Update on recent advances in pharmacotherapy for obesity

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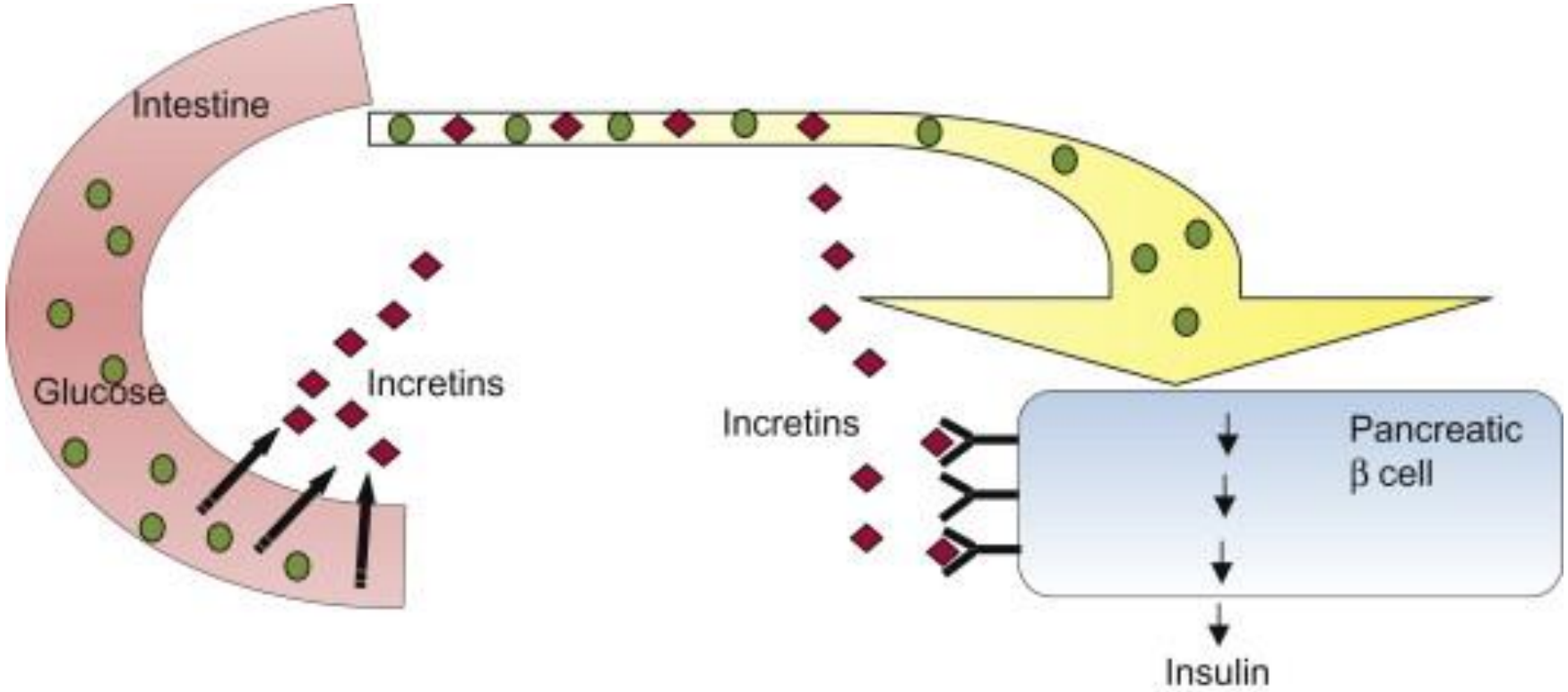
Conflict of Interest Disclosure

A/Prof Samantha L Hocking has received research grants from The Diabetes Australia Research Trust/Program and The National Health and Medical Research Council of Australia; received honoraria for lectures from Eli Lilly, Novo Nordisk, Inova, Sanofi Aventis, Astra Zeneca, Servier and Amgen and has been or is on advisory boards for Novo Nordisk, Eli Lilly, Inova, Seqirus and Pfizer; and has been an investigator for industry-sponsored clinical trials run by Novo Nordisk, Eli Lilly, Rhythm pharmaceuticals, Millendo, Spruce Biosciences and Amgen.

Overview

- What are incretin-based therapies and how do they work?
- Incretin-based therapies for the treatment of obesity
- Safety profiles of incretin-based therapies
- Emerging pharmacotherapies for obesity management

What are incretins?

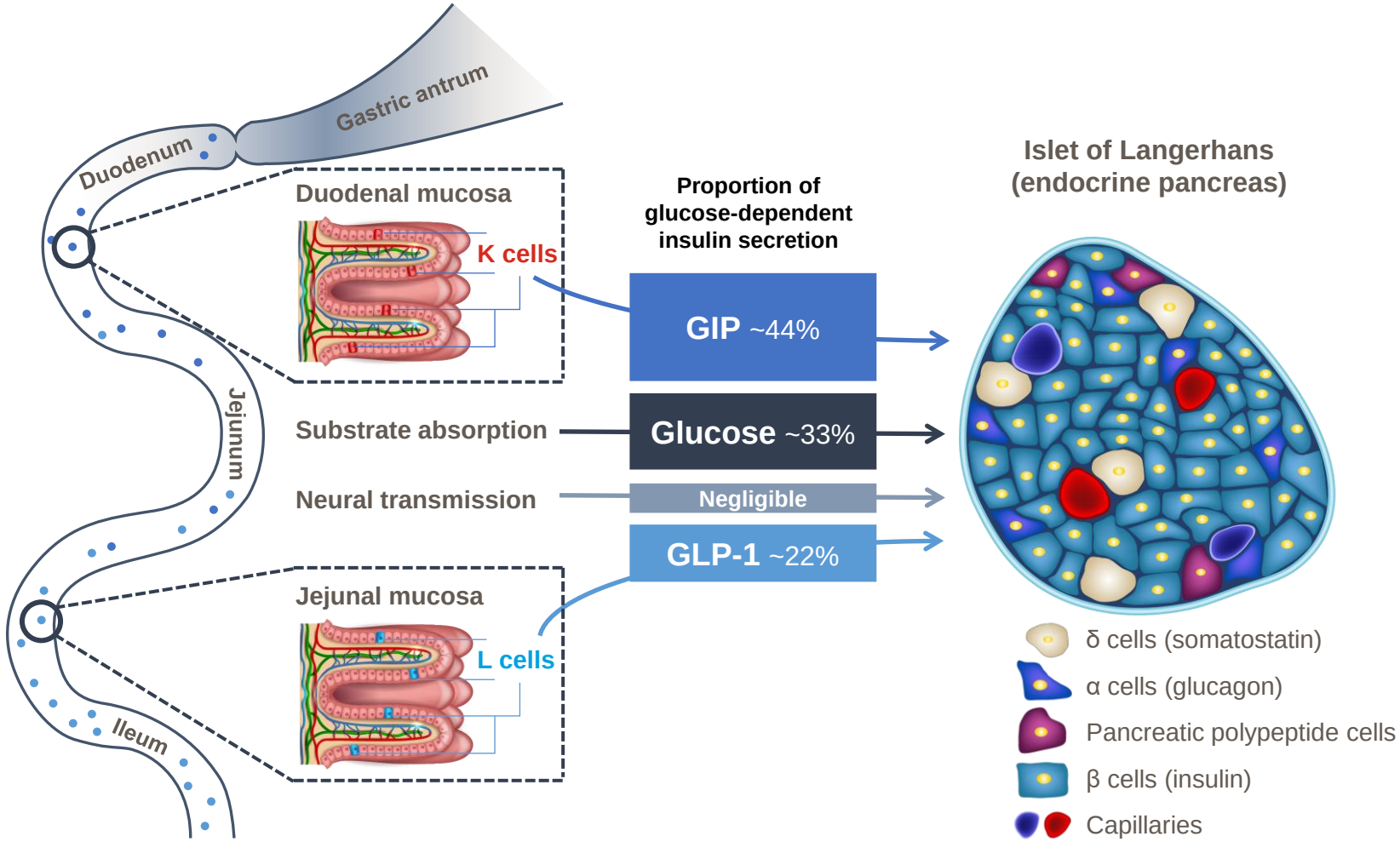


Nutrients in the small intestine stimulates incretin release.

Incretins are carried through the circulation to their target tissue: the pancreatic β-cells. Incretin stimulation of β-cells causes them to secrete more insulin in response to the same amount of blood glucose

https://doi.org/10.1016/C2013-1-13458-2

The two main incretins are GLP-1 and GIP



- Nutrient load in the gut stimulates the release of incretin hormones GIP and GLP-1
- GIP and GLP-1 send signals to pancreatic islets to enhance glucose-dependent insulin secretion
- This "incretin effect" is a major contributor to the regulation of PPG clearance in healthy people

GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose

Nauck MA, Meier JJ. Diabetes. 2019;68(5):897-900.

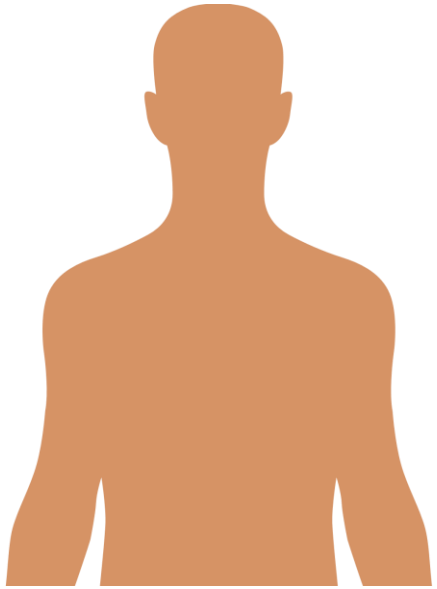
GLP-1 receptor agonists have multifactorial effects

Pancreas (beta cell)
- ↑ Insulin secretion
- ↑ Insulin biosynthesis
- ↓ Apoptosis

Liver
- ↓ Inflammation
- ↑ ↓ Steatosis[7]

↓ Inflammation
indirectly in many tissues

Brain
- ↓ Body weight
- ↓ Food intake[1]
- ↑ Neuroprotection
- ↑ Aversive responses



T2D

Pancreas (alpha cell)
- ↓ Glucagon secretion[1]

GI tract
- ↓ Gastric emptying
- ↓ Post prandial lipids

Kidneys
- ↑ Natriuresis
- ↑ Diuresis
- ↓ Albuminuria

Heart and cardiovascular
- ↑ Heart rate
- ↑ Cardioprotection
- ↓ Blood pressure
- ↓ Atherosclerosis

Drucker DJ and Holst JJ, Diabetologia 2023;66:1765–1779

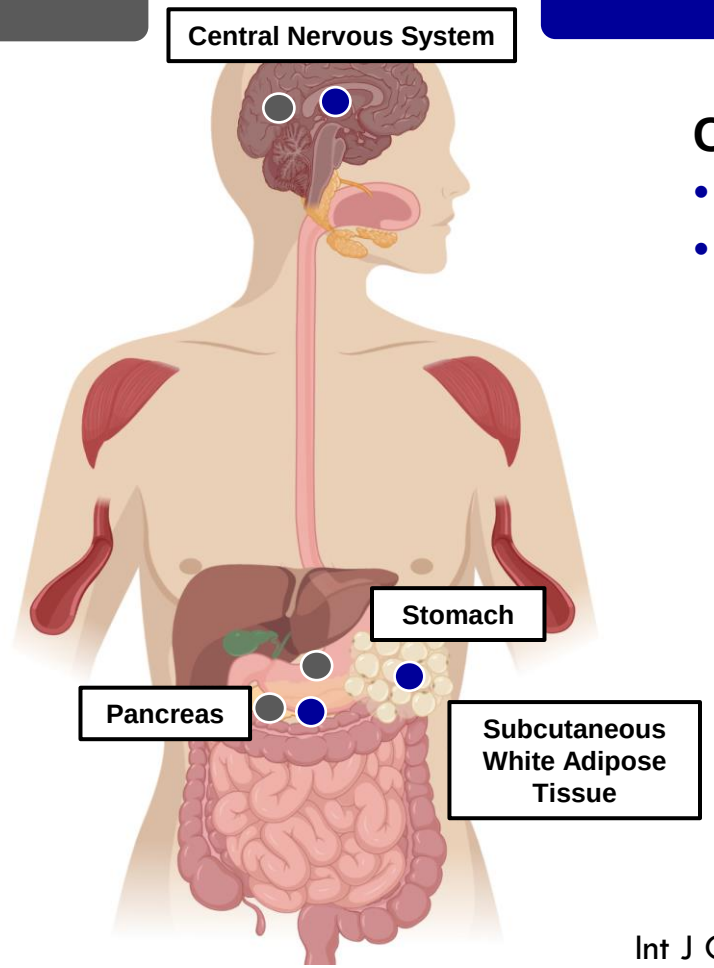
Proposed Actions of GIP Receptor Agonist and GLP-1 Receptor Agonist in Humans

GLP-1 Receptor Agonism

Central Nervous System
- ↓ Appetite
- ↓ Food Intake
- ↑ Nausea

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying



GIP Receptor Agonism

Central Nervous System
- ↓ Appetite
- ↓ Nausea

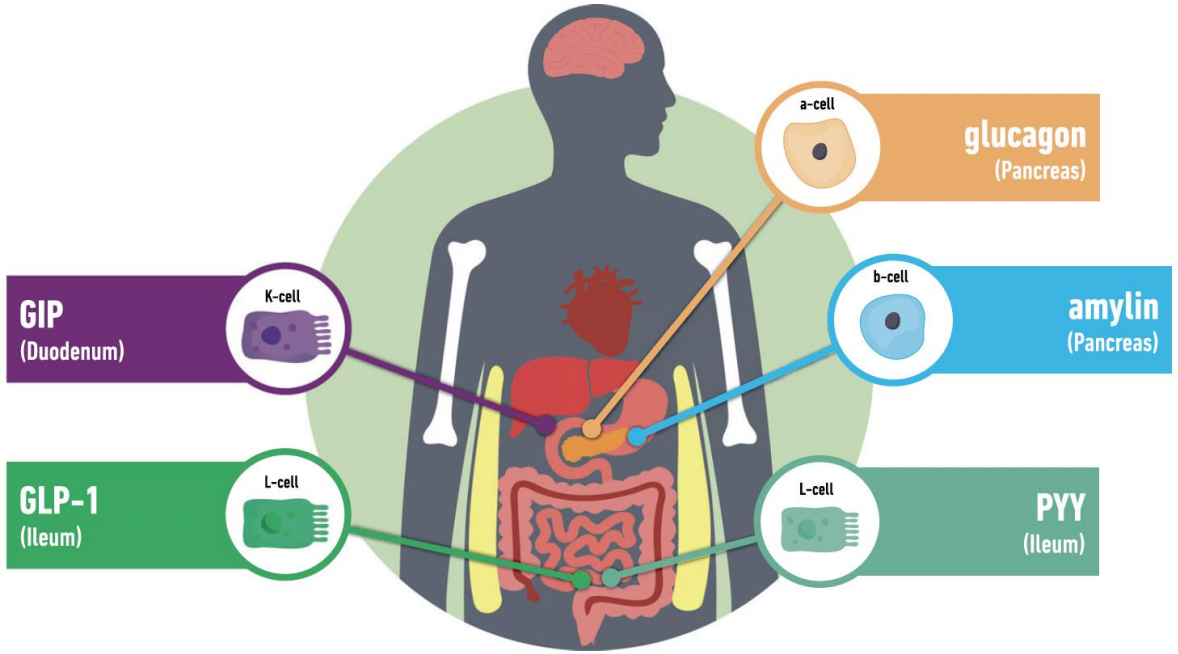
Pancreas
- ↑ Insulin
- ↑ Glucagon

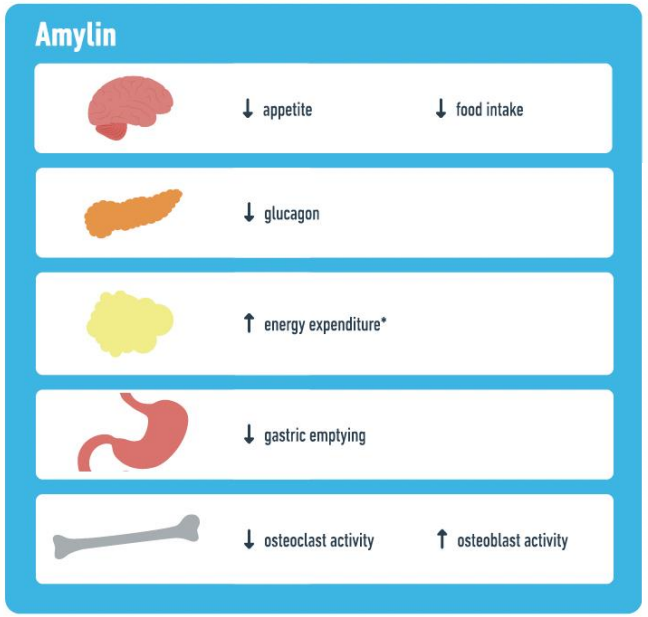
Subcutaneous White Adipose Tissue
- ↑ Lipid deposition
- ↑ Lipogenesis

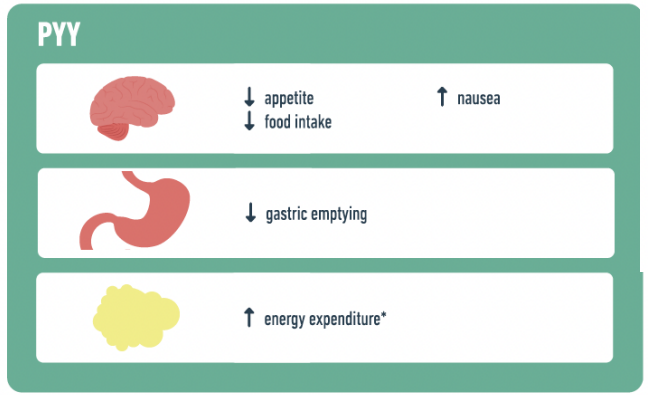
● GLP-1 Receptor Agonism
● GIP Receptor Agonism

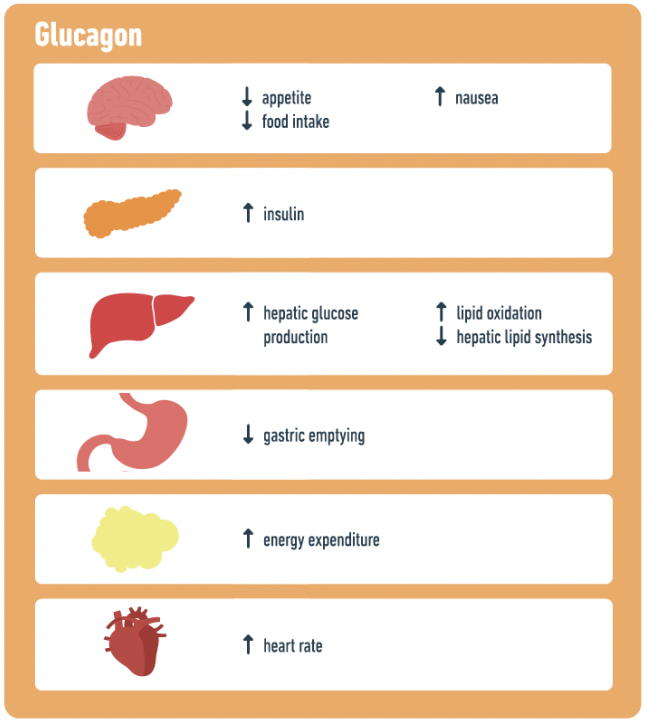
Int J Obesity; https://doi.org/10.1038/s41366-024-01473-y

Secretion and main actions of the gut hormones used in pipeline obesity treatments









International Journal of Obesity; https://doi.org/10.1038/s41366-024-01473-y

* Data mainly from animal studies

New incretin medications for obesity

Semaglutide 2.4 mg for the management of obesity

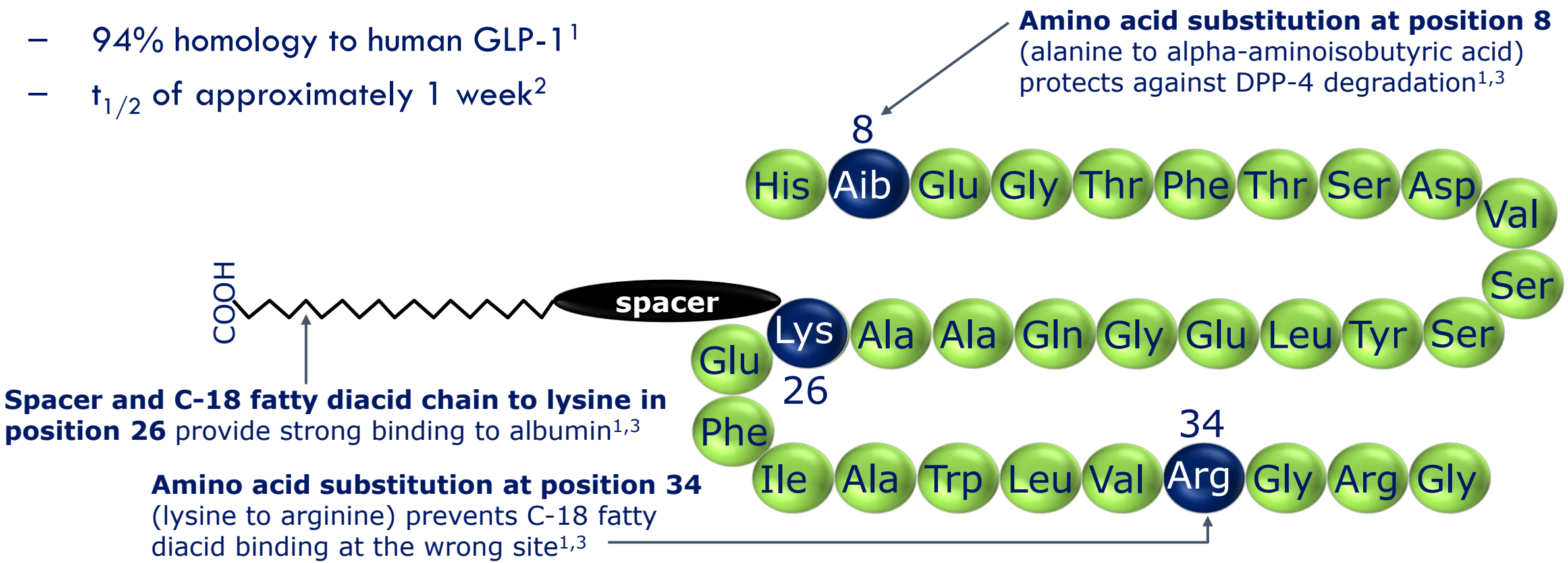
Tirzepatide for the management of obesity

Tirzepatide is not indicated for the treatment of obesity in Australia

What is semaglutide?

Semaglutide is a once-weekly human glucagon-like peptide-1 (GLP-1) receptor agonist.

- 94% homology to human GLP-1[1]
- $t_{1/2}$ of approximately 1 week[2]



– DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{1/2}$, 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. Lund A et al. *Eur J Intern Med* 2014;25:407–14.

ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

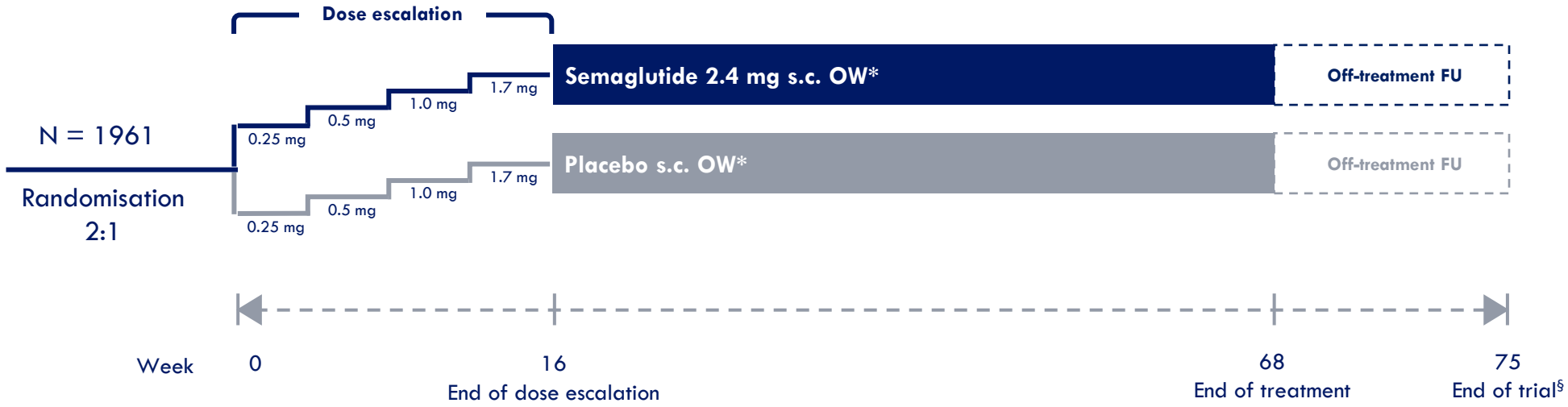
John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

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

Study Design and Inclusion Criteria of Participants

Inclusion criteria

- Male or female
- ≥18 years
- BMI: ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 comorbidity
- HbA_{1c} ≤ 6.5%



*As an adjunct to lifestyle intervention (–500 kcal/day diet + 150 min/week physical activity). §End of trial for main phase.

Primary endpoints (Week 68)

- % weight loss from baseline
- ≥5% responders

Confirmatory secondary endpoints (Week 68)

- ≥10% and ≥15% responders
- Waist circumference, systolic blood pressure, SF-36 physical functioning, IWQOL-Lite-CT physical function

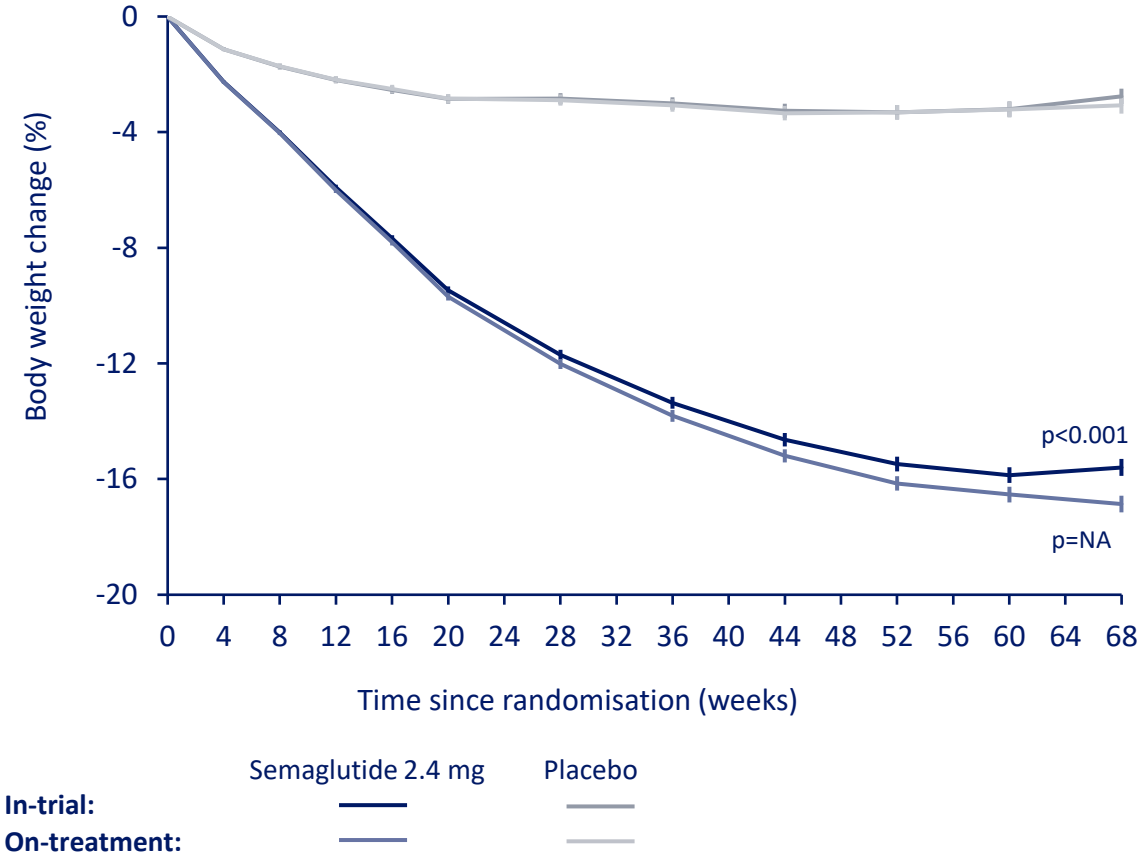
BMI: body mass index. **FU:** follow-up. **HbA_{1c}:** glycated haemoglobin. **IWQOL-Lite-CT:** Impact of Weight on Quality of Life–Lite Clinical Trials Version questionnaire. **OW:** once weekly. **s.c.:** subcutaneous. **SF-36:** Short-Form 36-item Health Survey.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Semaglutide 2.4mg as an adjunct to lifestyle modification

Observed body weight change over time

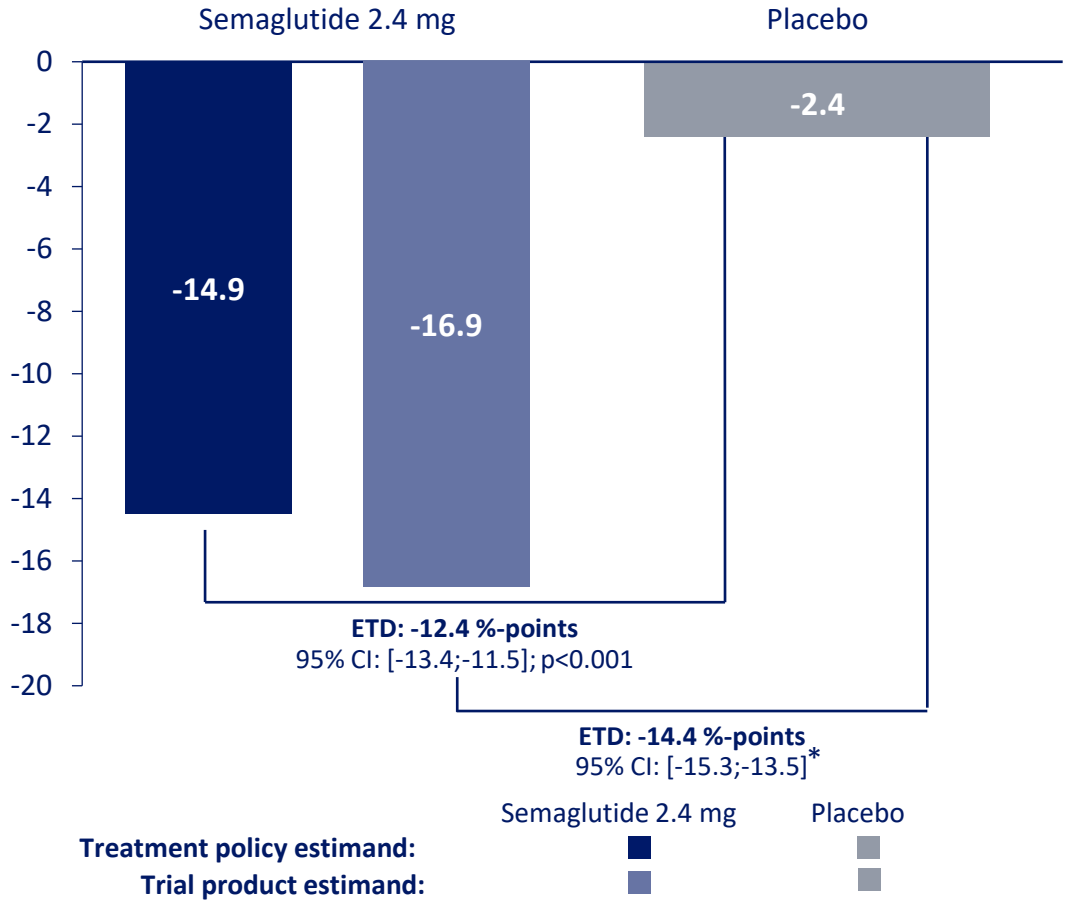
(Mean at baseline: 105.3 kg)



94.9% of participants randomised to semaglutide completed the STEP 1 study (n=1240/1306) and of these, 89.6% were receiving the 2.4 mg maintenance dose at Week 68.

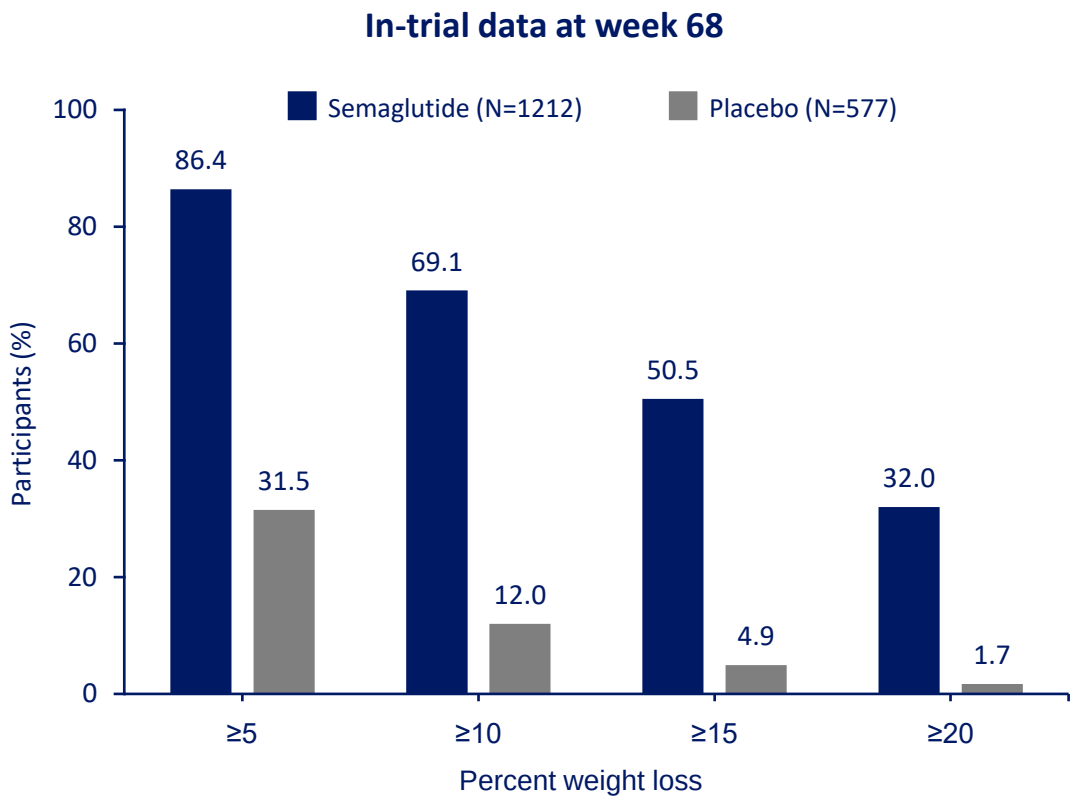
Estimated change from baseline to Week 68

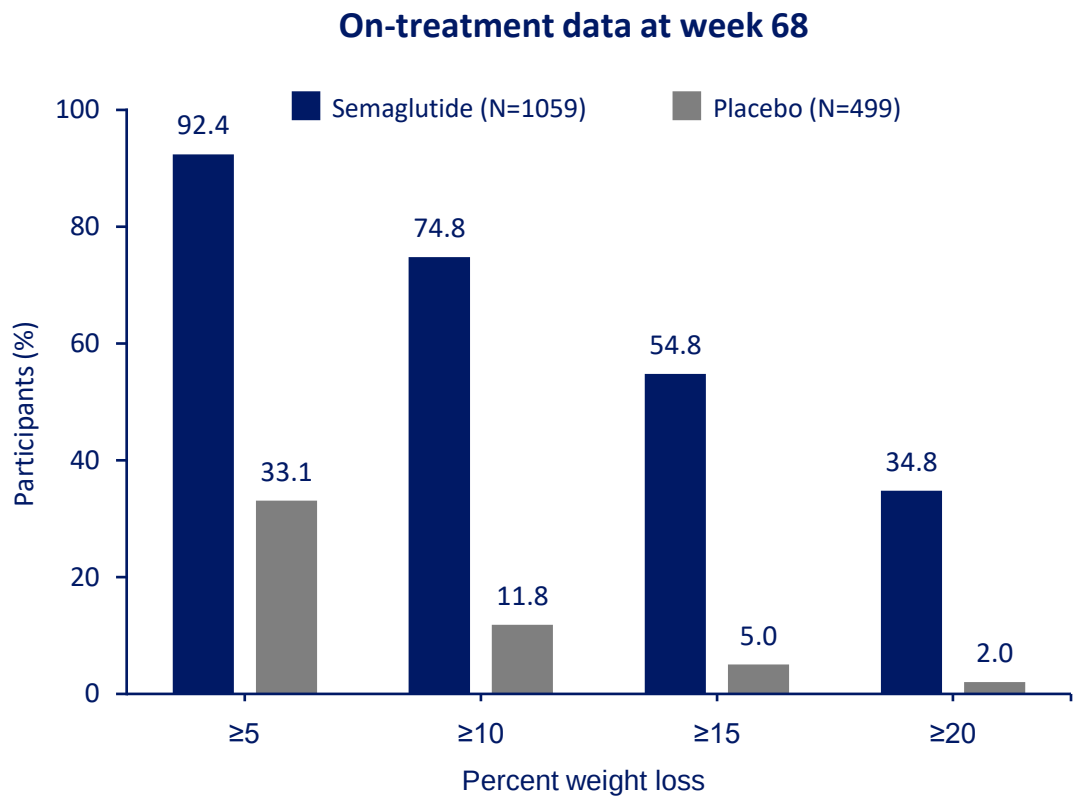
(Treatment policy and trial product estimands)



Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Semaglutide 2.4 mg - Achievement of categorical body weight reductions at week 68





Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Improvements in health parameters at Week 68

CONFIRMATORY SECONDARY ENDPOINTS

-13.5 cm
with semaglutide 2.4 mg vs -4.1 cm placebo, p<0.001
Waist circumference

-6.2 mmHg
with semaglutide 2.4 mg vs -1.1 mmHg placebo, p<0.001
Systolic blood pressure

+2.2
with semaglutide 2.4 mg vs +0.4 placebo, p<0.001
SF-36 physical function score

+14.7
with semaglutide 2.4 mg vs +5.3 placebo, p<0.001
IWQOL-Lite-CT physical function score

SUPPORTIVE SECONDARY ENDPOINTS

-0.45%
with semaglutide 2.4 mg vs -0.15% placebo, p=NA*
HbA_{1c}

-8.4 mg/dL
with semaglutide 2.4 mg vs -0.5 mg/dL placebo, p=NA*
Fasting plasma glucose

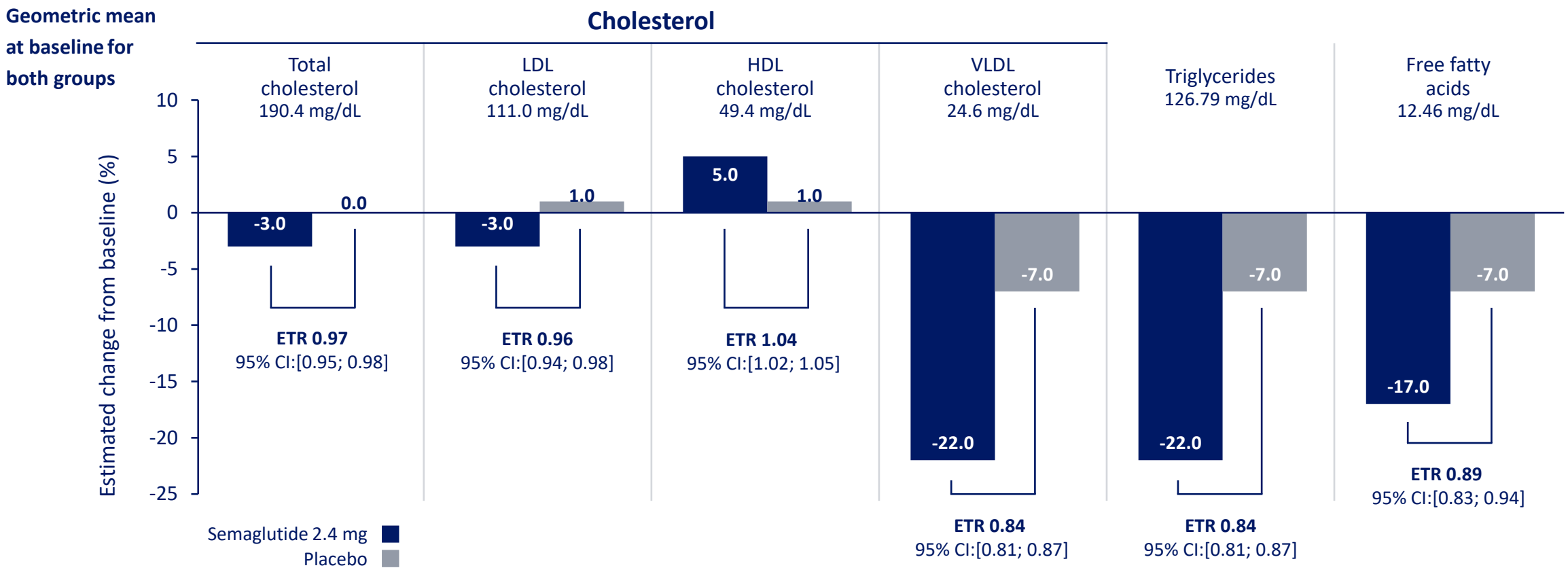
-2.8 mmHg
with semaglutide 2.4 mg vs -0.4 mmHg placebo, p=NA*
Diastolic blood pressure

-53.0%
with semaglutide 2.4 mg vs -15.0% placebo, p=NA*
C-reactive protein

***Not part of the statistical testing hierarchy; p-value not available (NA).**
All values are estimated for the treatment policy estimand.
HbA_{1c}: glycated haemoglobin. **IWQOL-Lite-CT:** Impact of Weight on Quality of Life–Lite Clinical Trials Version questionnaire. **SF-36:** Short-Form 36-item Health Survey.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Changes in fasting lipids at Week 68*

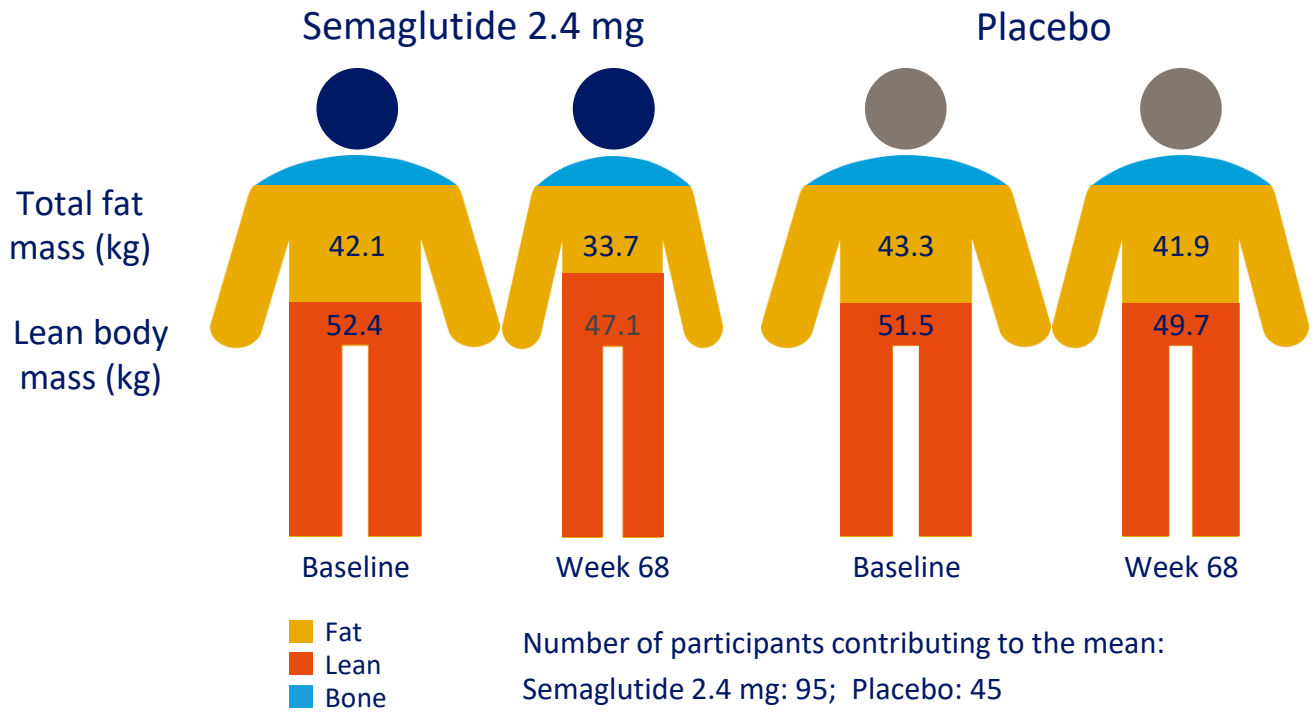


***Not part of the statistical testing hierarchy; p-value not available**.
All values are estimated for the treatment policy estimand.
CI: confidence interval. **ETR:** estimated treatment ratio. **HDL:** high-density lipoprotein. **LDL:** low-density lipoprotein. **VLDL:** very low-density lipoprotein.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Changes in body composition at Week 68*

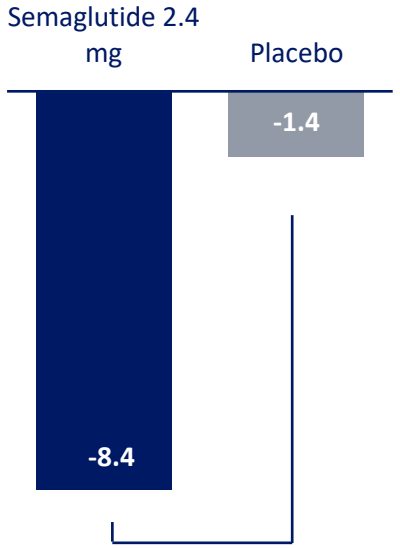
In-trial§



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

Total fat mass (kg)#

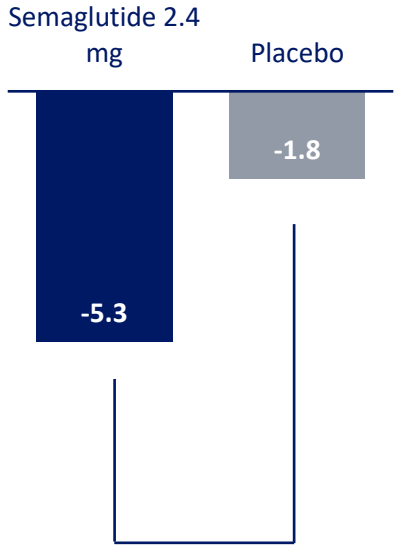
Mean baseline: 42.5 kg



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

Lean body mass (kg)#

Mean baseline: 52.1 kg



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

***Not part of the statistical testing hierarchy; p-value not available.**
§Observed data for the in-trial period; #Estimated data for the treatment policy estimand.
CI: confidence interval. **ETD:** estimated treatment difference.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Common adverse events ≥10% of participants (68 weeks)

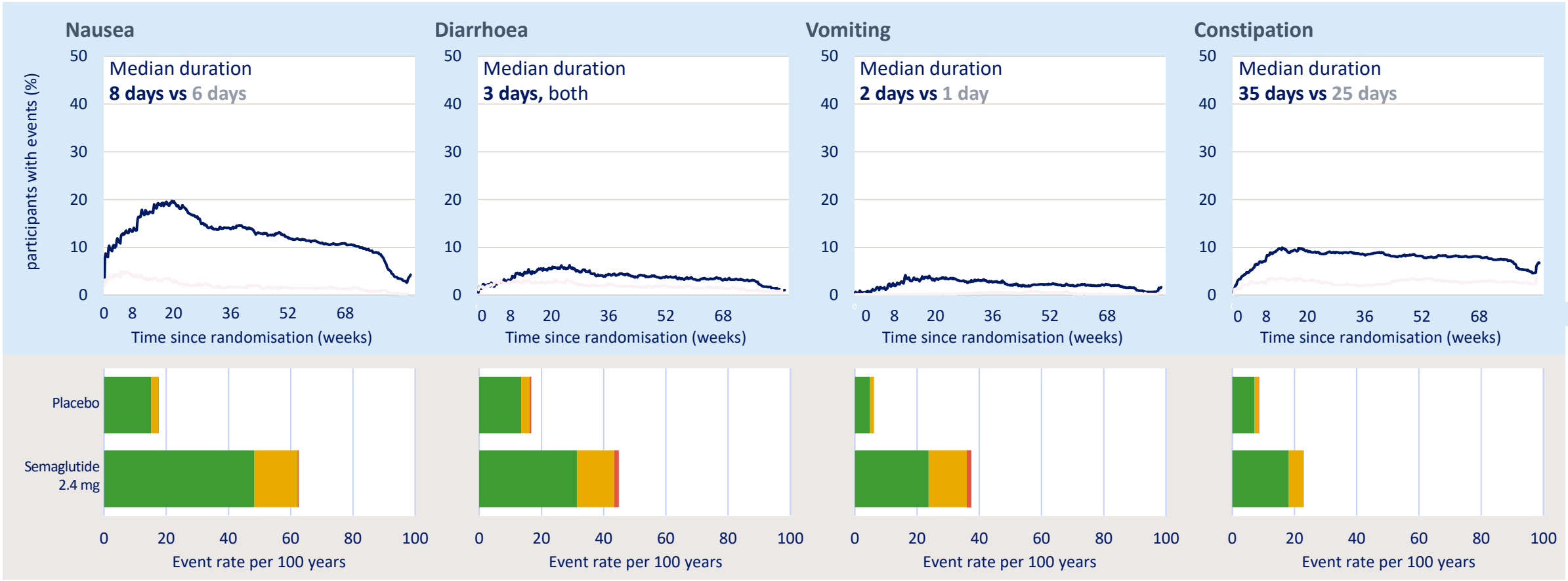
Preferred term	Semaglutide 2.4 mg (N=1306)		Placebo (N=655)	
	N	%	N	%
Nausea	577	**44.2**	114	**17.4**
Diarrhoea	412	**31.5**	104	**15.9**
Vomiting	324	**24.8**	43	**6.6**
Constipation	306	**23.4**	62	**9.5**
Nasopharyngitis	281	**21.5**	133	**20.3**
Headache	198	**15.2**	80	**12.2**
Dyspepsia	135	**10.3**	23	**3.5**
Abdominal pain	130	**10.0**	36	**5.5**
Upper respiratory tract infection	114	**8.7**	80	**12.2**

Semaglutide 2.4 mg
Placebo

Data are for the on-treatment observation period.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Prevalence and severity of selected GI events (68 weeks)



Data are for the on-treatment observation period.

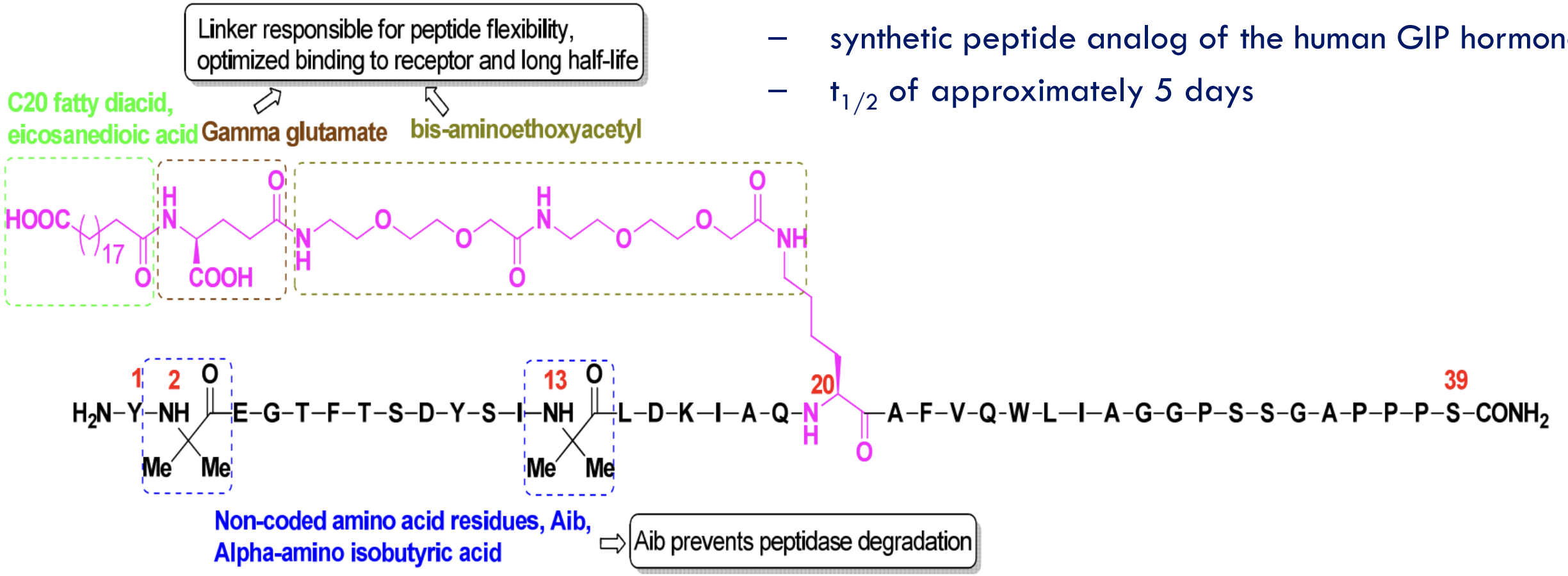
GI: gastrointestinal.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

What is tirzepatide?

Tirzepatide is a once-weekly human GLP-1 and GIP receptor co-agonist.

- synthetic peptide analog of the human GIP hormone
- $t_{1/2}$ of approximately 5 days



Molecules 2022, 27(13), 4315; https://doi.org/10.3390/molecules27134315

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide Once Weekly for the Treatment of Obesity

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

Tirzepatide is not indicated for the treatment of obesity in Australia

Study Design and Inclusion Criteria of Participants

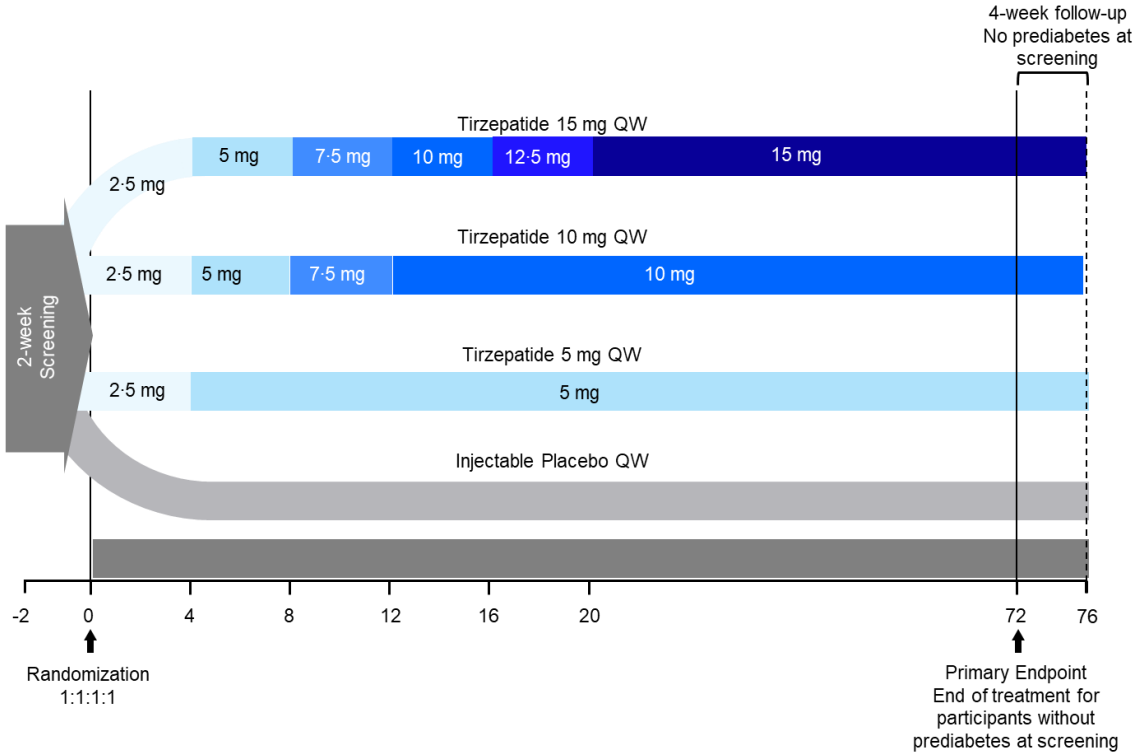
Phase 3, multicenter, randomized, double-blind, placebo-controlled trial at 118 sites in 9 countries (NCT04184622)

1 Key Inclusion Criteria

- Age ≥18 years
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)
- History of ≥1 self-reported unsuccessful dietary efforts to lose body weight

2 Key Exclusion Criteria

- Type 1 or Type 2 Diabetes mellitus
- Change in body weight >5 kg within 3 months prior to screening
- Obesity induced by other endocrinologic disorders or monogenetic or syndromic forms of obesity
- History of pancreatitis



Note: Tirzepatide was administered once weekly (QW) subcutaneously as an adjunct to a reduced-calorie diet and increased physical activity

Tirzepatide is not indicated for the treatment of obesity in Australia

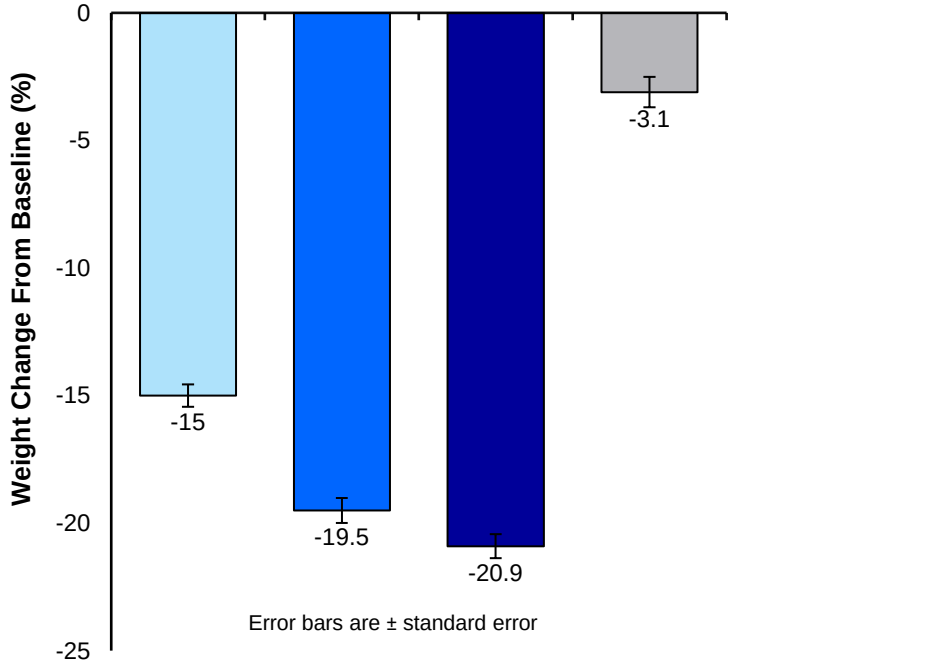
BMI = Body Mass Index; QW = Once Weekly.

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

Change in Body Weight From Baseline to 72 Weeks

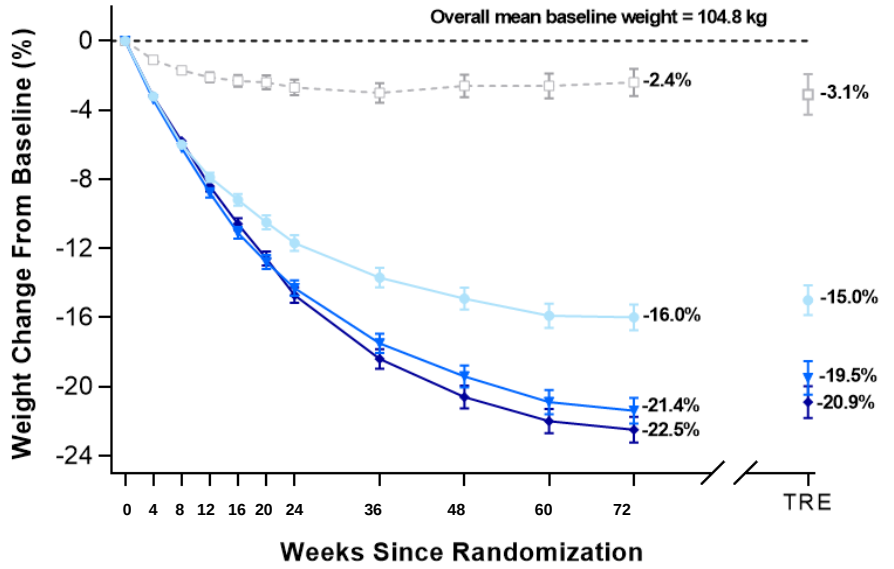
Tirzepatide 5 mg Tirzepatide 10 mg

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-11.9 (-13.4, -10.4)	-16.4 (-17.9, -14.8)	-17.8 (-19.3, -16.3)
P value		<.001	



Tirzepatide āa5 mg Placebo

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	−13.5 (−14.6 to −12.5)	−18.9 (−20.0, −17.8)	−20.1 (−21.2, −19.0)
P value		<.001	



Note: Data derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown
Error bars are ± standard error

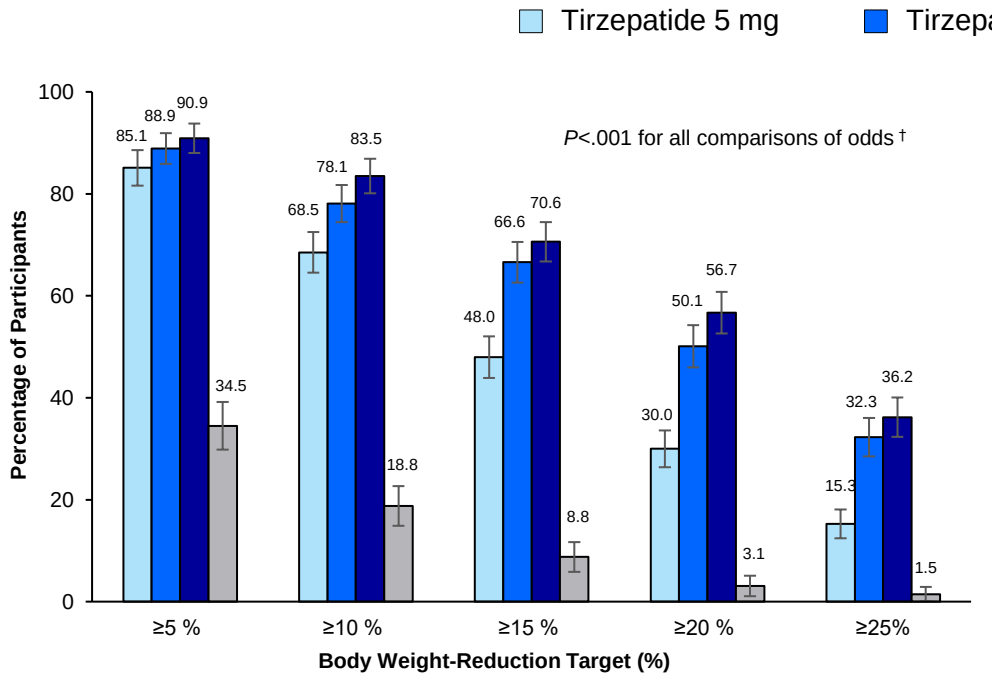
CI = Confidence Interval; ETD = Estimated Treatment Difference; TRE = Treatment Regimen Estimand; TZP = Tirzepatide; PBO = Placebo.

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

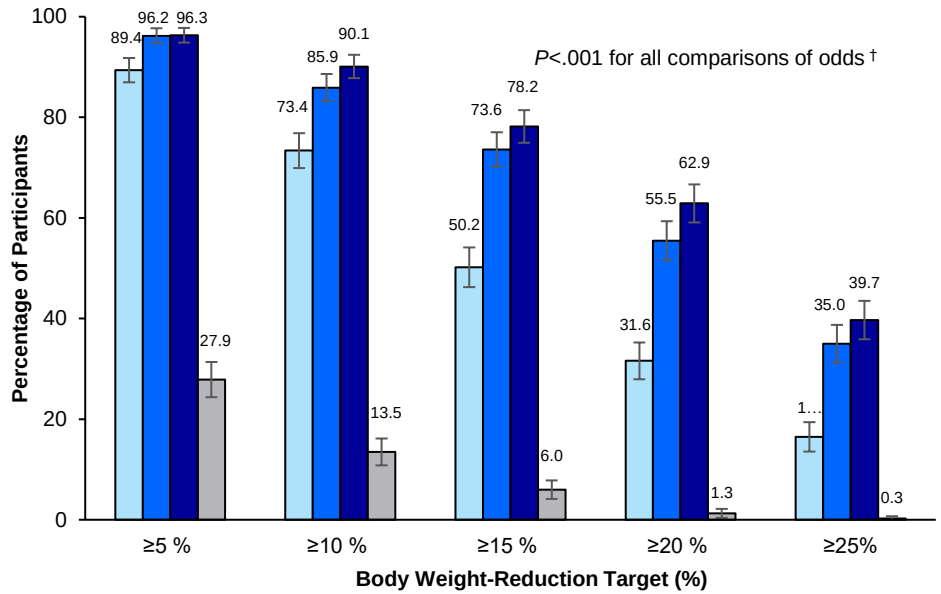
Percentage of Participants Achieving Body Weight Reductions Targets

Treatment Regimen Estimand*



Note: The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. Missing value at week 72 was imputed using MMRM if missing was solely due to COVID-19 and using multiple imputation if missing was not due to COVID-19

Efficacy Estimand*



Note: The percentage of participants achieving weight loss targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at week 72 was predicted from MMRM analysis. Logistic regression analysis was used for all comparisons to placebo

*Least-squares means are presented, unless otherwise noted. Error bars indicate the 95% confidence interval

† Participants with weight reduction ≥25% is an exploratory endpoint and hence not controlled for type 1 error; therefore *P*-values are not shown

MMRM = Mixed-model or Repeated-measures..

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

Improvements in health parameters

-18.5 cm
with tirzepatide 15 mg vs -4.0 cm placebo, p<0.001
Waist circumference

-42.9 mIU
with pooled tirzepatide vs -6.6 mIU placebo, p <0.001
Fasting insulin††

-7.2 mmHg
with with pooled tirzepatide vs -1.0 mmHg placebo, p<0.001
Systolic blood pressure

95.3%
with pooled tirzepatide vs 61.9% placebo, p=NA*
patients reverting to normoglycemia

+3.6
with pooled tirzepatide vs +0.4 placebo, p<0.001
SF-36 physical function score *†

-4.8 mmHg
with pooled tirzepatide vs -0.8 mmHg placebo, p=NA*
Diastolic blood pressure

-24.8 mg/dL
with pooled tirzepatide vs -5.6 placebo, p<0.001
Triglycerides††

8 mg/dL
with pooled tirzepatide vs – 0.7 mg/dL placebo, p <0.001
HDL cholesterol ††

Note: Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated ; *Data are for the pooled tirzepatide 10 mg and 15 mg groups †Change from baseline in SF-36 score was assessed using analysis of covariance model with terms for baseline SF-36 PF score, treatment, and stratification factors
††Lipid parameters and fasting insulin were analyzed using log-transformation. Data presented are model-based estimate ± SE Note: All changes are from baseline to week 72, unless otherwise stated

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

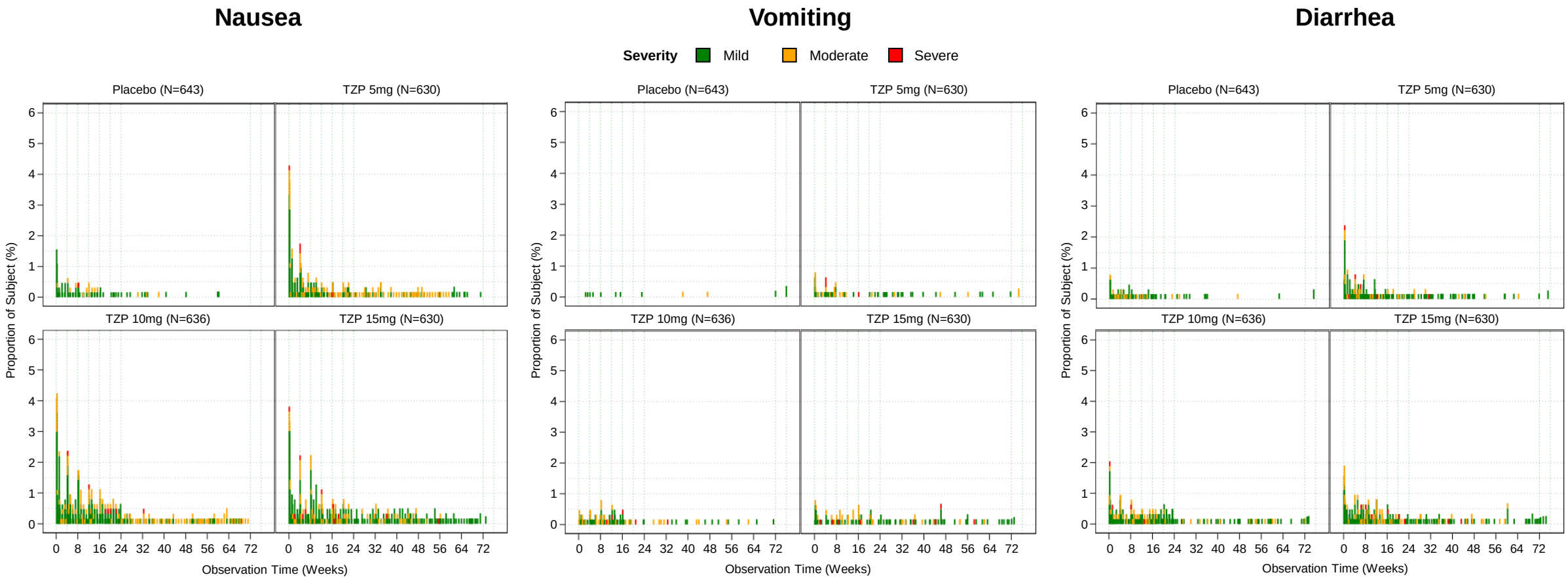
Common adverse events ≥5% of participants (72 weeks)

Adverse Events n (%)	Tirzepatide 5 mg N=630	Tirzepatide 10 mg N=636	Tirzepatide 15 mg N=630	Placebo N=643
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group (preferred term)				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
COVID-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Decreased appetite	59 (9.4)	73 (11.5)	54 (8.6)	21 (3.3)
Headache	41 (6.5)	43 (6.8)	41 (6.5)	42 (6.5)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection site reaction	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

Incidence of Nausea, Vomiting, and Diarrhoea Over Time

Most gastrointestinal events were transient, occurring primarily during the dose-escalation period, and were mostly mild to moderate in severity



Note: Percentages are based on number of participants at risk at specific observation time

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

What happens when incretin-based therapy is stopped?

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ORIGINAL ARTICLE

WILEY

Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension

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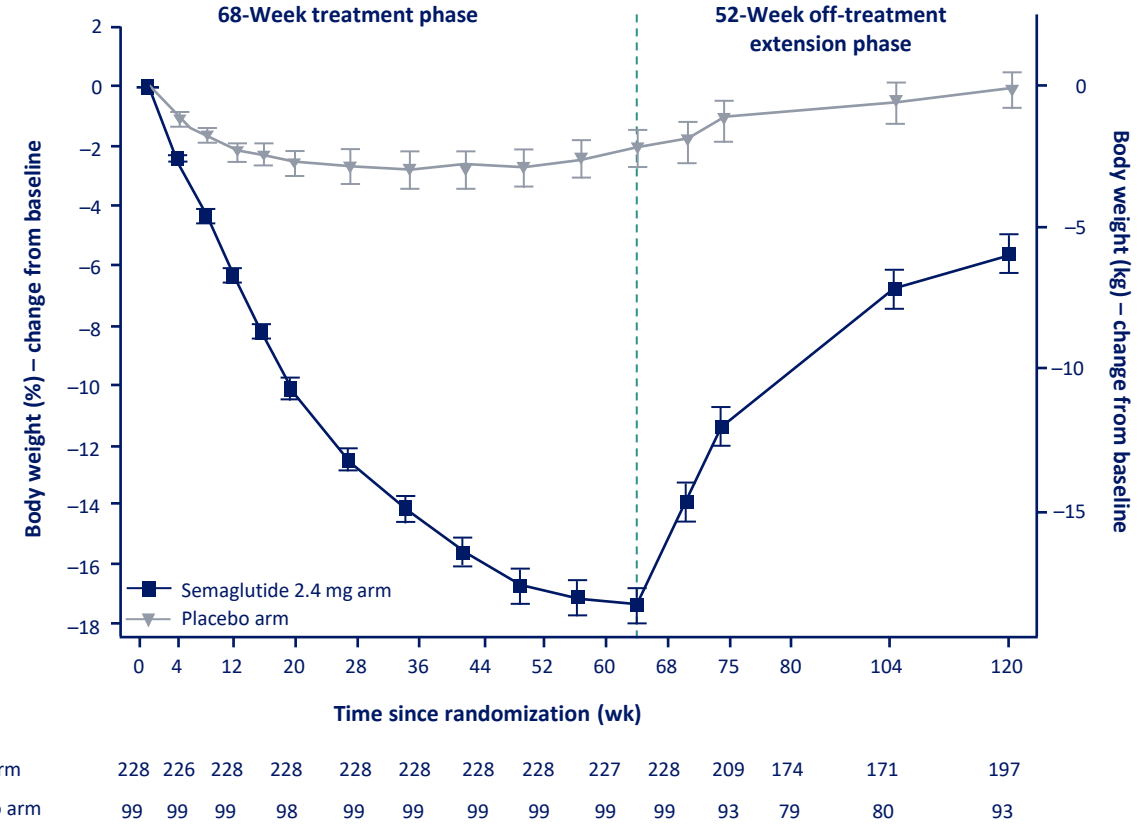
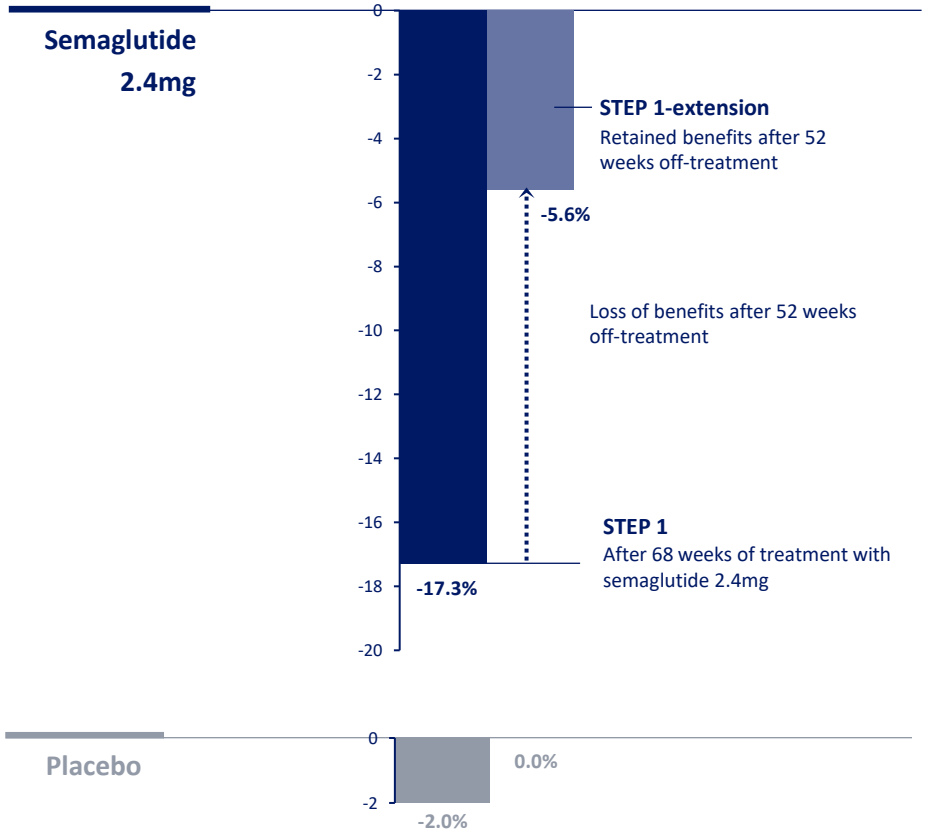
Change in body weight

STEP 1 trial extension

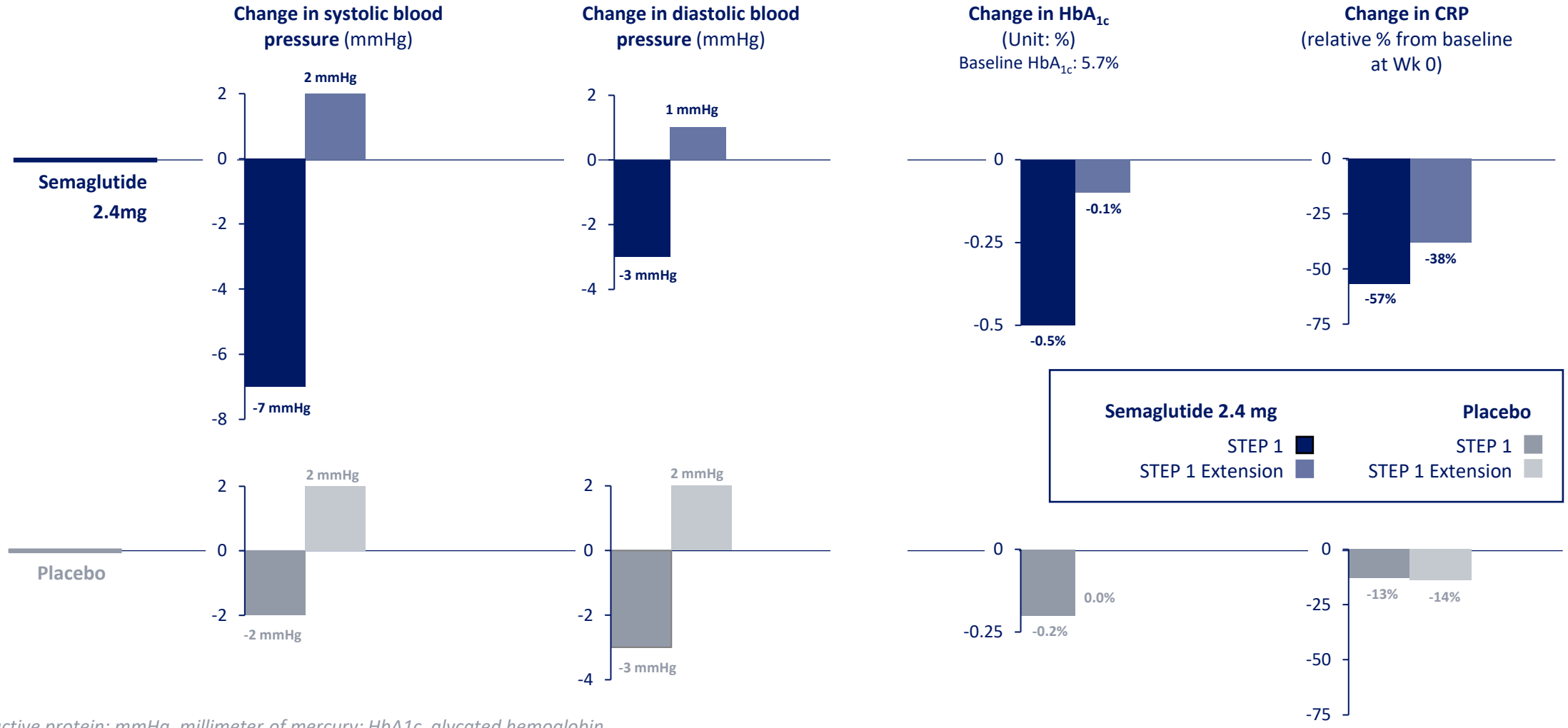




Wilding et al. Diabetes Obes Metab. 2022 Apr 19. doi: 10.1111/dom.14725.

Change in cardiometabolic parameters

STEP 1 trial extension



CRP, C-reactive protein; mmHg, millimeter of mercury; HbA1c, glycated hemoglobin

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

Anti-obesity pharmacotherapies in the pipeline

AMYLIN/GLP-1 Receptor agonists

- Cagri-Sema (Phase 3 ongoing)

GLUCAGON/GLP-1 Receptor agonists

- Survodutide (Phase 3)
- Mazdutide (Phase 3 ongoing)

GIP / GLUCAGON / GLP-1 Receptor agonists

- Retatrutide (Phase 3 ongoing)

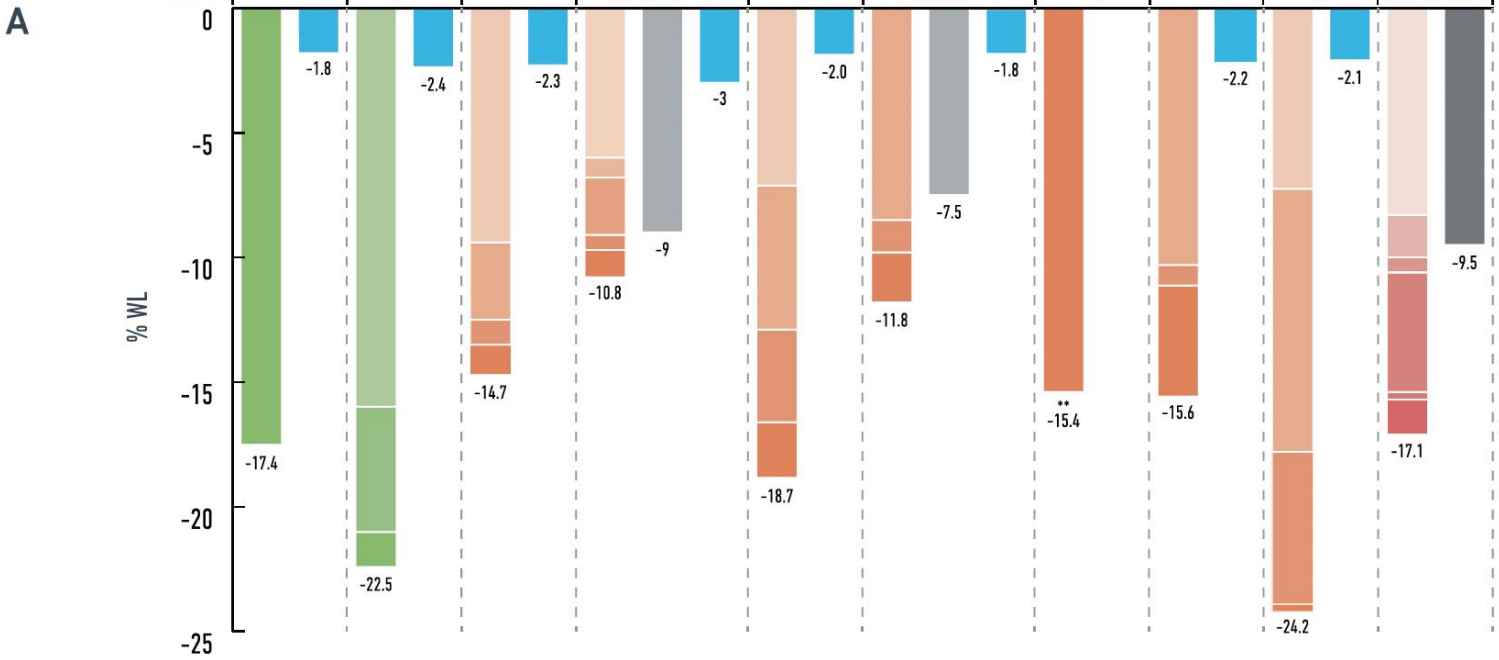
ORAL GLP-1 Receptor agonists

- Oral semaglutide (Phase 3)
- Orforglipron (Phase 3 ongoing)
- Danuglipron (Phase 2)

THESE THERAPIES ARE NOT APPROVED FOR THE MANAGEMENT OF OBESITY IN AUSTRALIA

Weight loss with the obesity pharmacotherapies pipeline in people without diabetes

	Oral Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Cagrilintide[A]	Survodutide[A*]	Efinopegdutide[B]	Mazdutide[C*]	Pemvidutide[A*]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.4/10mg OW	9mg OW	1.2/1.8/2.4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Number of participants	667	2539	272	706	387	474	80	391	338	95
Timepoint (weeks)	68	72	36	26	46	26	24	48	48	20
Baseline weight (kg)	105.4	104.8	108.7	107.4	105.7	113.3	96.9	104	107.7	95.7 - 99.6
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg



KEY:
- Phase 3
- Phase 2
- Phase 1
- Placebo
- Active Comparator

Lowest dose → Highest dose

OD once daily, OW once weekly, PO oral, SC subcutaneous, GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, GCG glucagon, PBO placebo, LIRA liraglutide, SEMA semaglutide, WL weight loss, NR not reported or not available.
A for efficacy estimand data,
B main analysis presented, as efficacy estimand not available,
C unclear whether efficacy estimand or treatment-regimen estimand,
*data from published abstract, presentation, clinicaltrial.gov or from press-release by the manufacturing company,
**estimated treatment difference.

International Journal of Obesity; https://doi.org/10.1038/s41366-024-01473-y

Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial

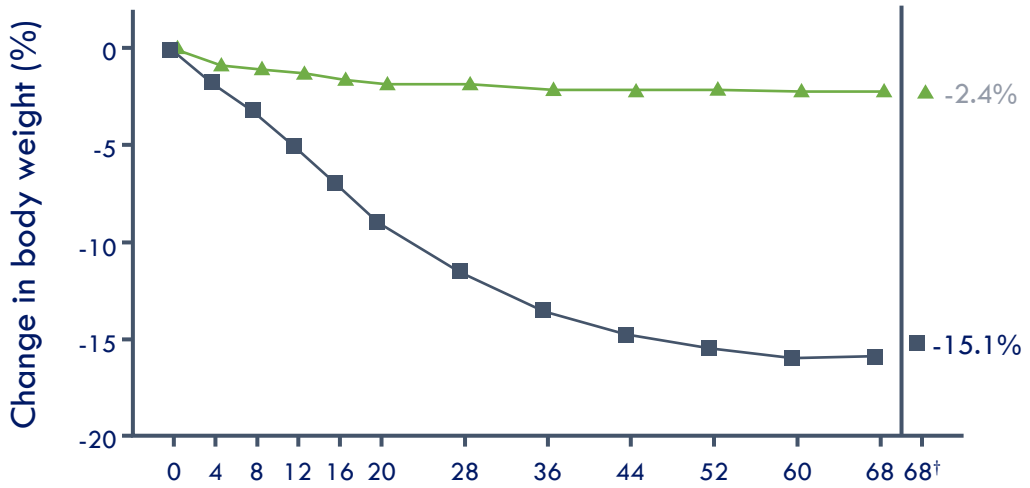
*Filip K Knop, Vanita R Aroda, Ruben D do Vale, Thomas Holst-Hansen, Peter N Laursen, Julio Rosenstock, Domenica M Rubino, W Timothy Garvey, for the OASIS 1 Investigators**

Change in body weight (%) over time

Primary endpoint

Treatment policy estimand

Mean baseline body weight: 105.4 kg



Number of participants

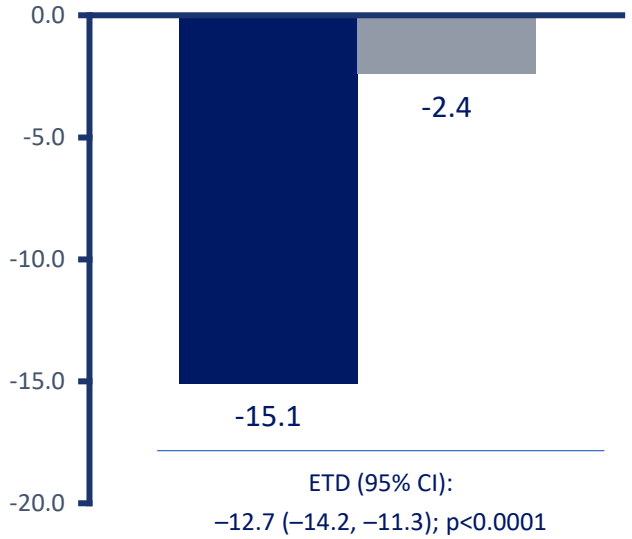
Oral semaglutide 50 mg	334	329	320	318	318	320	314	315	310	309	304	317	334
Placebo	333	325	316	316	320	318	312	303	290	294	279	295	333

Oral semaglutide 50 mg Placebo

Data are observed (i.e., as-measured) mean (standard error) changes from baseline in body weight; numbers below the graphs are the number of participants contributing to the mean (full analysis set); .

Treatment policy estimand

Mean baseline body weight: 105.4 kg



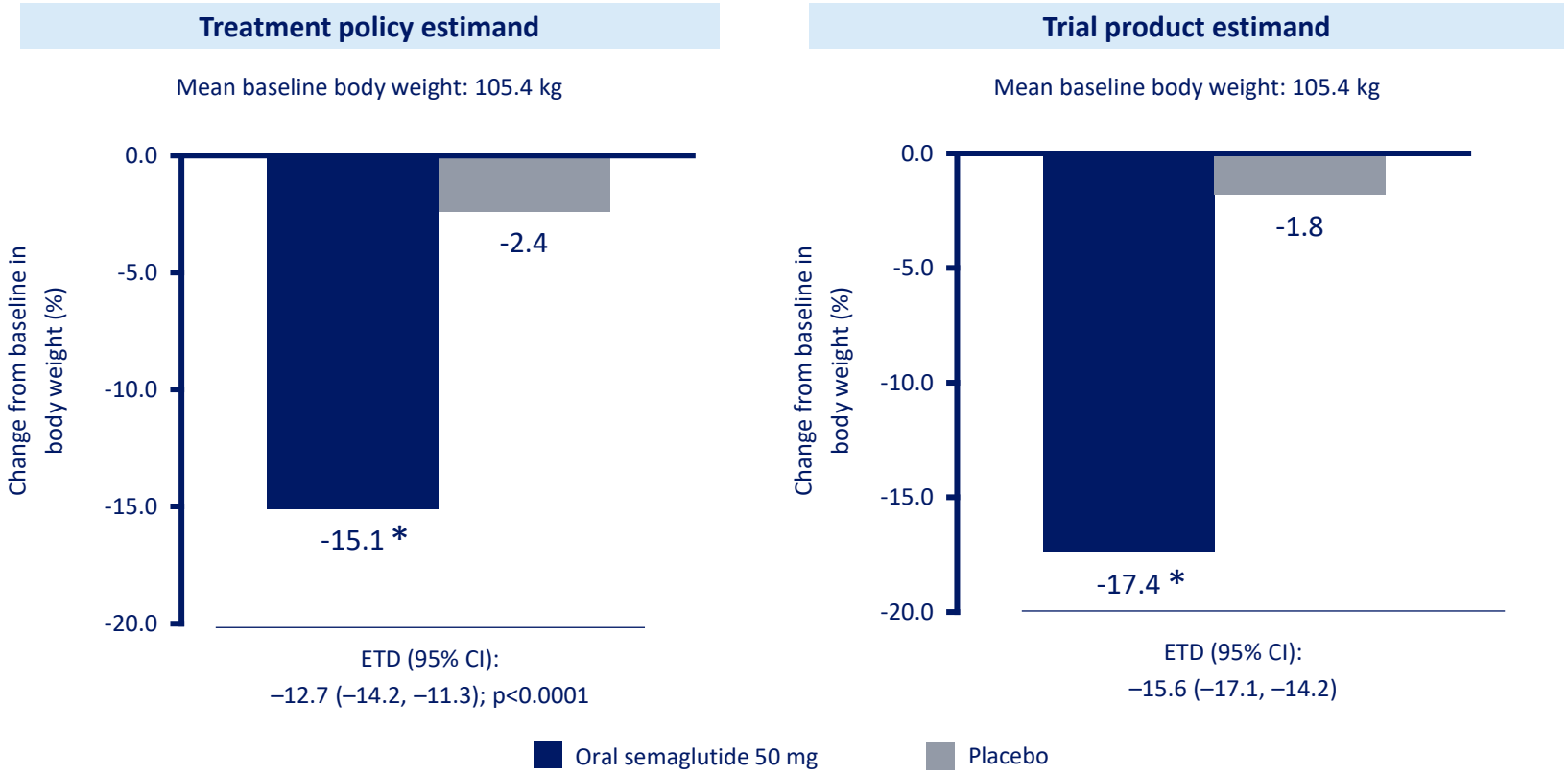
*Statistically significant vs placebo (full analysis set).
CI, confidence interval; ETD, estimated treatment difference.

Knop et al. The Lancet 2023; doi:https://doi.org/10.1016/S0140-6736(23)01185-6

Change in body weight (%) at week 68

Primary endpoint

Significantly greater body weight reduction for oral semaglutide 50 mg vs placebo



**Statistically significant vs placebo (full analysis set).*
CI, confidence interval; ETD, estimated treatment difference.
Knop et al. The Lancet 2023; doi:https://doi.org/10.1016/S0140-6736(23)01185-6

Key learning points

- Currently available incretin therapies target GLP-1 or both GLP-1 and GIP receptors

- Semaglutide and tirzepatide in people with obesity result in:
  - a significant and clinically meaningful reduction in body weight
  - improvement in cardiovascular risk factors
  - Improvements in quality of life

- Incretin therapy must be combined with lifestyle modification to achieve optimal weight loss

- The most common AEs with incretin therapy are gastrointestinal in nature, mostly mild or moderate in severity and occur early (during dose-escalation)

Tirzepatide is not indicated for the treatment of obesity in Australia