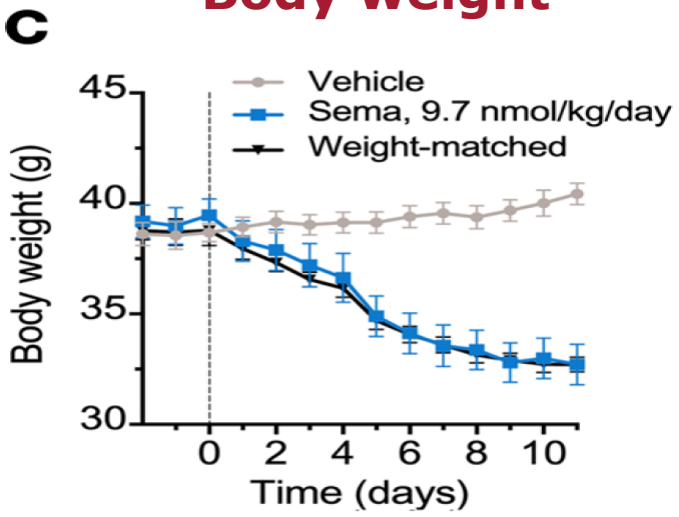


Apolzan JW, Annals of Internal Medicine, 2019

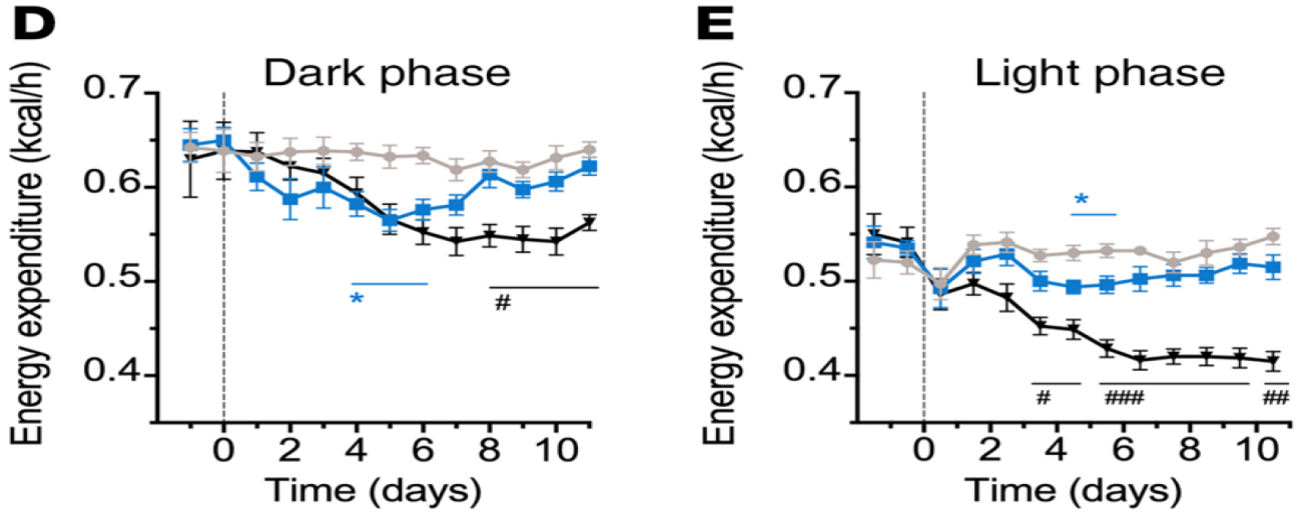
Semaglutide-induced weight loss is associated with blunting of metabolic adaptation

- Vehicle (placebo)
- Semaglutide, 9.7 nmol/kg/day
- Calorie restricted, weight-matched to semaglutide group

Body weight



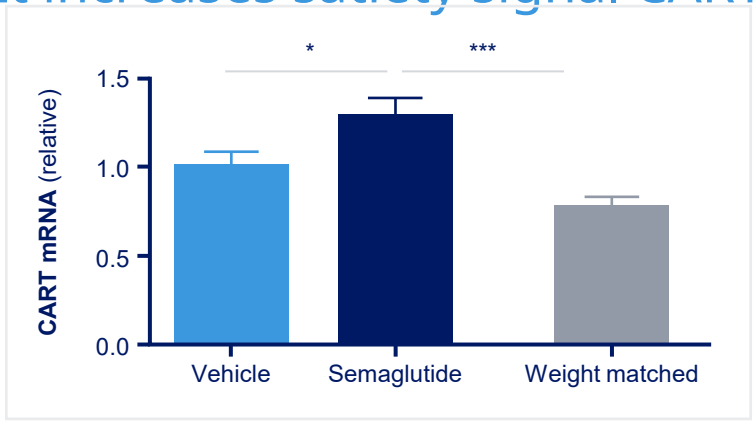
Energy expenditure

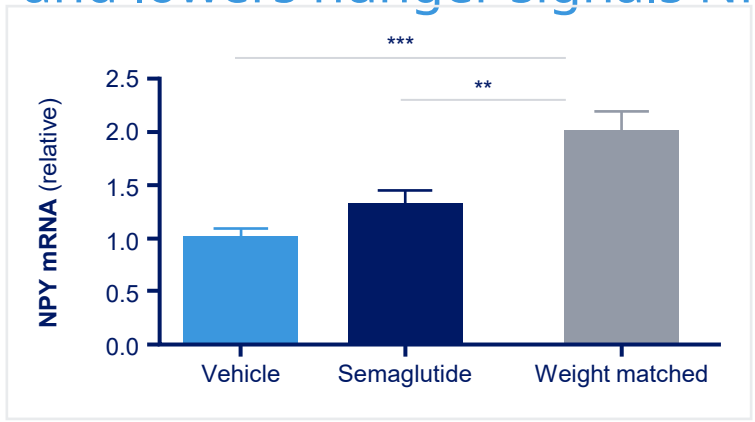


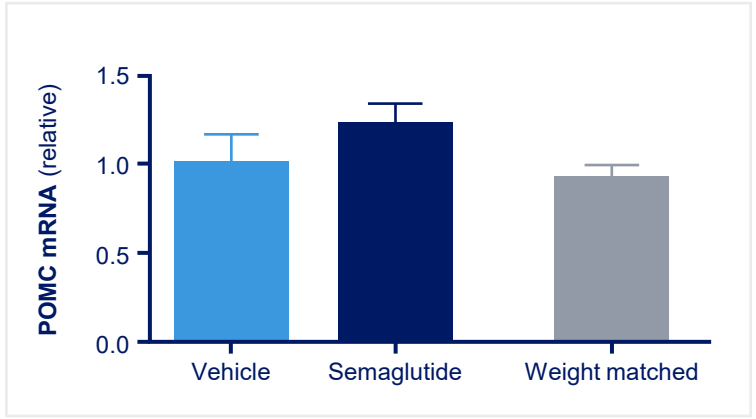
Gavery S *et al*., *JCI Insight* 2020; 5:e133429; doi.org/10.1172/jci.insight.133429. Used with permission.

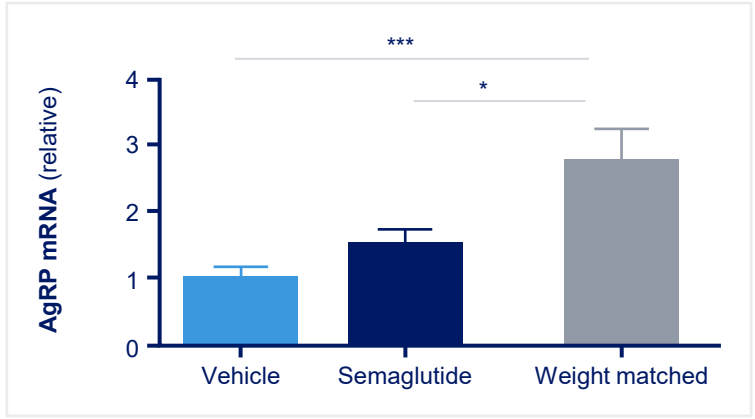
Semaglutide acts on hypothalamic arcuate nucleus

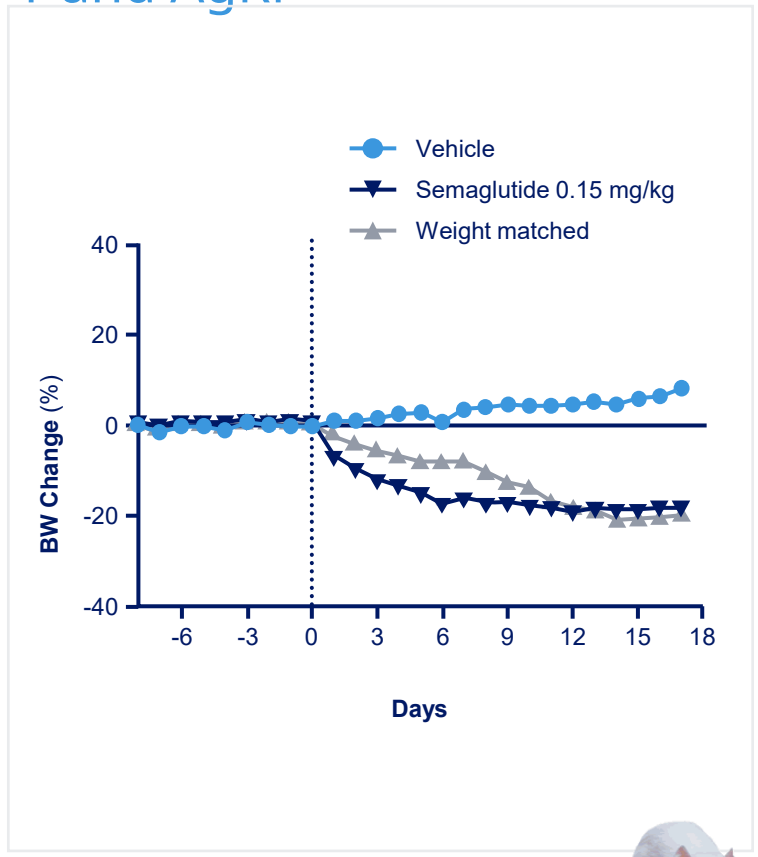
It increases satiety signal CART and lowers hunger signals NPY and AgRP







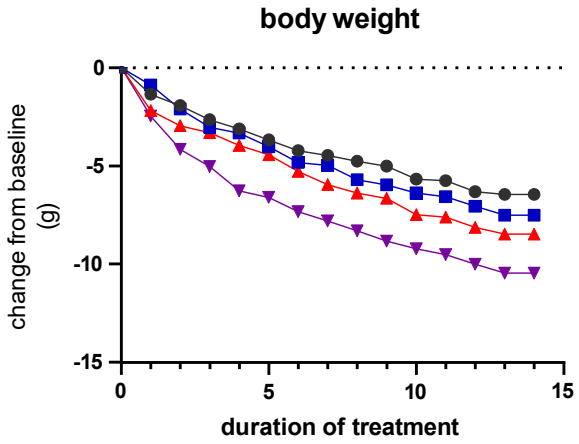




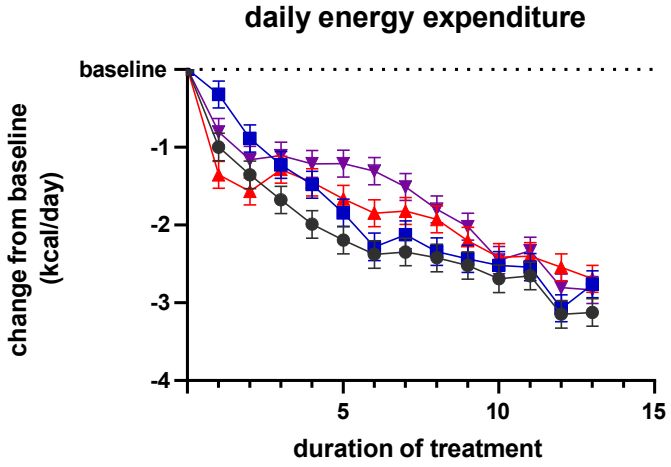
Adapted from Gabery S et al. JCI Insight 2020;5:e133429.

GIPR agonism synergistically regulates energy expenditure with GLP-1R agonism during caloric restriction

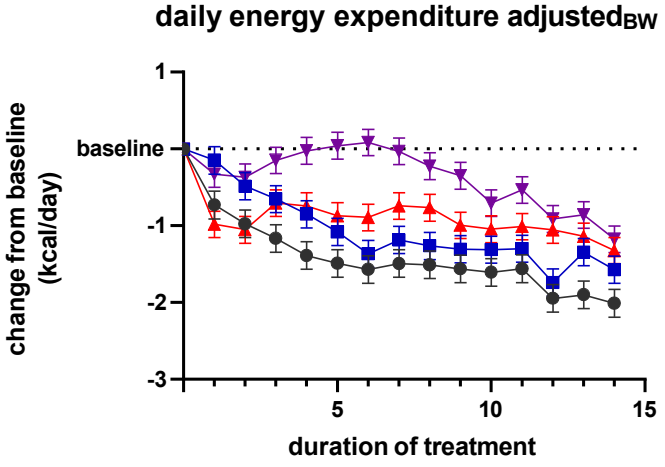
GIP+GLP-1 reduces body weight beyond GLP-1 alone



GIP+GLP-1 maintains energy expenditure despite reduced caloric intake/body weight



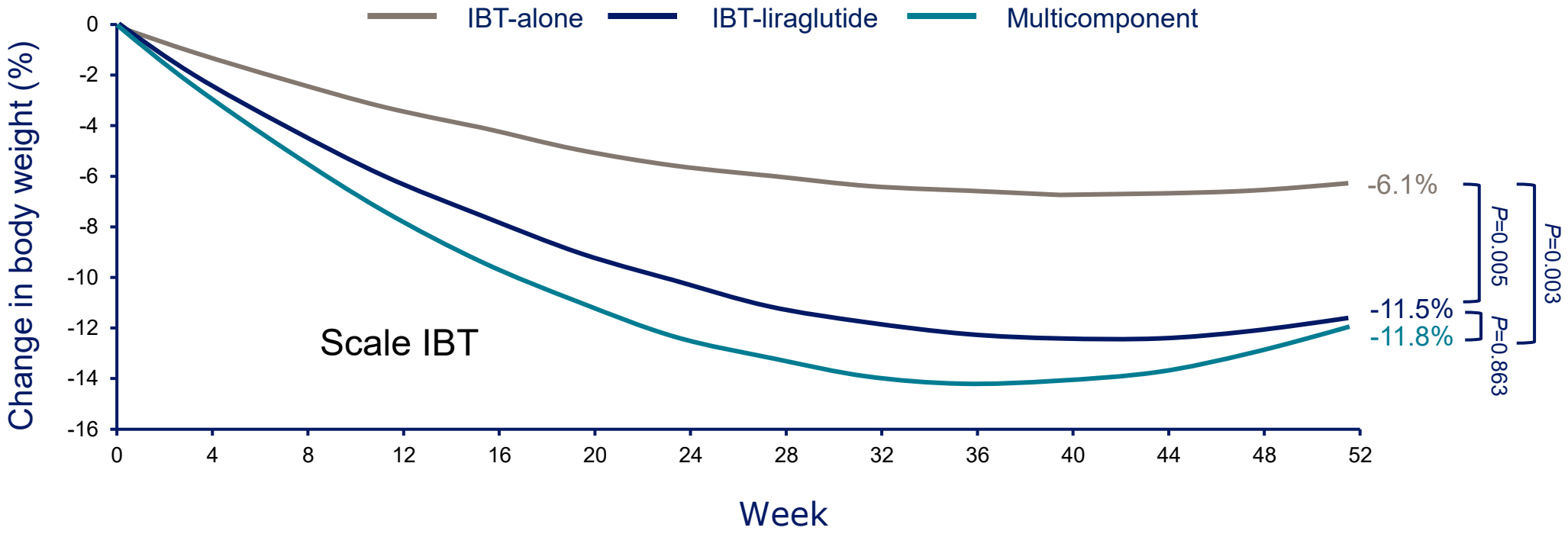
GIP+GLP-1 attenuates metabolic adaptation



Notion 3 : Semaglutide-induced weight loss is associated with blunting of metabolic adaptation and Hunger in Animal Study.

How long Can we maintain Weight Loss effectively ?

SCALE IBT



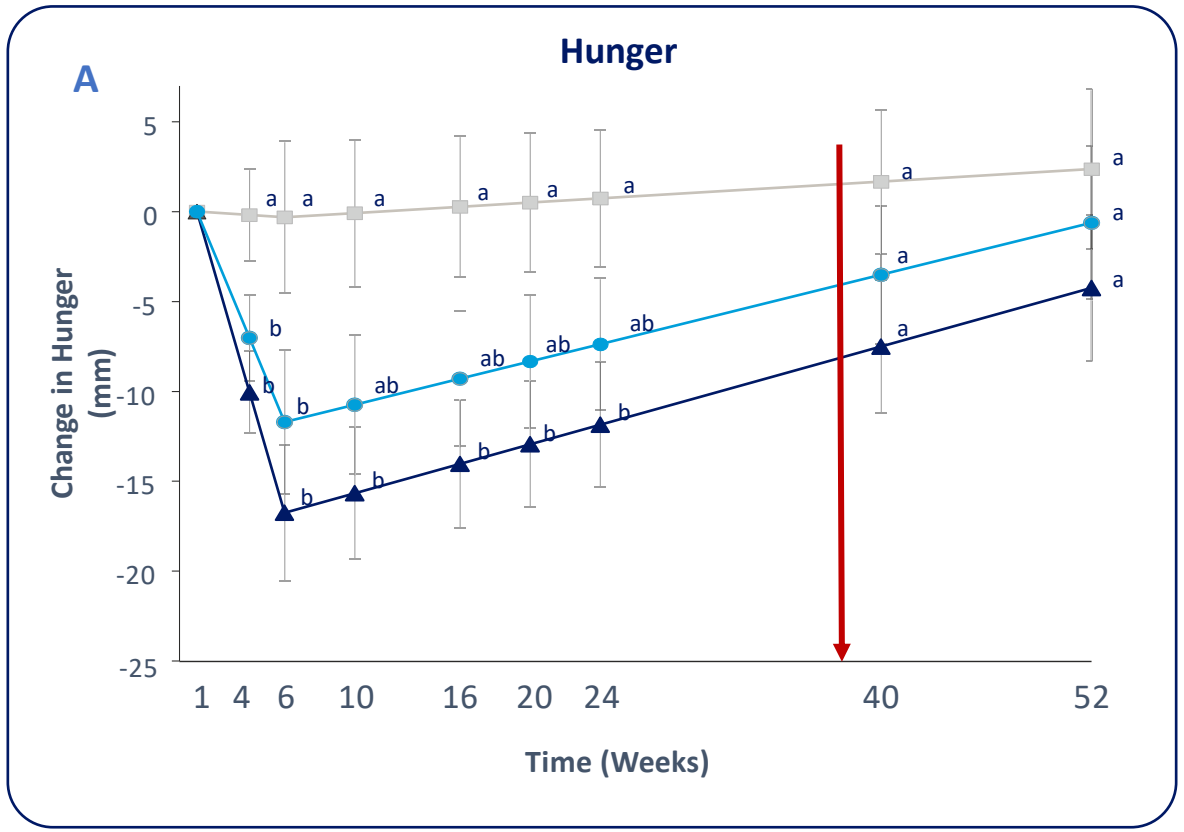
IBT (IBT-alone), providing 21 counselling visits; IBT combined with liraglutide (IBT-liraglutide); or IBT-liraglutide combined for 12 weeks with a 1,000- to 1,200-kcal/d meal-replacement diet (Multicomponent).

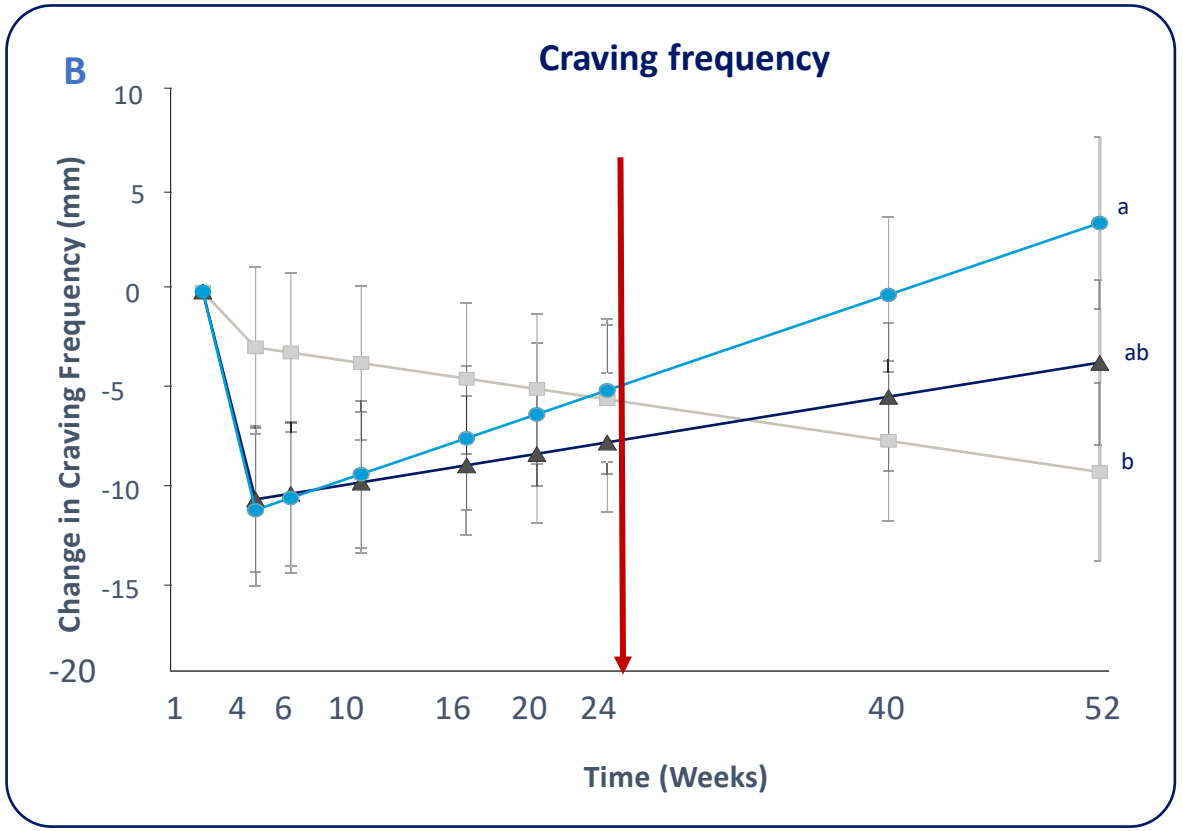
Data are estimated mean percentage reduction in the ITT population. ITT, intention to treat

Wadden, T.A., et al., Obesity (Silver Spring), 2019; 27(1): 75-86.

SCALE IBT

Multi-component | IBT-liraglutide | IBT- alone

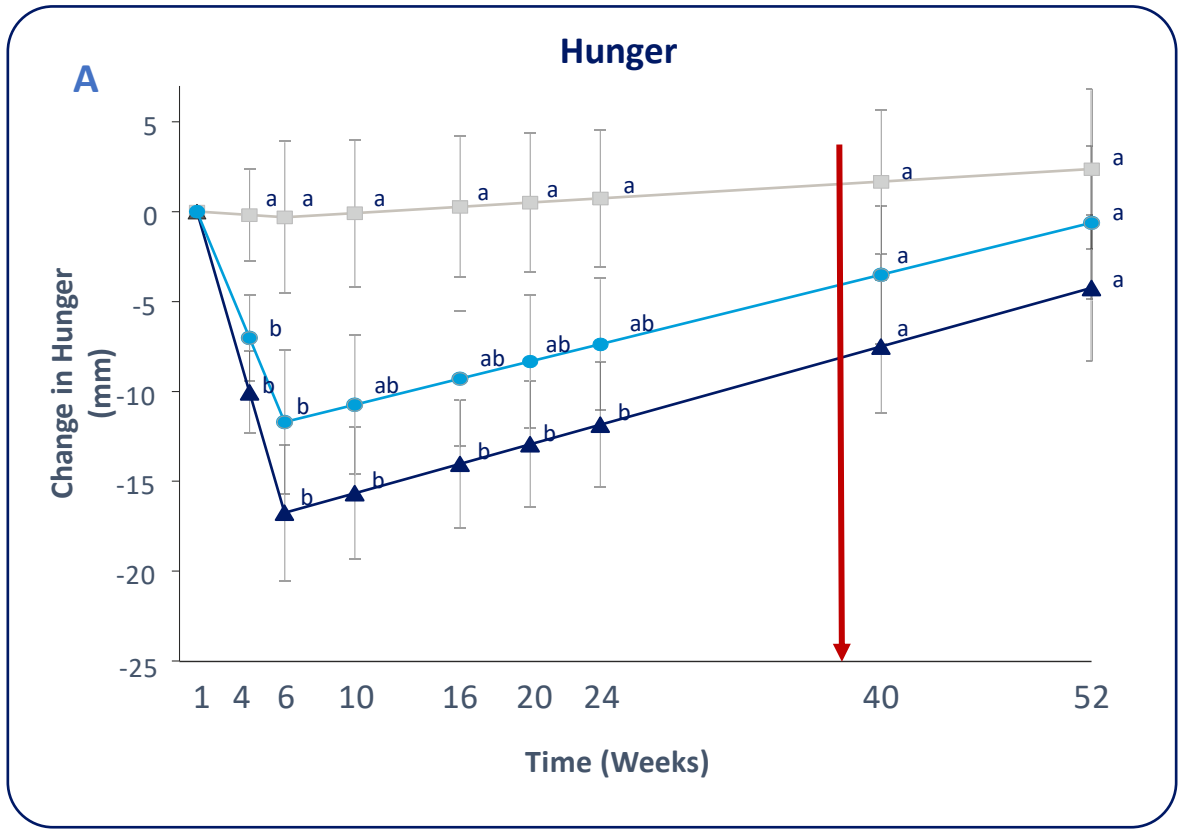


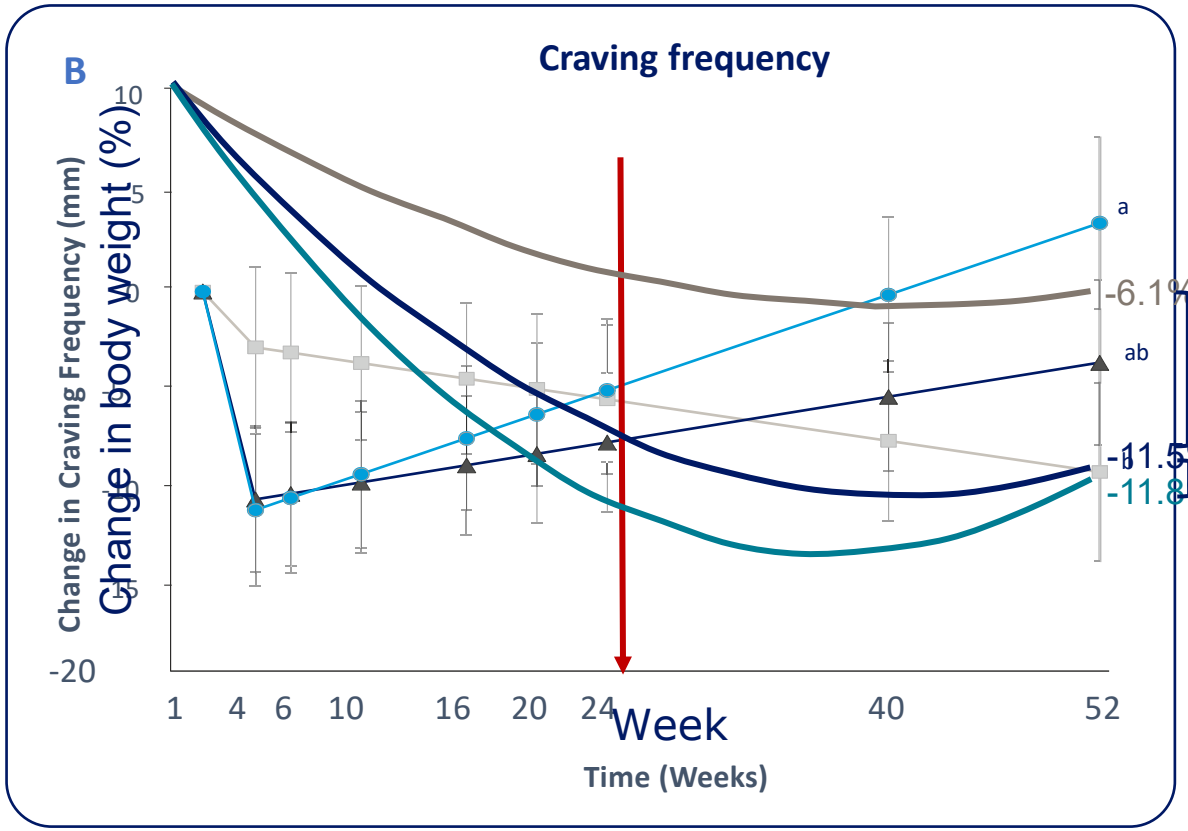


Tronieri, J.S., et al., *Int J Obes (Lond)*, 2019; doi: 10.1038/s41366-019-0348-6

SCALE IBT

Multi-component | IBT-liraglutide | IBT- alone

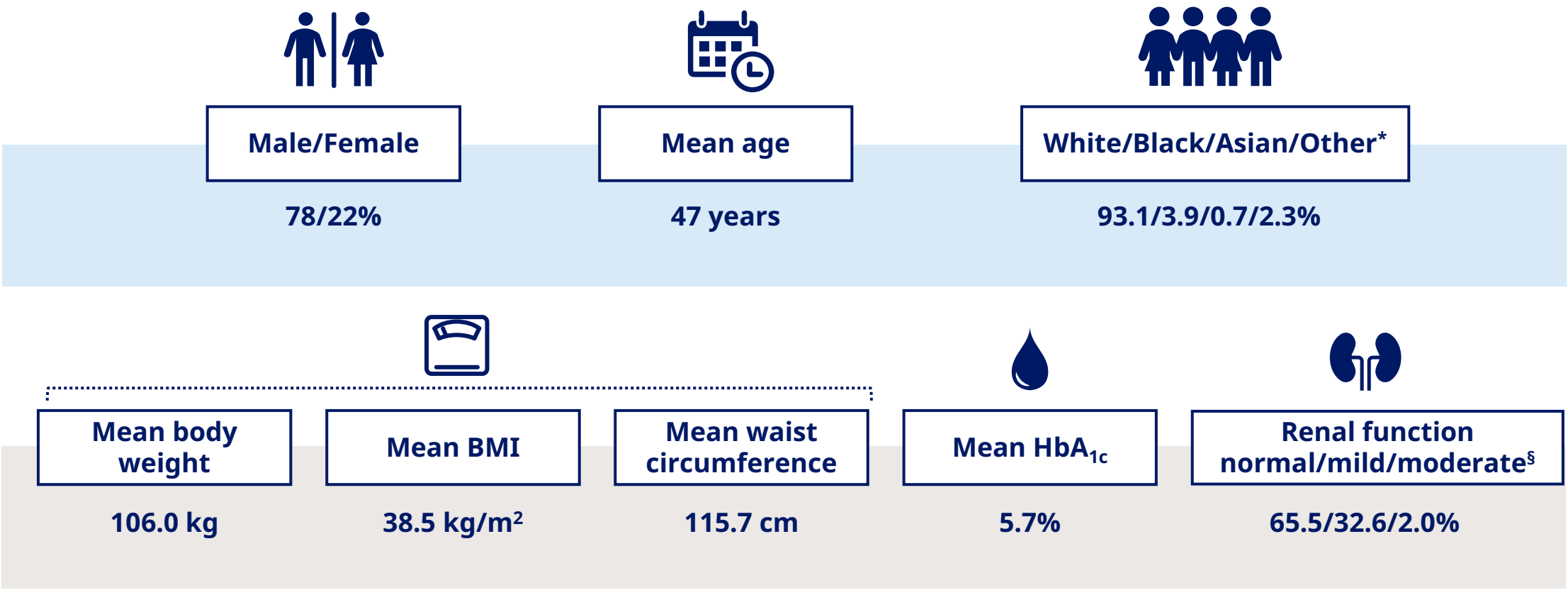




Tronieri, J.S., et al., *Int J Obes (Lond)*, 2019; doi: 10.1038/s41366-019-0348-6

Demographics and baseline characteristics

STEP 5



Participant demographics and baseline characteristics were similar between semaglutide and placebo groups

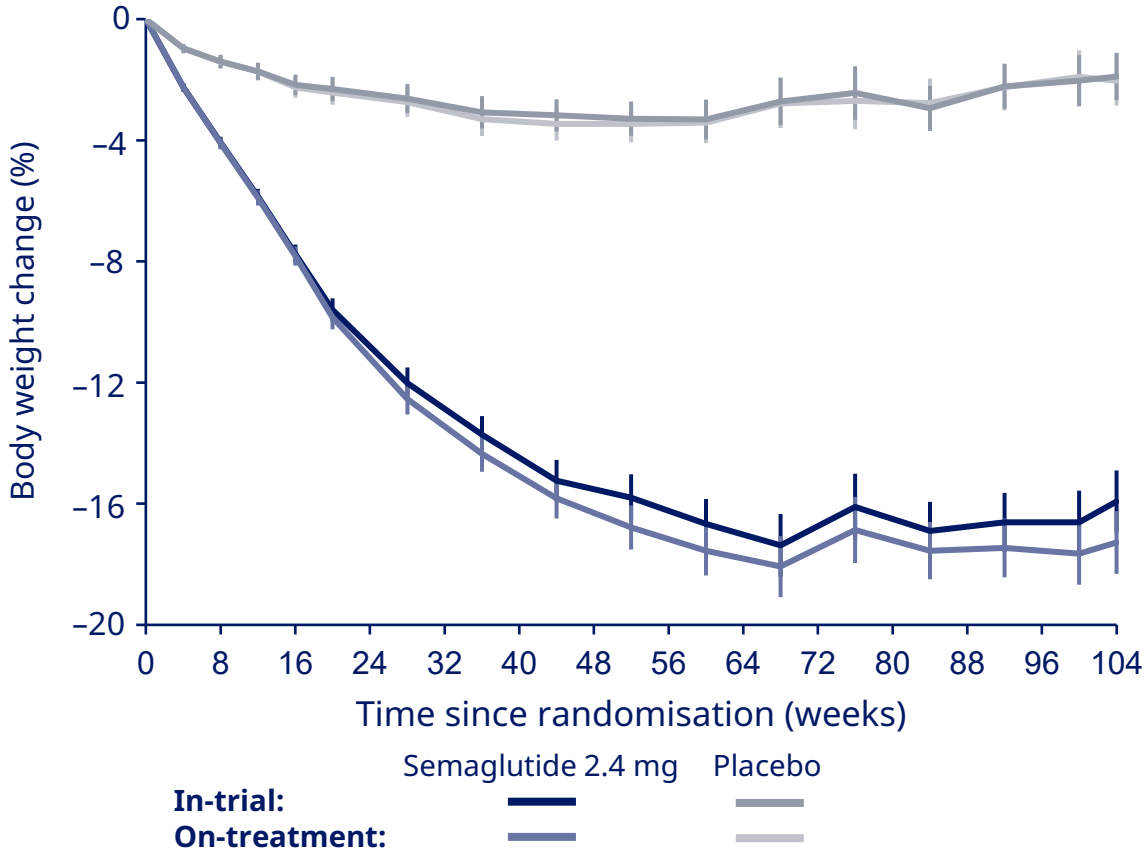
**Not applicable, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, or other; †Normal: eGFR≥90, Mild: 60–<90, Moderate: 30–<60 mL/min/1.73 m².*
BMI, body mass index; eGFR, estimated glomerular filtration rate.
Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Body weight change

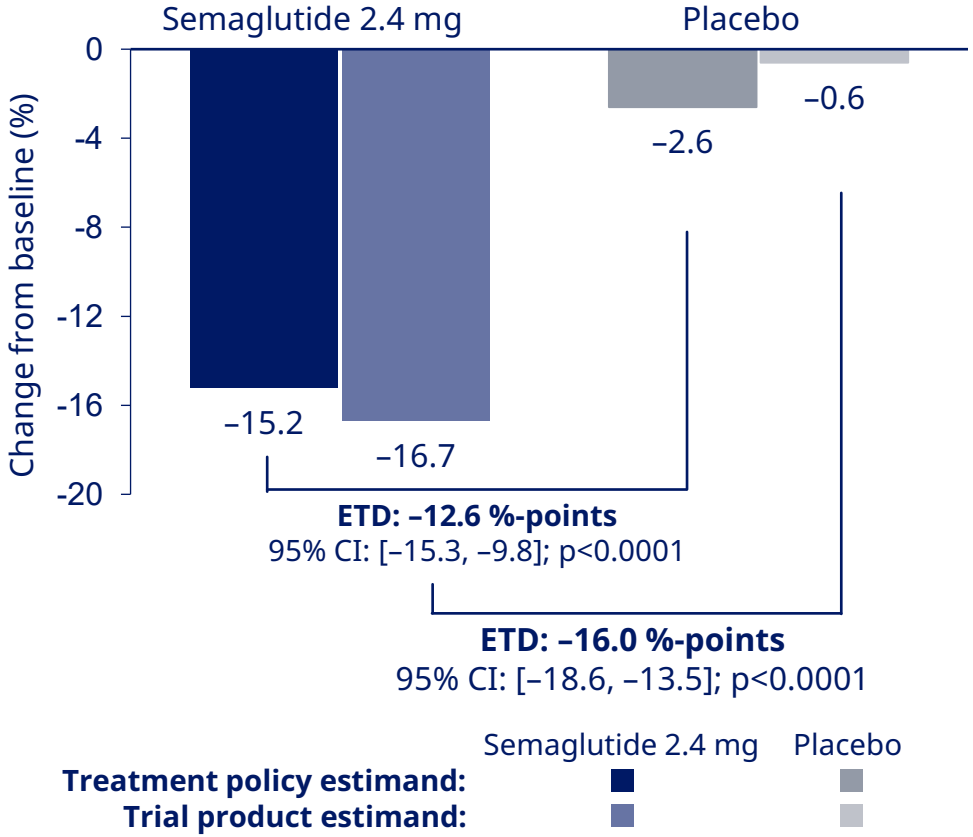
STEP 5

Observed mean change over time

(Mean at baseline: 106.0 kg)



Estimated mean change from baseline to week 104

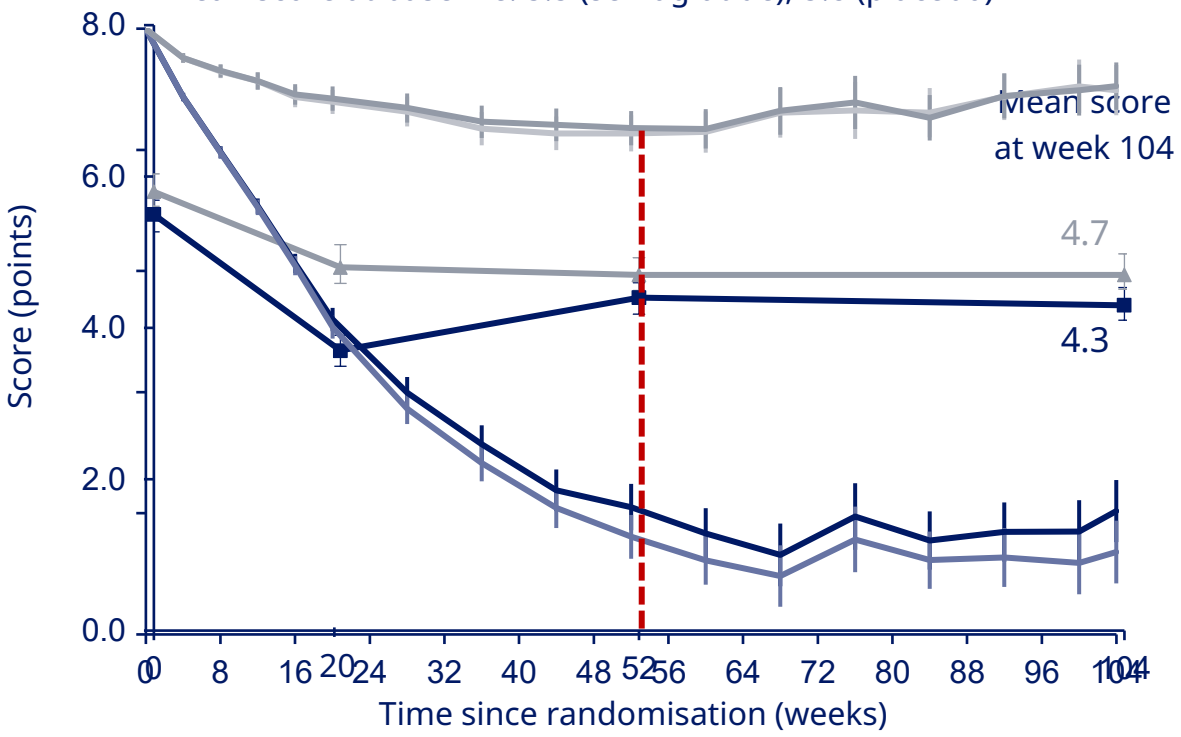


Treatment policy estimand assesses treatment effect regardless of treatment discontinuation or rescue intervention); Trial product estimand assesses treatment effect if trial product was taken as intended.
CI, confidence interval; ETD, estimated treatment difference.
Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Change over time in selected individual components

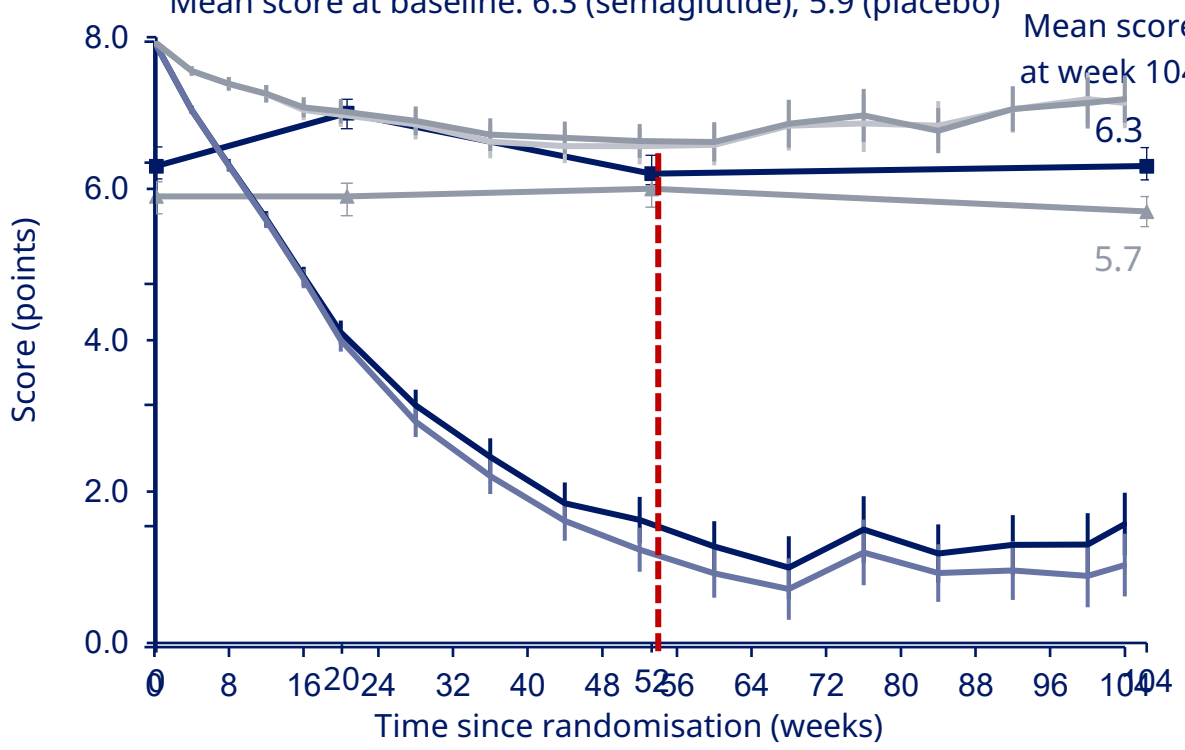
Hunger

Mean score at baseline: 5.5 (semaglutide); 5.8 (placebo)



Fullness

Mean score at baseline: 6.3 (semaglutide); 5.9 (placebo)

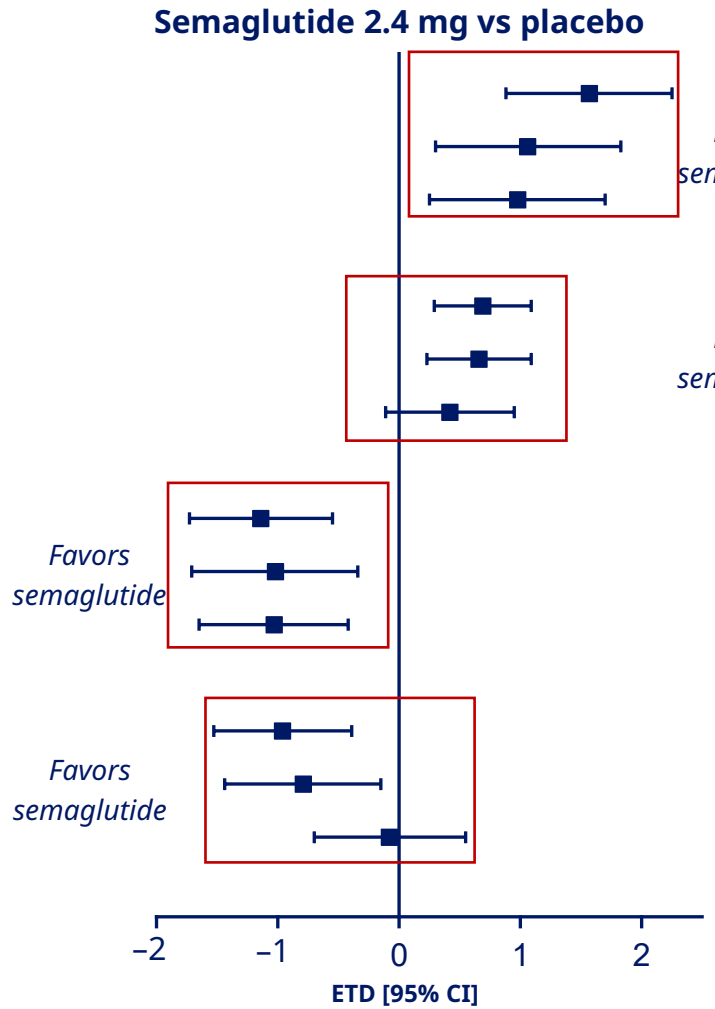


Semaglutide 2.4 mg (N=88)

Placebo (N=86)

Data are for the in-trial observation period. Item scores represent subject experience from 0 (not at all) to 10 (extremely) over the last 7 days. Scores on the graph are the mean scores at week 104. The CoEQ is only applicable for US and Canada.
CoEQ, control of eating questionnaire.
Wharton et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

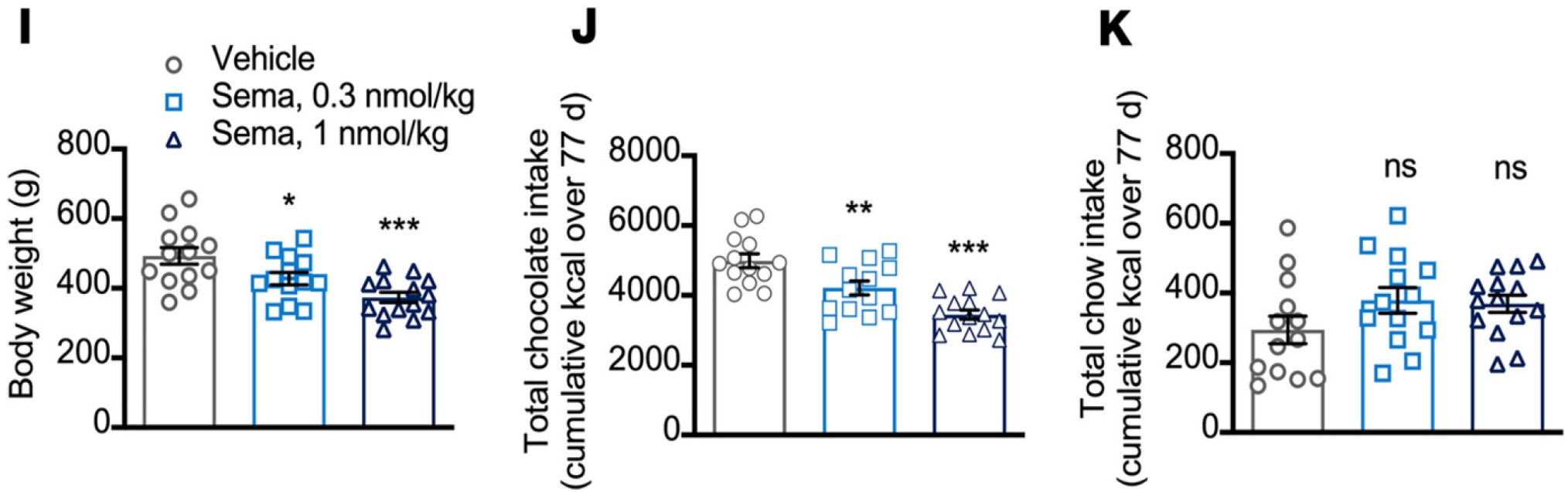
Change in CoEQ domain scores



		Semaglutide 2.4 mg vs placebo	p value
Craving control	Week 20	1.57 [0.88, 2.25]	**<0.0001**
	Week 52	1.06 [0.30, 1.83]	**0.0064**
	Week 104	0.98 [0.25, 1.70]	**0.0082**
Positive mood	Week 20	0.69 [0.29, 1.09]	**0.0006**
	Week 52	0.66 [0.23, 1.09]	**0.0027**
	Week 104	0.42 [–0.11, 0.95]	0.1220
Craving for savory	Week 20	–1.14 [–1.73, –0.55]	**0.0001**
	Week 52	–1.02 [–1.71, –0.34]	**0.0036**
	Week 104	–1.03 [–1.65, –0.42]	**0.0010**
Craving for sweet	Week 20	–0.96 [–1.53, –0.39]	**0.0009**
	Week 52	–0.79 [–1.44, –0.15]	**0.0163**
	Week 104	–0.08 [–0.70, 0.55]	0.8067

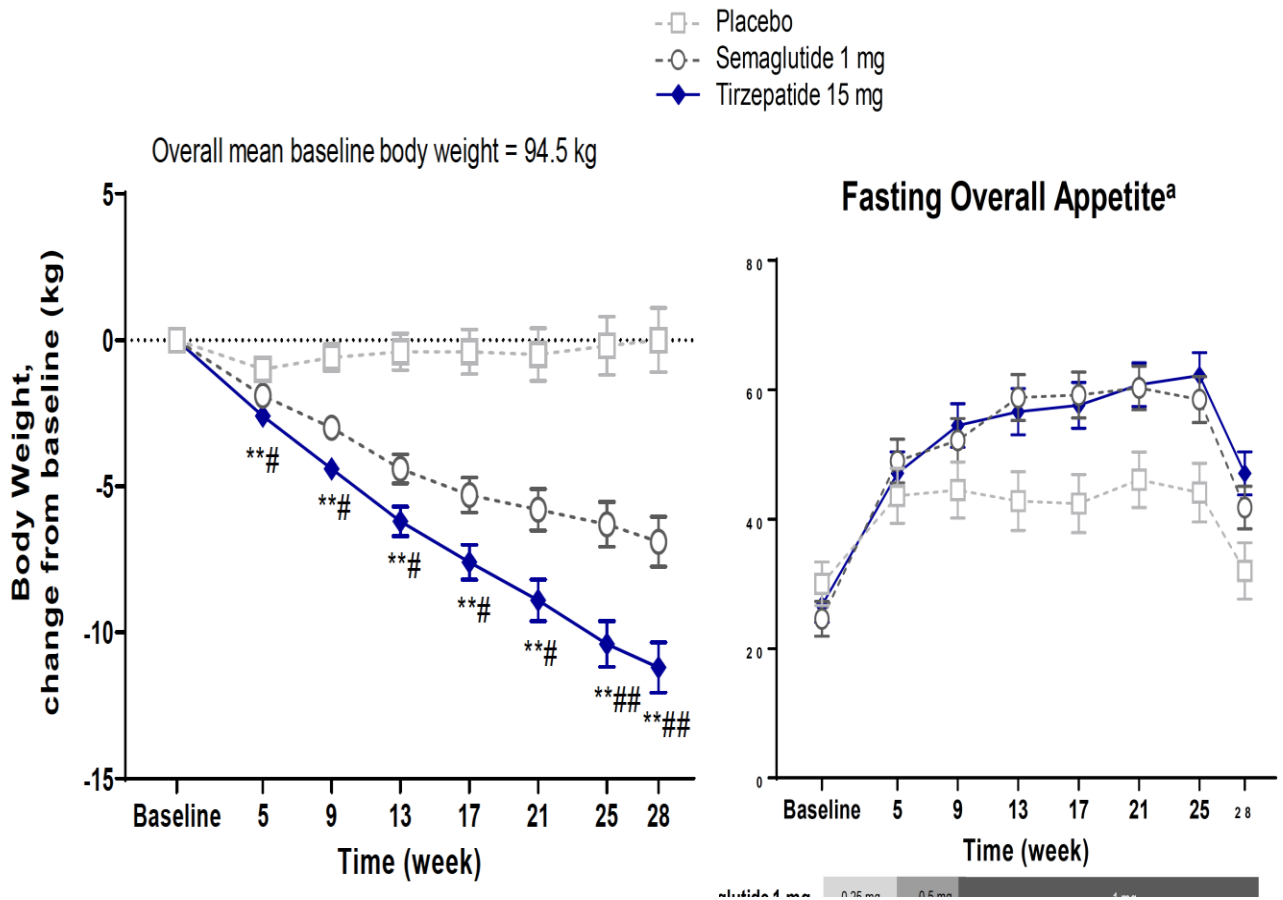
CoEQ was assessed in 88 participants in the semaglutide group and 86 in the placebo group. P values are not adjusted for multiplicity. CI, confidence interval; CoEQ, control of eating questionnaire; ETD, estimated treatment difference. Data are based on the treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention).
Wharton et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

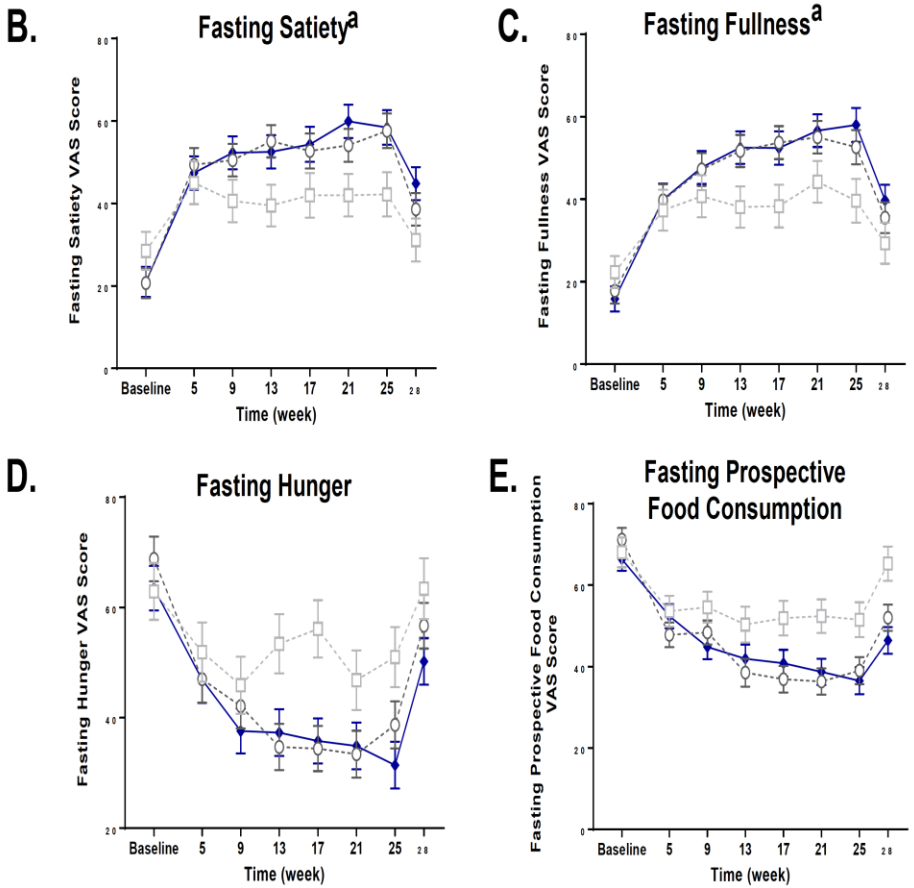
Reduction in energy intake was driven by decreased chocolate intake with semaglutide treatment compared with vehicle



Adapted from Gabery S et al. JCI Insight 2020;5:e133429.

Semaglutide and Tirzepatide Increased Overall Appetite VAS Scores, Indicating Reduced Appetite





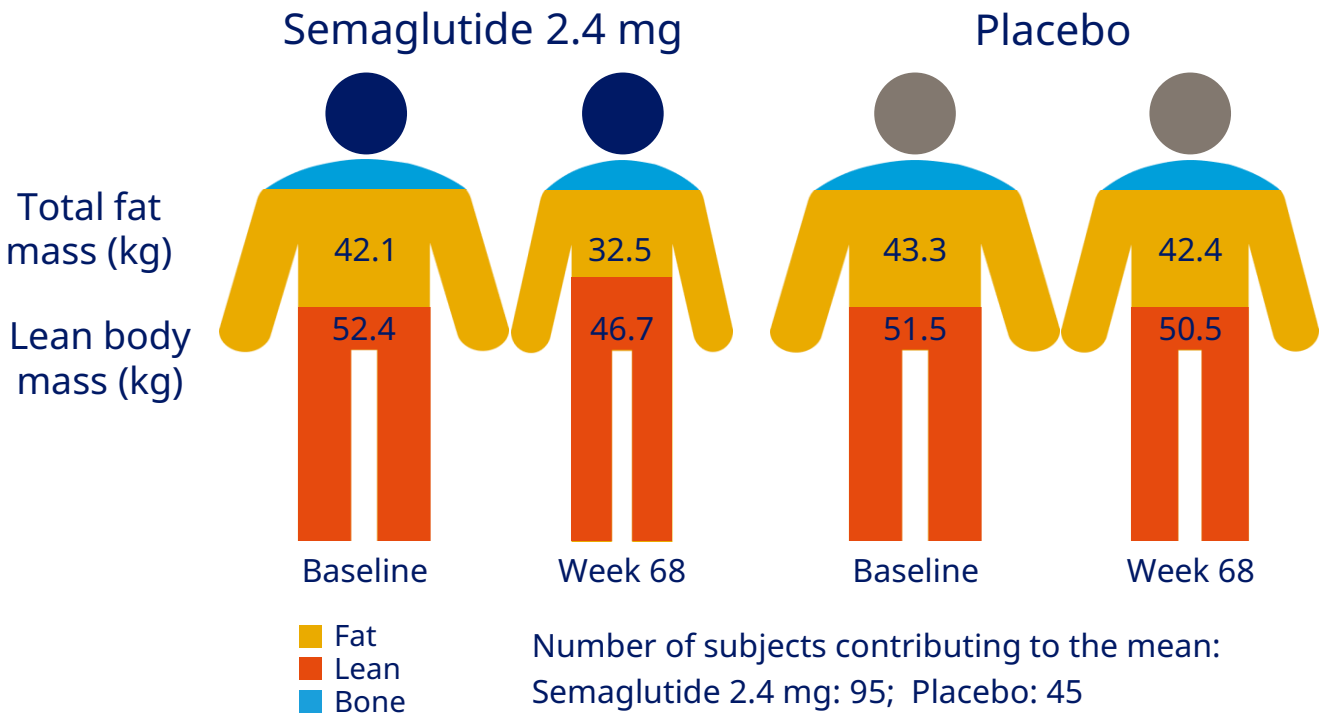
Dune J,ObesityWeek Nov, 2022

Notion 3 : Treatment with Semaglutide 2.4 mg induce weight maintenance for 2 years, while craving control is maintained the effect on craving for sweet is reduced

What about Fat Free Mass Loss ?

STEP 1: Change in body composition (DEXA)

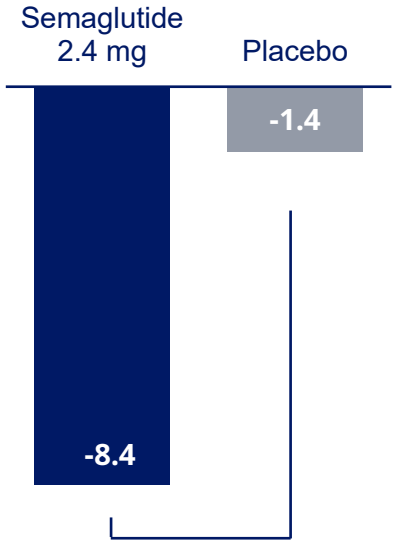
In-trial§



Number of subjects contributing to the mean:
Semaglutide 2.4 mg: 95; Placebo: 45

Total fat mass (kg)#

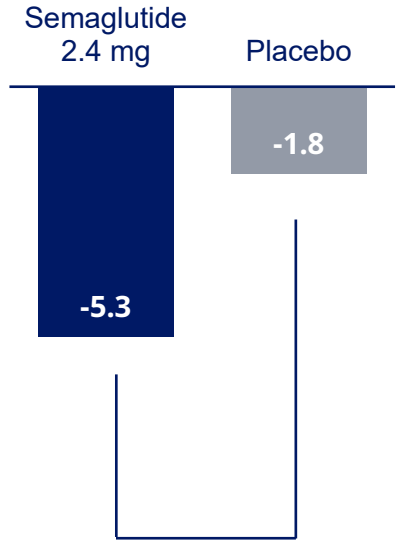
Mean baseline: 42.5 kg



ETD: -7.0 kg
95% CI: [-9.79;-4.19];
p<0.0001

Lean body mass (kg)#

Mean baseline: 52.1 kg

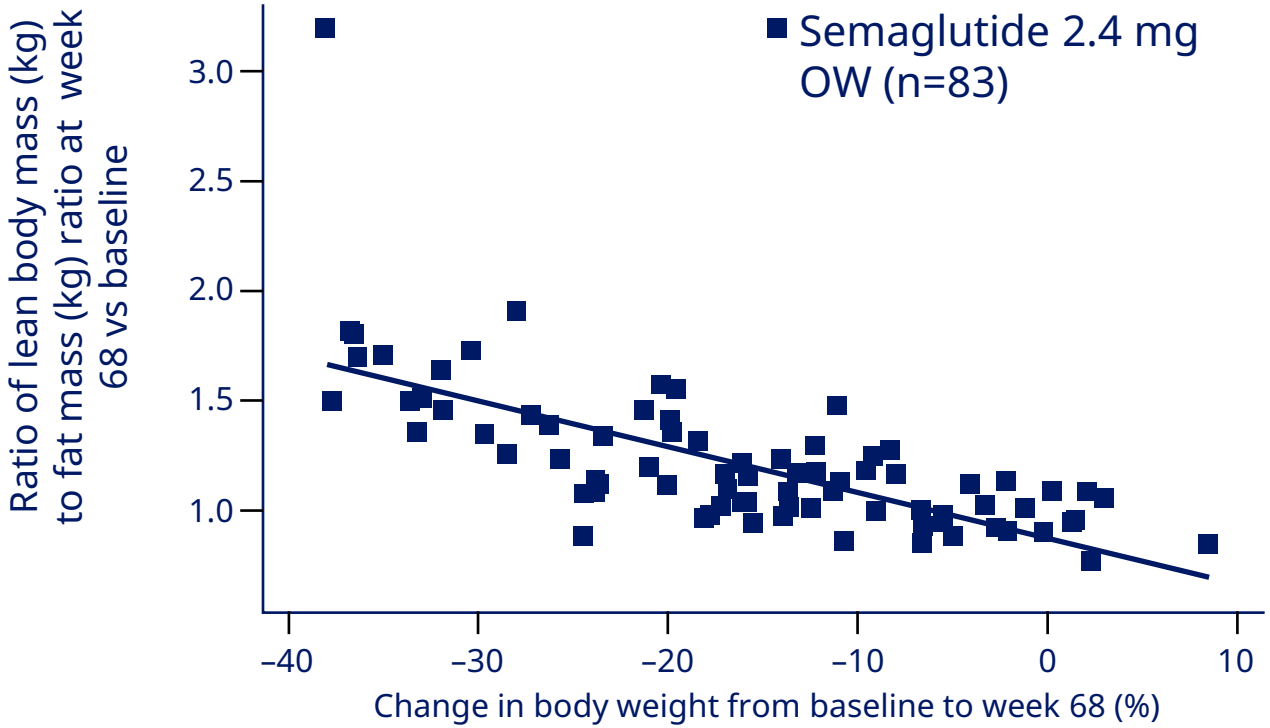


ETD: -3.4 kg
95% CI: [-4.74;-2.13];
p<0.0001

§ Observed data for the in-trial period; # Estimated data for the treatment policy estimand.
CI, confidence interval; DEXA, dual energy x-ray absorptiometry; ETD, estimated treatment difference.
Wilding JPH, et al. presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

Change from baseline to week 68 in ratio of lean body mass to total body mass: Overall and by weight change

Ratio of week 68 vs baseline lean body mass (kg) to fat mass (kg) ratio plotted by change from baseline to week 68 in body weight



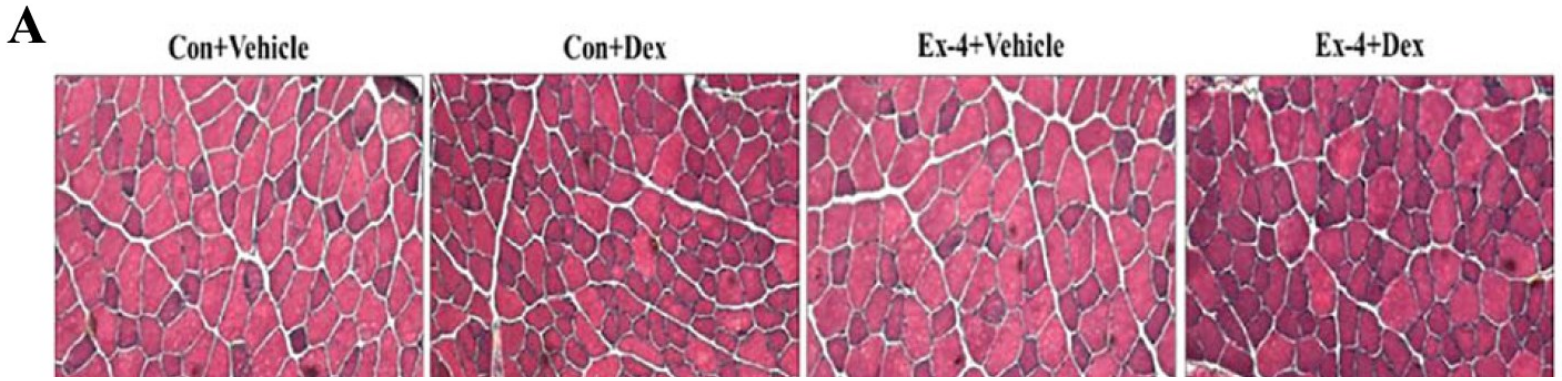
Lean body mass (kg) to total body fat mass (kg) ratio in the semaglutide group

	Mean [95% CI]
Baseline (n=83)	1.34 [1.22, 1.47]
Week 68 (n=83)	1.57 [1.44, 1.71]
Change from baseline to week 68	
Overall treatment group (n=83)	0.23 [0.14, 0.32]
Pts with weight loss ≥15% (n=44)	0.41 [0.28, 0.53]
Pts with weight loss <15% or not known (n=39)	0.03 [-0.05, 0.12]

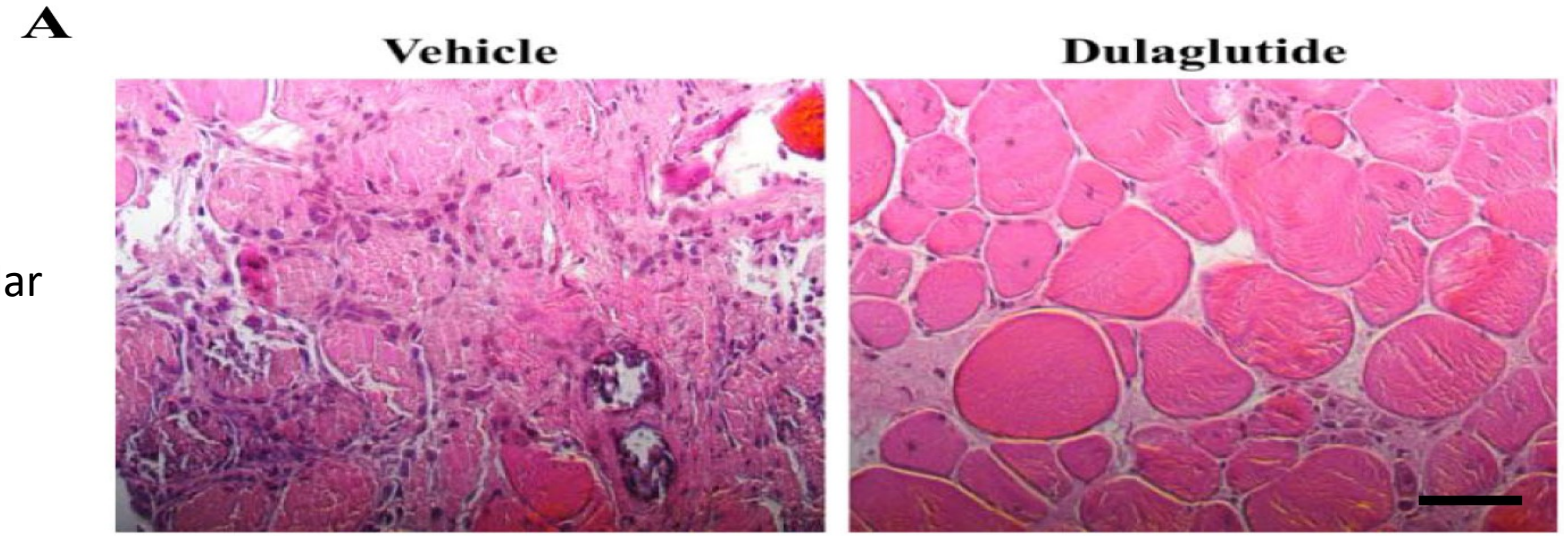
Observed data; no imputation for missing data.
CI, confidence interval; OW, once-weekly; Pt, participants.
Wilding et al. Presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

GLP-1R agonists ameliorate muscle wasting by suppressing MSTN and muscle atrophic factors and enhancing myogenic factors through GLP-1R-mediated signalling pathways

effects of Ex-4 in the presence or absence of dexamethasone (Dex)



Duchenne muscular dystrophy model

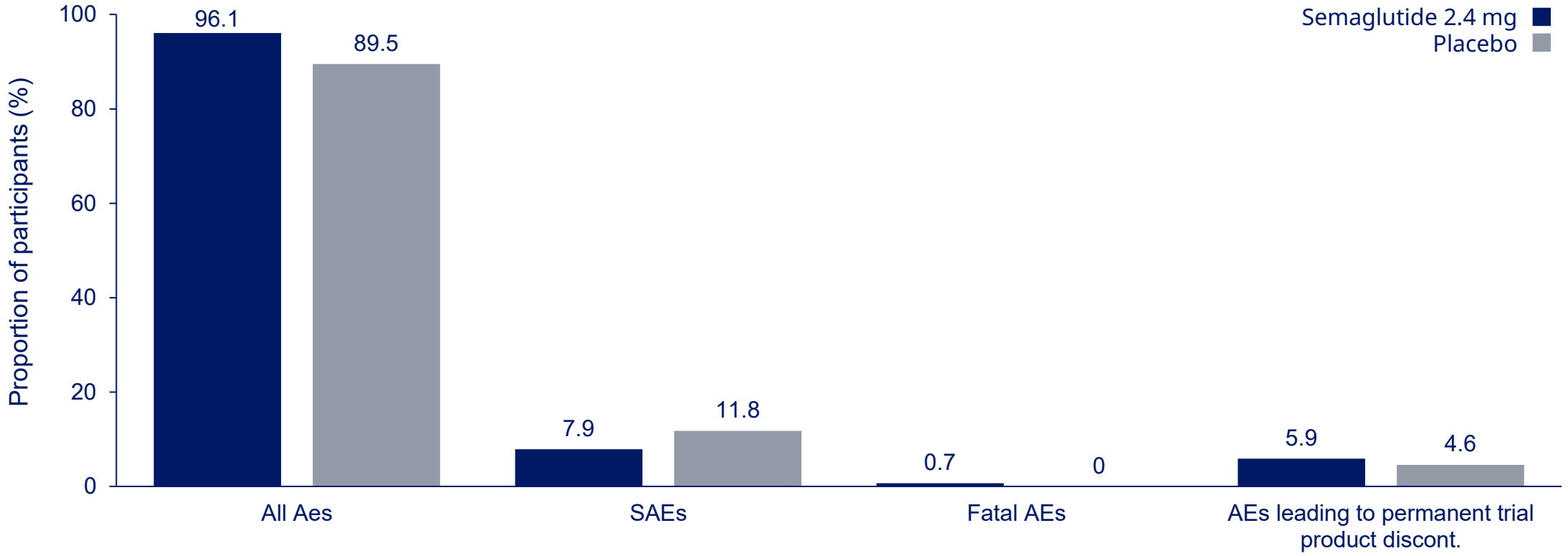


Hong Y, Journal of Cachexia, Sarcopenia and Muscle 2019

Notion 4 : Weight loss with Semaglutide 2.4 mg Led to improvement in the Lean/Fat mass. GLP-1RA may have protective effect on muscle function.

Adverse events overview

STEP 5



On-treatment data.

AE, adverse event; discont., discontinuation; N, number of participants with event(s); SAE, serious adverse event; %, proportion of participants with event(s).

Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Overview of safety focus areas

STEP 5

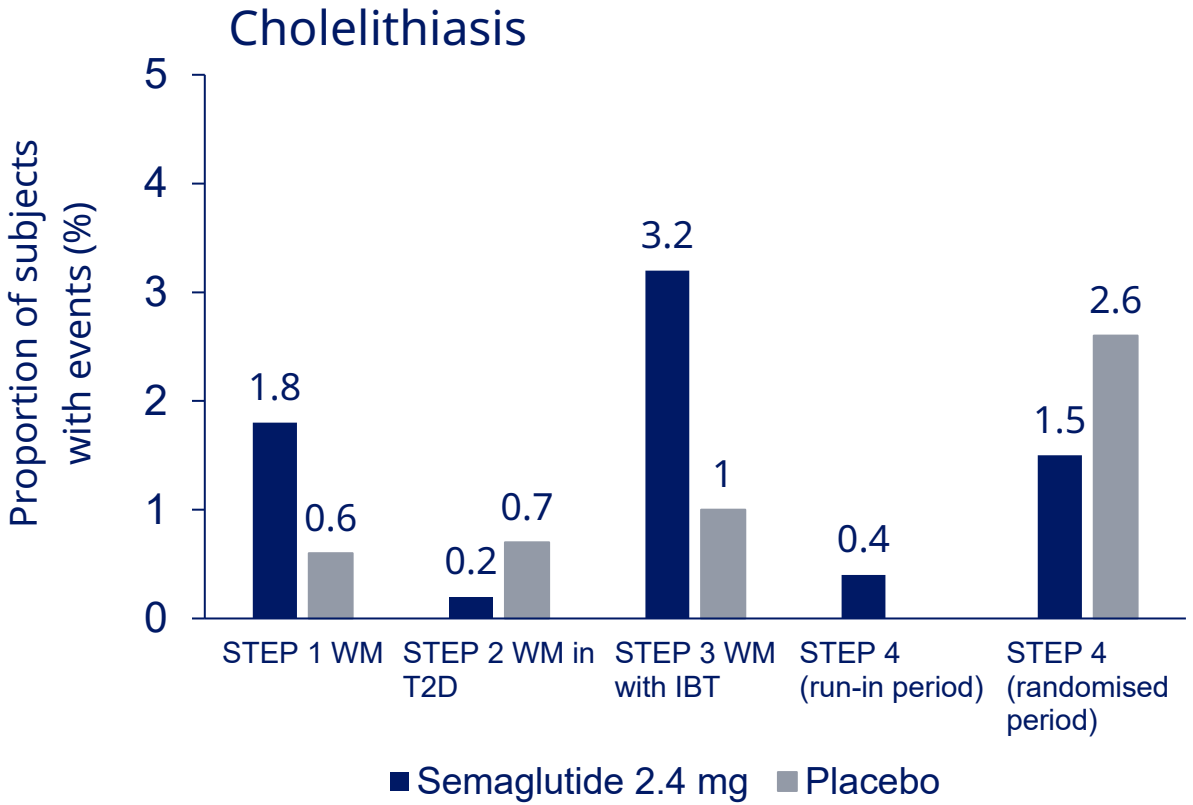
Adverse events within safety focus areas	Semaglutide 2.4 mg (N=152)		Placebo (N=152)	
	N	%	N	%
Gastrointestinal disorders	125	82.2	82	53.9
Gallbladder-related disorders	4	2.6	2	1.3
Hepatic disorders	3	2.0	3	2.0
Acute pancreatitis	0		0	
Cardiovascular disorders*	17	11.2	30	19.7
Allergic reactions	23	15.1	8	5.3
Injection site reactions	10	6.6	15	9.9
Malignant neoplasms*	2	1.3	4	2.6
Psychiatric disorders	26	17.1	25	16.4
Acute renal failure	0		0	
Hypoglycaemia	4	2.6	0	
Rare events	0		1	0.7
Overdose	0		1	0.7

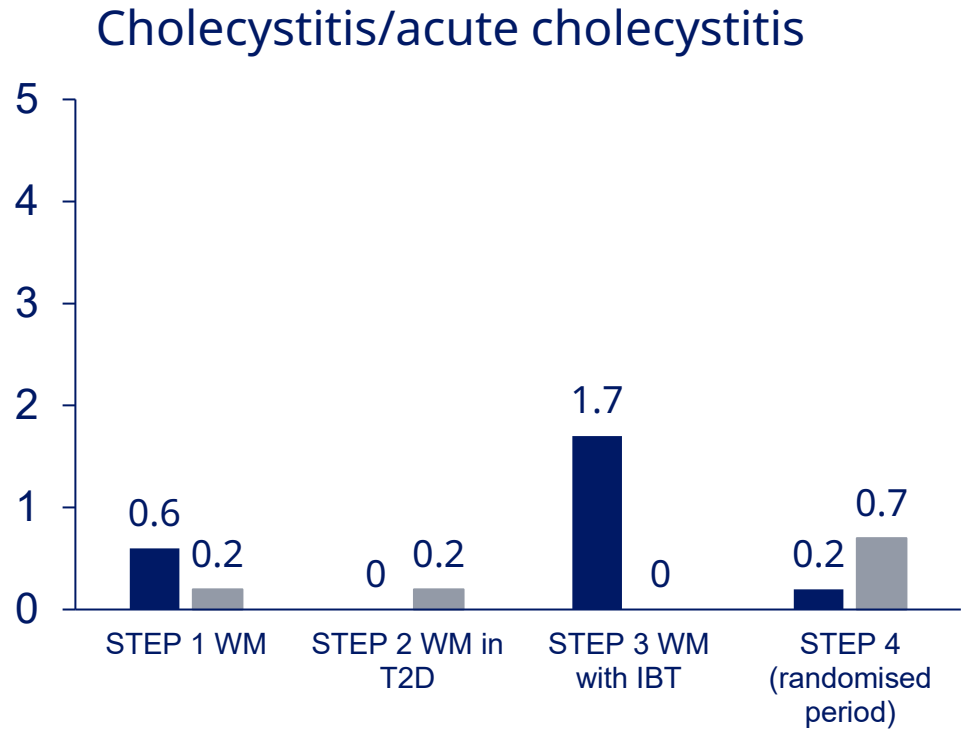
**Events occurred during the in-trial period.*

Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Acute gallbladder disorders by trial

Most common gallbladder disorders by PT



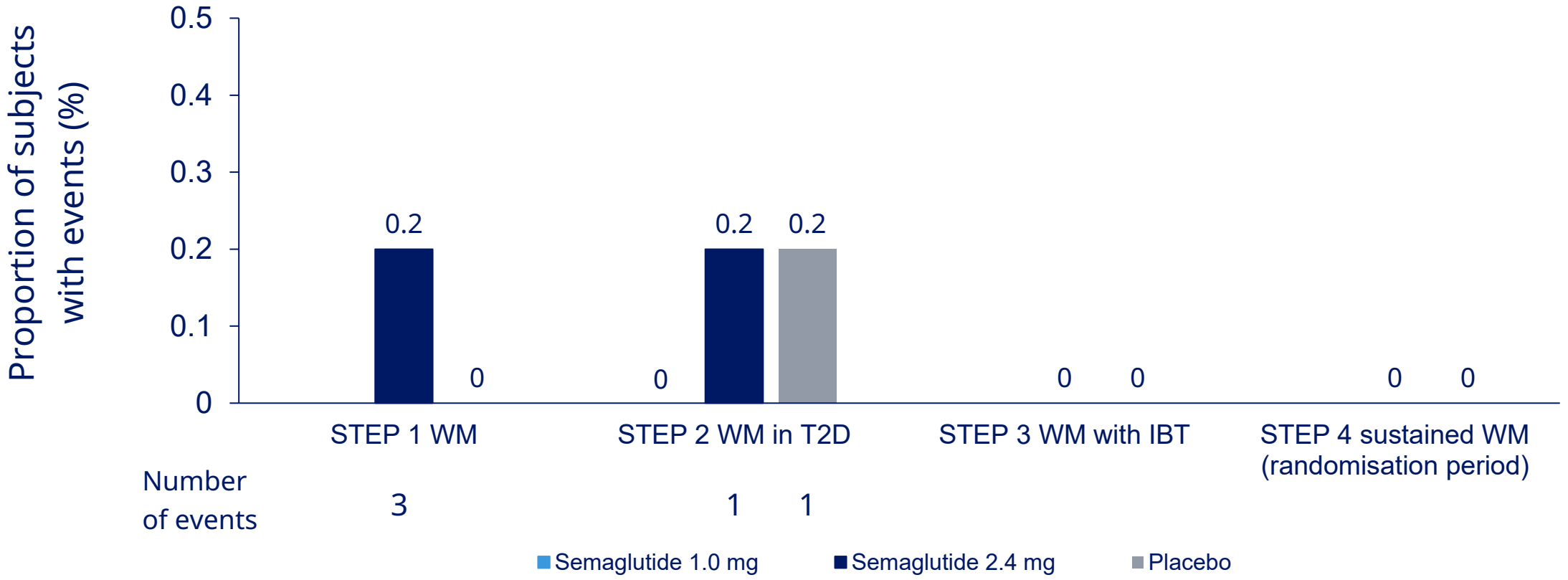


In all cases cholecystitis/ acute cholecystitis was a complication to cholelithiasis

PT, preferred term. Data are for the on-treatment observation period.
IBT, intensive behavioural therapy; PT, preferred term; T2D, type 2 diabetes; WM, weight management.
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print; Davies M et al. Lancet 2021; doi: 10.1016/S0140-6736(21)00213-0. Online ahead of print; Wadden TA et al. JAMA 2021; doi: 10.1001/jama.2021.1831. Online ahead of print; Rubino DM et al. Presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

Acute pancreatitis events by trial

Acute pancreatitis (EAC confirmed events)



Data are for the on-treatment observation period.
EAC, event adjudication committee; IBT, intensive behavioural therapy; PT, preferred term; T2D, type 2 diabetes; WM, weight management.
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print; Davies M et al. Lancet 2021; doi: 10.1016/S0140-6736(21)00213-0. Online ahead of print; Wadden TA et al. JAMA 2021; doi: 10.1001/jama.2021.1831. Online ahead of print; Rubino DM et al. Presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

All listed AOMs are not approved for weight management in Israel

Nutrient-stimulated hormone (NuSH)-based therapies in development

2022 | 2023 | 2024 | 2025

GIP / GLP-1 Receptor Agonist

- TIRZEPATIDE – SURMOUNT – PHASE 3

GLP-1 Receptor Agonist

- SEMAGLUTIDE 2.4 STEP-TEENS – PHASE 3

AMYLIN / GLP-1 Receptor Agonist

- CAGRILINTIDE – PHASE 2
- CAGRI-SEMA – PHASE 2
- CAGRI-SEMA – REDEFINE – PHASE 3

GLUCAGON / GLP-1 Receptor Agonist

- PEMVIDUTIDE – PHASE 2
- BI 456906 – PHASE 2

GIP / GLUCAGON / GLP-1 Receptor Agonist

- RETATRUTIDE – PHASE 2

ORAL GLP-1 RA

- SEMAGLUTIDE ORAL – OASIS – PHASE 3
- DANUGLIPRON – PHASE 2
- LY 3502970 – PHASE 2

Slide: Ania Jastreboff, MD, PhD

Beyond (just) weight reduction… treating obesity!

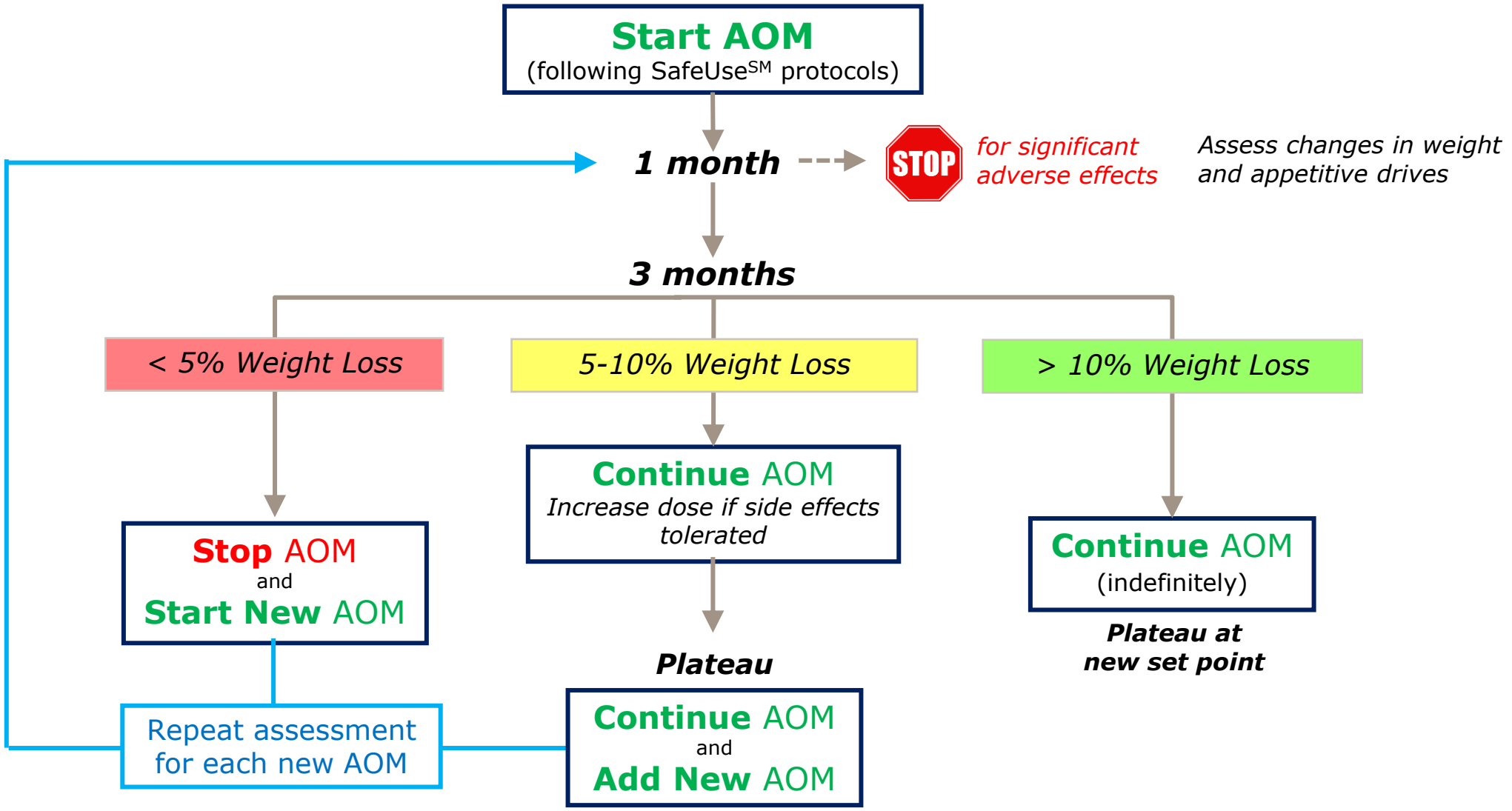
- Target the neurometabolic **pathophysiology of obesity**
- Target **different mechanisms**
  - Heterogeneity of response – different types of obesity
- Individualize **combination therapy** – target different mechanisms
  - Combination therapy with various anti-obesity medications
  - Combination therapy with metabolic-bariatric surgery
- Consider the **quality of weight reduction**
  - Reduction in adiposity & preservation of lean mass → gain of lean mass
  - Rate of weight reduction
- Improve **health outcomes** and **lives of people living with obesity**

Access & affordability!

- We should aim for 15-20% weight loss.
- In 15-20% weight loss IBT doesn’t add much to the Pharmacotherapy weight loss.
- Semaglutide & Tirzepatide induced weight loss is associated with blunting of metabolic adaptation and Hunger in animal Study.
- Weight loss with Semaglutide 2.4 mg Lead to improvement in the Lean/Fat mass. GLP-1RA may have protective effect on muscle function.

Thank you!

Pharmacology algorithm



Kaplan LM, 2022

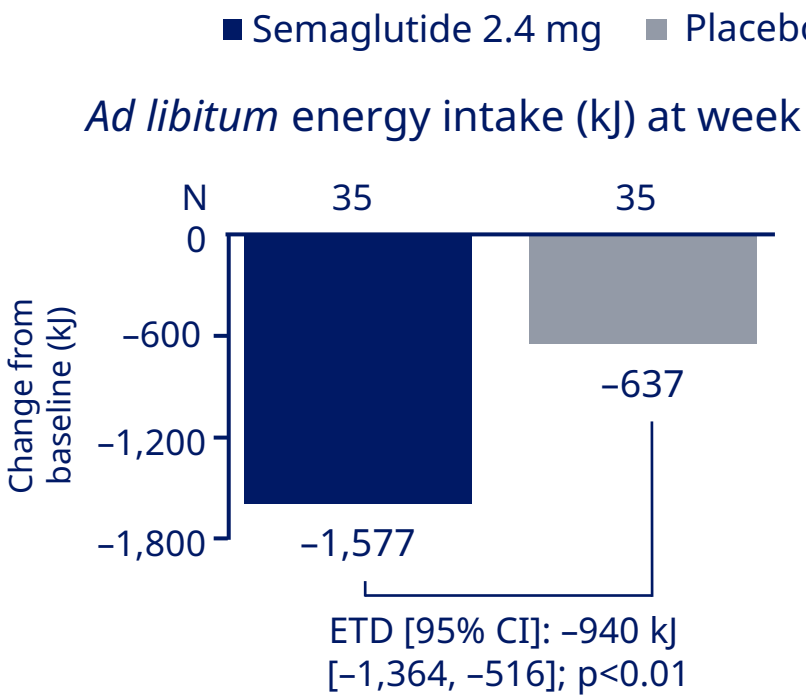
Semaglutide mechanism of action

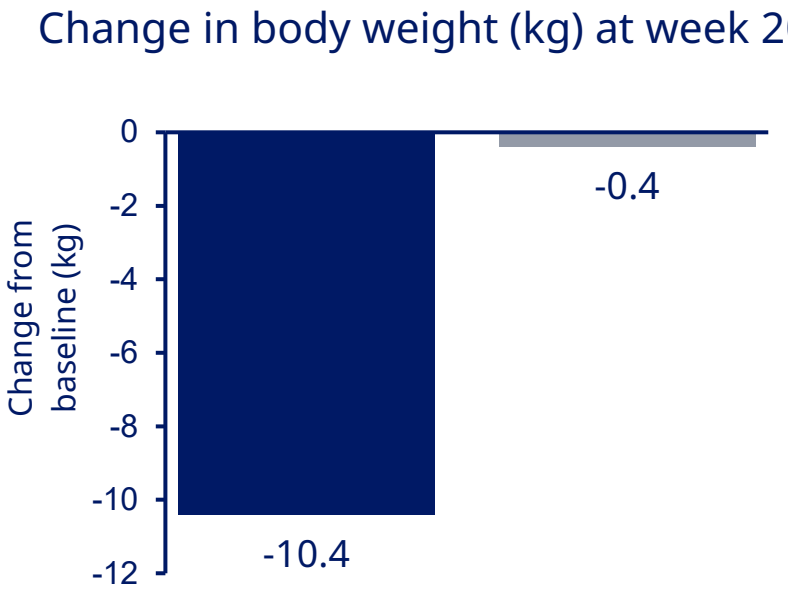
Appetite regulation in adults with obesity

With semaglutide 2.4 mg vs placebo

- Hunger
- Prospective food consumption
- Desire and craving for savory foods
- Desire for sweet foods

- Satiety
- Fullness



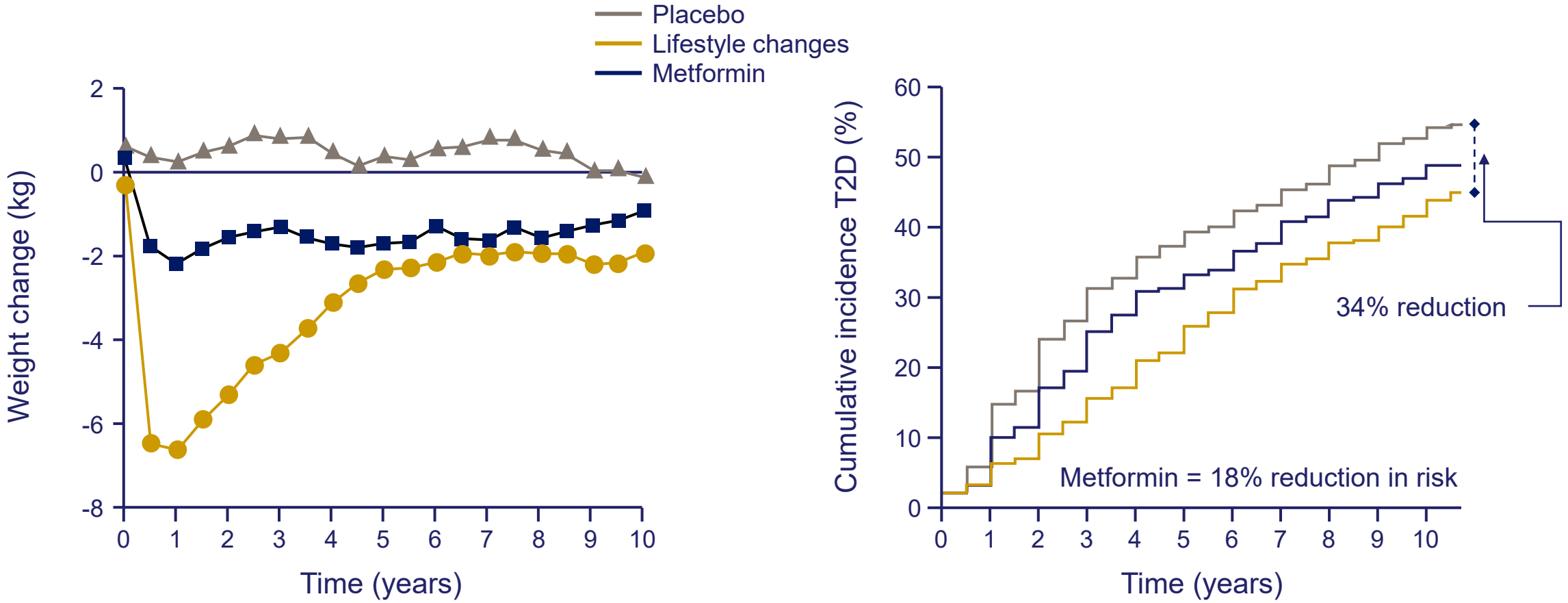


Energy intake was **35% lower** with semaglutide 2.4 mg compared to placebo

BW decreased by **10.4 kg** with semaglutide 2.4 mg compared to 0.4 kg with placebo

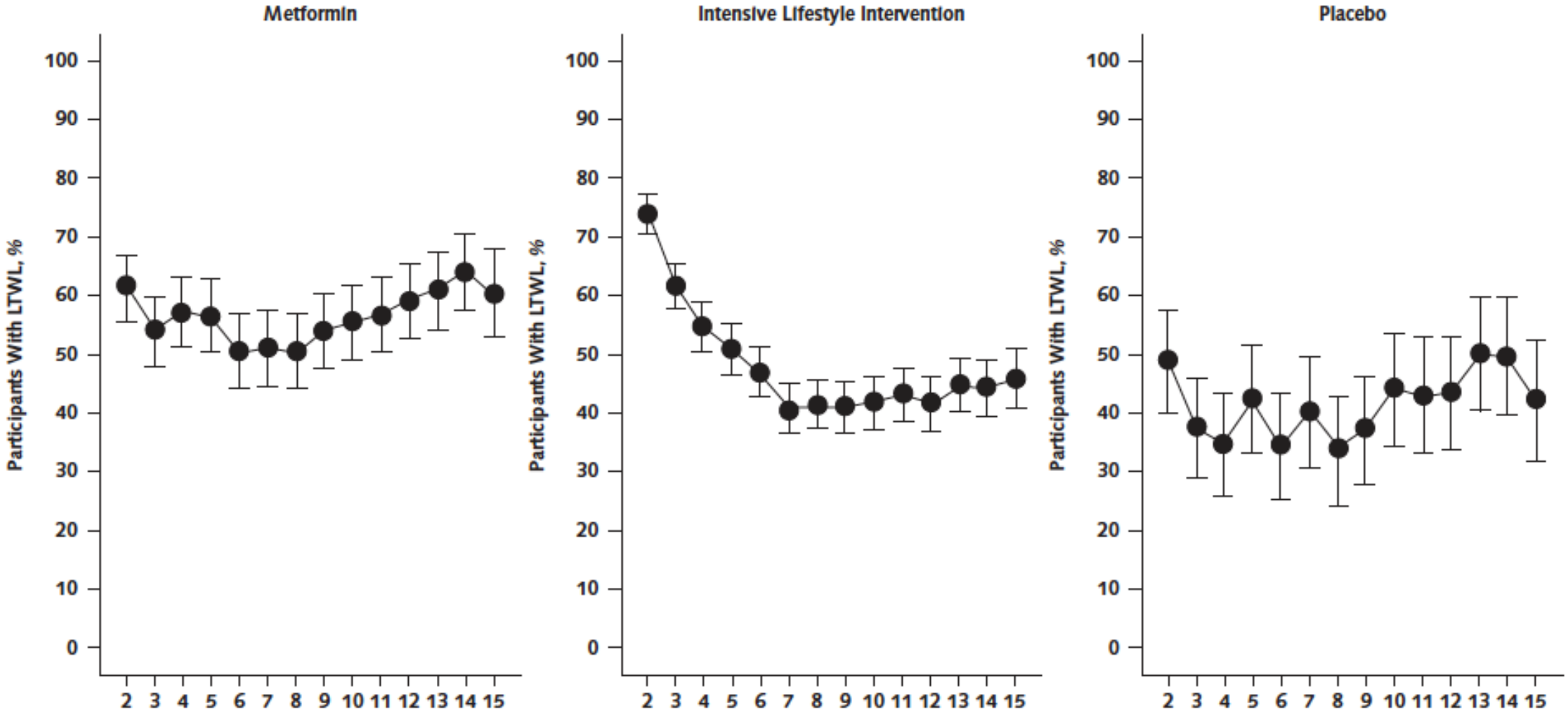
BW, body weight; CI, confidence interval; ETD, estimated treatment difference.
Friedrichsen M et al. Diabetes Obes Metab 2021;23:754–62.

הפחתת משקל והתפתחות סוכרת במחקר ה DPP



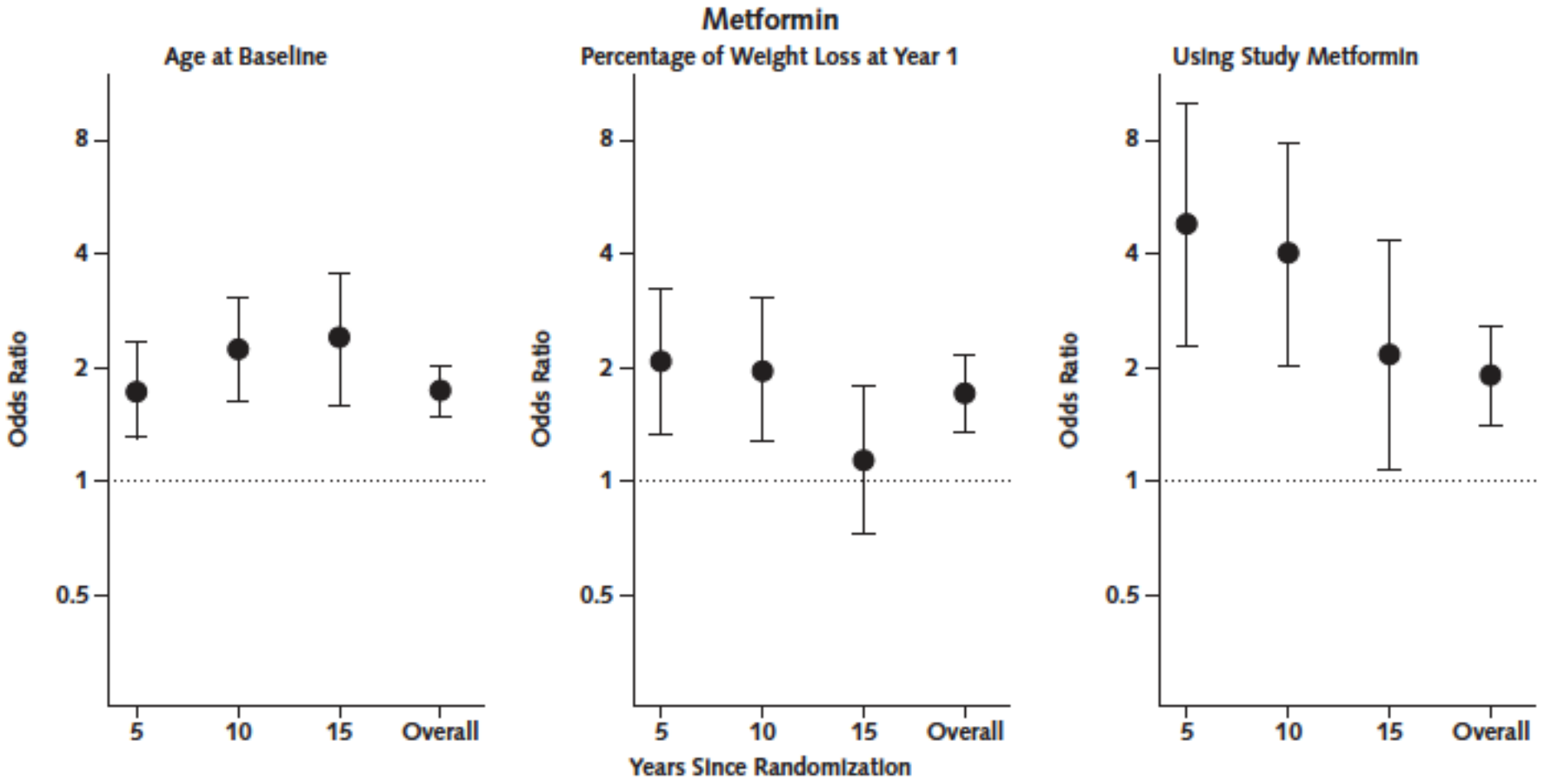
T2D, type 2 diabetes. Knowler et al. *Lancet* 2009;374:1677–86.

במעקב של DPP שימור הפחתת משקל של 5% במחקר ה 15 שנה



Apolzan JW, Annals of Internal Medicine, 2019

במעקב DPPמנבאים לשימור הפחתת משקל של 5% במחקר ה של 15 שנה



Apolzan JW, Annals of Internal Medicine, 2019