서 울 대 학 교 병 원
SEOUL NATIONAL UNIVERSITY HOSPITAL

GLP-1RA for obesity management, How can we maximize its clinical value?

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SNUH

Contents

SCALE phase 3 clinical development programme

Overview

Phase 3a

SCALE Obesity and Prediabetes [1]

- Weight management and delayed onset of diabetes
  - Liraglutide 3.0 mg n=2487
  - Placebo n=1244

SCALE Diabetes[2]

- Weight management in type 2 diabetes
  - Liraglutide 3.0 mg n=423
  - Liraglutide 1.8 mg n=211
  - Placebo n=212

SCALE Maintenance [3]

- Prevention of weight regain
  - Liraglutide 3.0 mg n=212
  - Placebo n=210

SCALE Sleep Apnoea [4]

- Effect of liraglutide in subjects with obesity and moderate to severe OSA
  - Liraglutide 3.0 mg n=180
  - Placebo n=179

Phase 3b

SCALE-Insulin[5]

- Clinical benefit of Liraglutide + IBT in patients taking basal insulin
  - Liraglutide 3.0 mg + IBT + basal insulin n=198
  - Placebo + IBT + basal insulin n=198

SCALE-IBT[6]

- Weight management with liraglutide 3.0 mg used as adjunct to IBT
  - Liraglutide 3.0 mg + IBT n=142
  - Placebo + IBT n=140

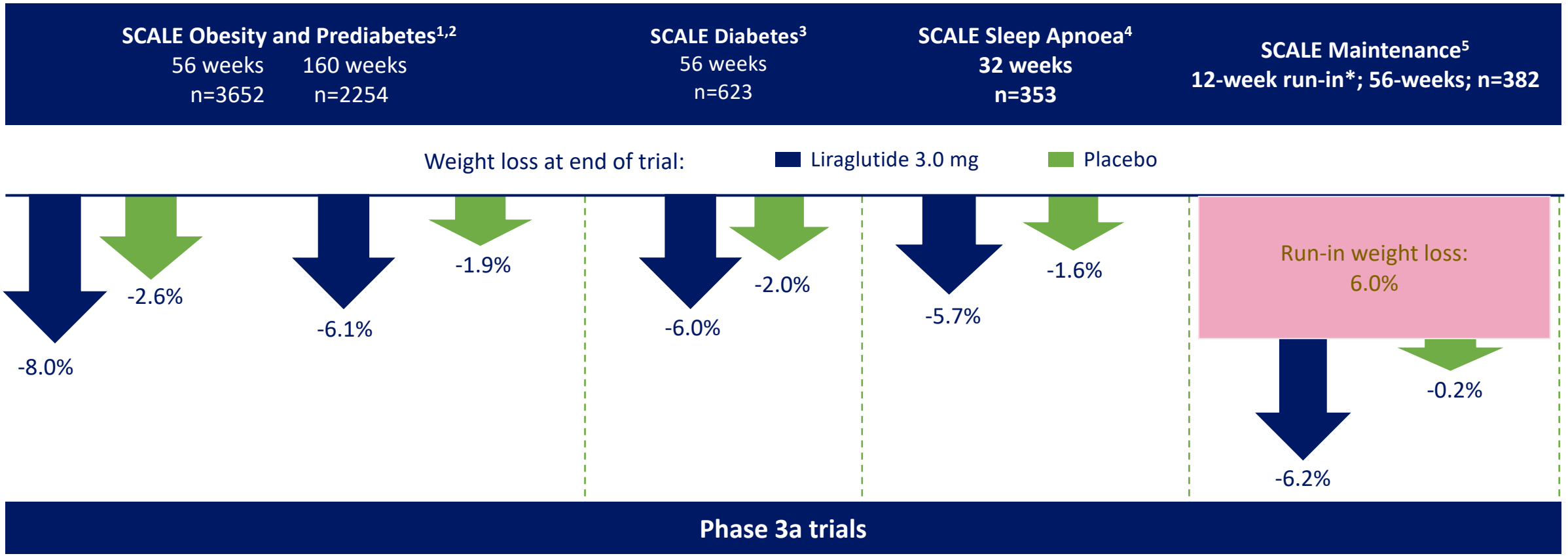
1. Pi-Sunyer et al. N Engl J Med 2015;373:11–22; 2. Davies et al. JAMA 2015;314:687–99; 3. Wadden et al. Int J Obes (Lond) 2013;37:1443–51;
4. Blackman et al. Int J Obes (Lond). 2016;40:1310-9; 5. Garvey et al. Diabetes Care 2020; 43(5): 1085-1093; 6. Wadden et al. Obesity (Silver Spring) 2020; 28(3): 529-536

SCALE Phase 3a primary publications

SCALE Obesity and Prediabetes *56 weeks*	SCALE Obesity and Prediabetes *160 weeks*	SCALE Diabetes	SCALE Maintenance	SCALE Sleep Apnoea
				
The NEW ENGLAND JOURNAL of MEDICINE	THE LANCET	JAMA The Journal of the American Medical Association	International Journal of Obesity	International Journal of Obesity

Hyperlinked to Medical toolbox publication decks; PDF images are linked to published article PDFs in the Medical toolbox

Weight loss across Phase 3a trials



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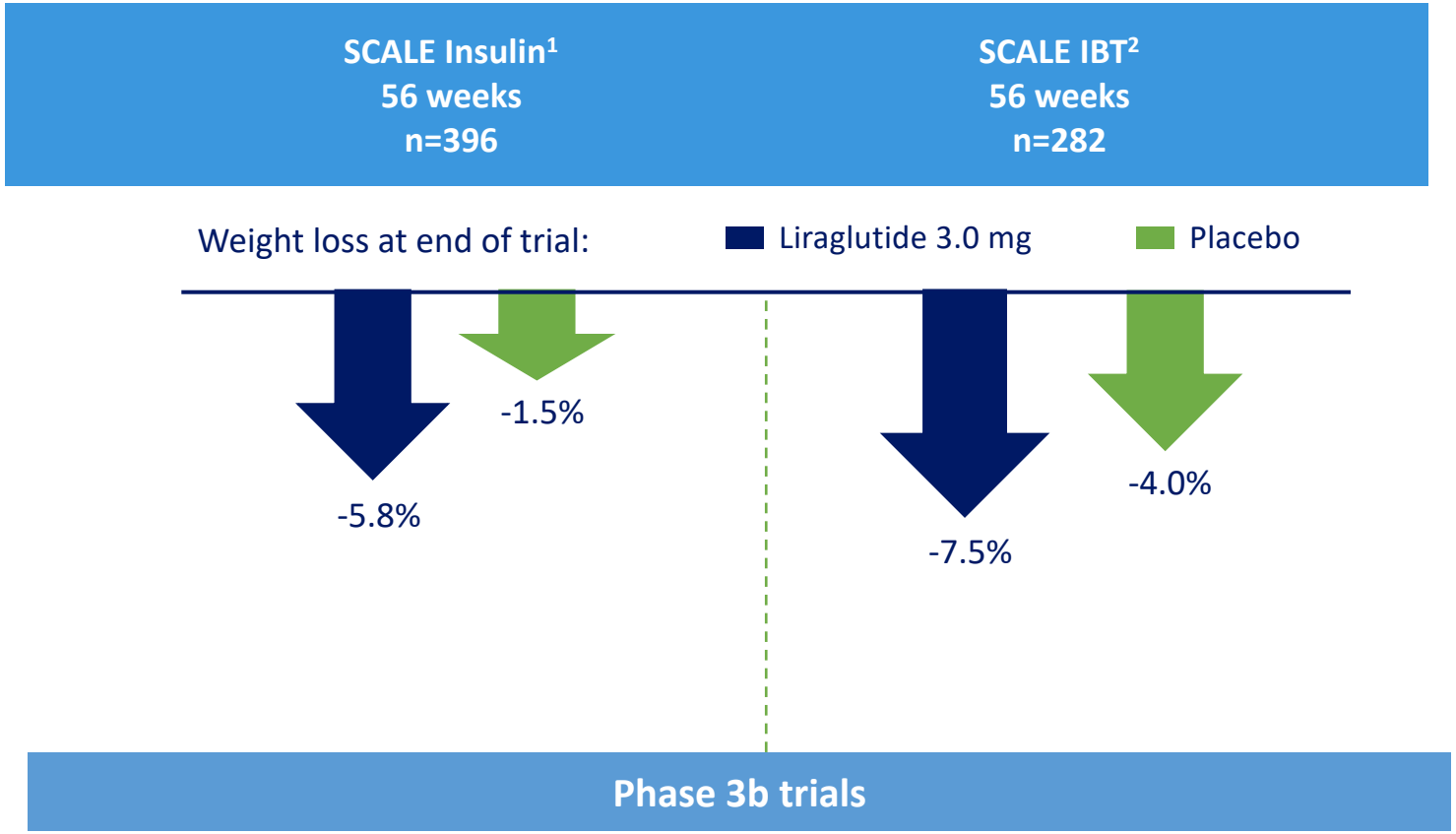
Weight loss across Phase 3b trials



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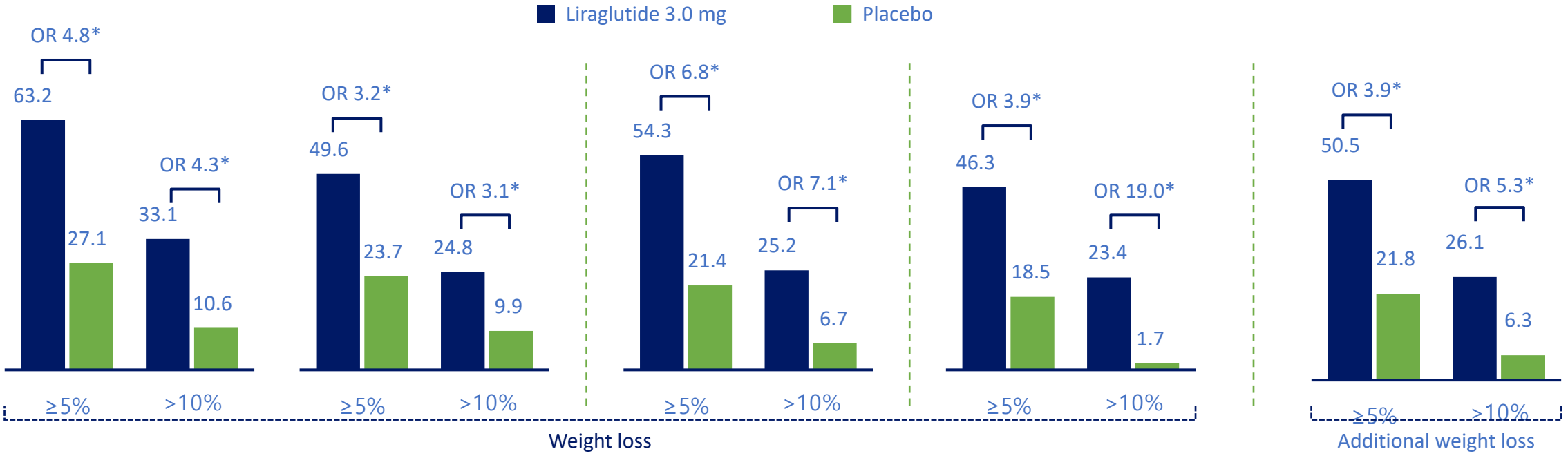
Categorical weight loss across Phase 3a trials

SCALE Obesity and Prediabetes[1,2]		SCALE Diabetes[3]	SCALE Sleep Apnoea[4]	SCALE Maintenance[5]
56 weeks; n=3652	160 weeks; n=2210†	56 weeks; n=623	32 weeks; n=353	12-week run-in‡; 56-weeks; n=382



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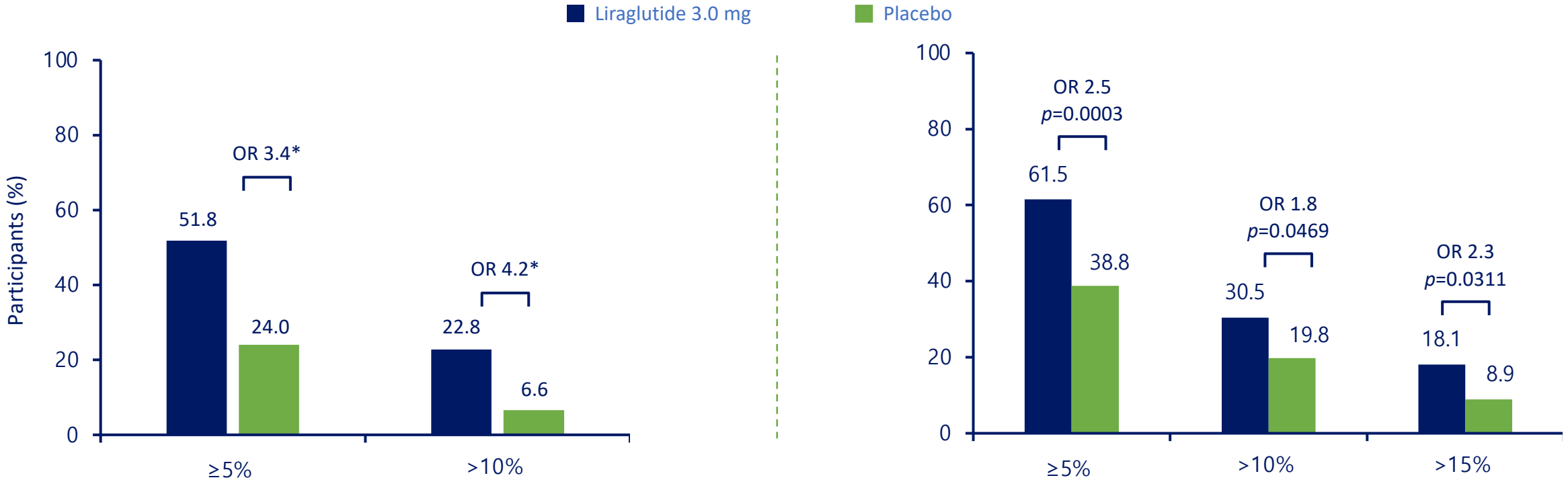
Categorical weight loss across Phase 3b trials

SCALE Insulin[1]

56 weeks
n=396

SCALE IBT[2]

56 weeks
n=282



*p<0.001. Full analysis set. Graphs are estimated proportions. Statistical analysis is logistic regression with J2R-MI
CI, confidence interval; J2R-MI, jump-to-reference multiple imputation; OR, odds ratio
1. Garvey et al. Diabetes Care 2020; 43(5): 1085-1093; 2. Wadden et al. Obesity (Silver Spring) 2020; 28(3): 529-536

Real World Data?

SNUH

Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Real-World Clinical Effectiveness of Liraglutide 3.0 mg for Weight Management in Canada

Sean Wharton[1], Aiden Liu[2], Arash Pakseresht[2], Emil Nørtoft[3], Christiane L. Haase[3], Johanna Mancini[4], G. Sarah Power[5], Sarah Vanderlelie[1], and Rebecca A. G. Christensen [1]

Objective: Real-world clinical effectiveness of liraglutide 3.0 mg, in combination with diet and exercise, was investigated 4 and 6 months post initiation. Changes in absolute and percent body weight were examined from baseline.

Methods: A cohort of liraglutide 3.0 mg initiators in 2015 and 2016 was identified from six Canadian weight-management clinics. Post initiation values at 4 and 6 months were compared with baseline values using a paired *t* test.

Results: The full cohort consisted of 311 participants, with 210 in the ≥4-month persistence group and 167 in the ≥6-month persistence group. Average baseline BMI was 40.7 kg/m^2, and weight was 114.8 kg. There was a significant change in body weight 6 and 4 months after initiation of treatment in persistent subjects (≥6-month: –8.0 kg, $P<0.001$; ≥4-month: –7.0 kg, $P<0.001$) and in All Subjects, regardless of persistence (–7.3 kg; $P<0.001$). Percentage change in body weight from baseline was –7.1% in the ≥6-month group and –6.3% in the ≥4-month group, and All Subjects lost 6.5% body weight. Of participants in the ≥6-month group, 64.10% and 34.5% lost ≥5% and >10% body weight, respectively.

Conclusions: In a real-world setting, liraglutide 3.0 mg, when combined with diet and exercise, was associated with clinically meaningful weight loss.

Obesity (2019) **27**, 917-924. doi:10.1002/oby.22462

Obesity (2019) 27, 917-924.

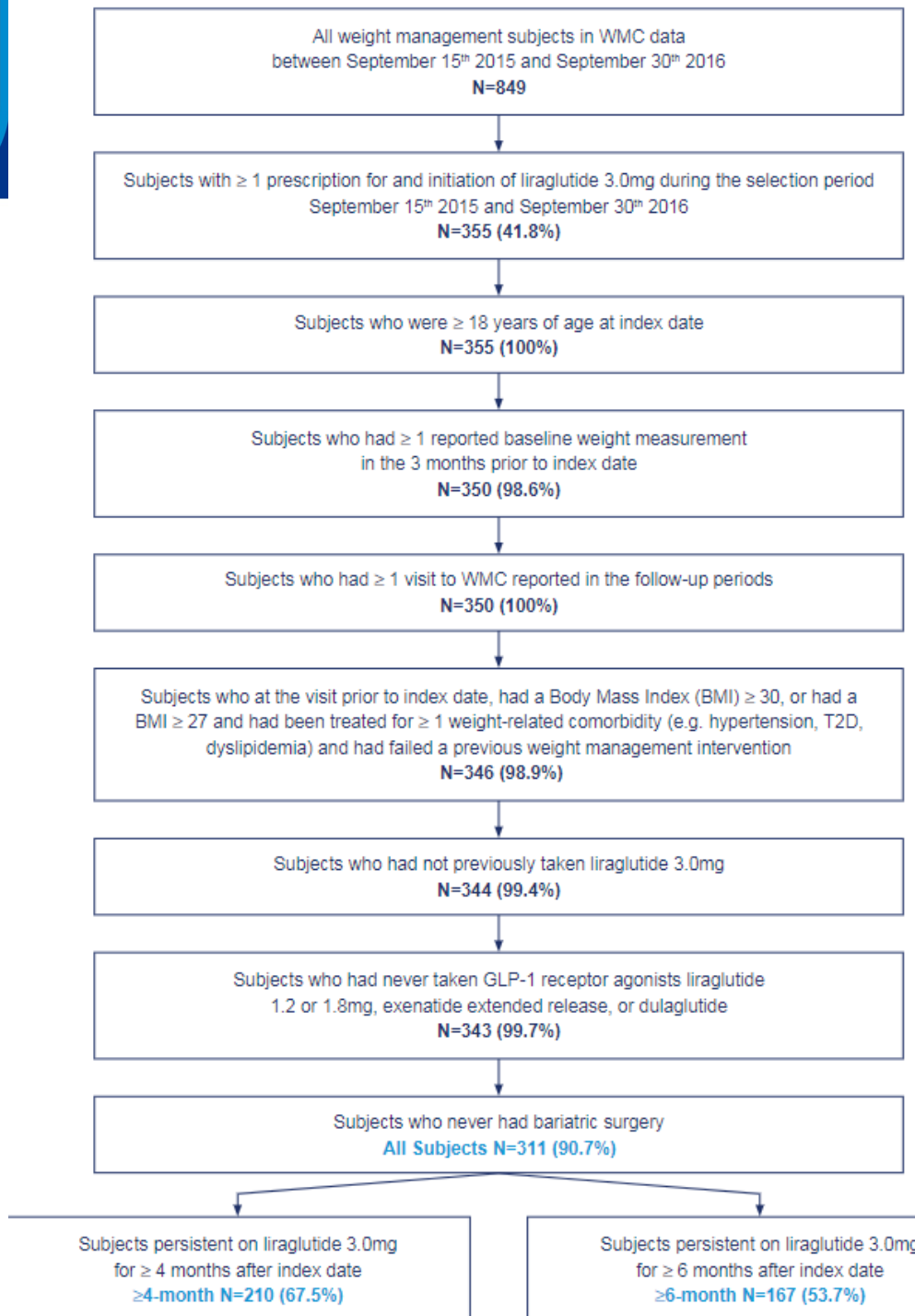


TABLE 2 Baseline characteristics

	All Subjects, *N* = 311
Age	
Mean (SD)	49.7 (11.6)
Median (IQR)	50.0 (42.0-58.0)
Sex, *n* (%)	
Male	53 (17.0)
Female	258 (83.0)
Ethnicity, *n* (%)	
Missing	22 (7.1)
White	241 (77.5)
Aboriginal	2-5 (0.6-1.6)
African American	2-5 (0.6-1.6)
African heritage	2-5 (0.6-1.6)
East Asian	2-5 (0.6-1.6)
South Asian	10 (3.2)
West Indian black	8 (2.6)
Other	17 (5.5)
Index year, *n* (%)	
2015	16 (5.1)
2016	295 (94.9)
BMI	
Mean (SD)	40.7 (7.1)
Median (IQR)	39.9 (35.1-44.9)
BMI categories, *n* (%)	
Overweight	2-5 (0.3-1.3)
Class 1 obesity	70 (22.5)
Class 2 obesity	83 (26.7)
Class 3 obesity	155 (49.8)
Weight	
Mean (SD)	114.8 (26.3)
Median (IQR)	111.1 (95.3-129.7)

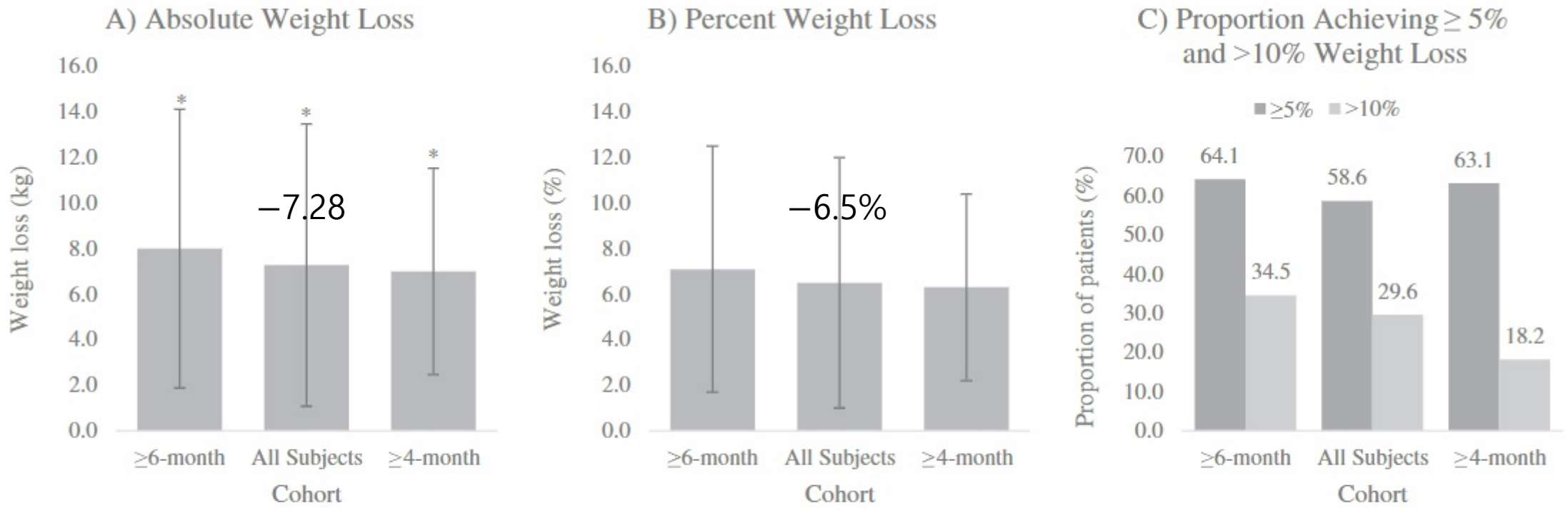
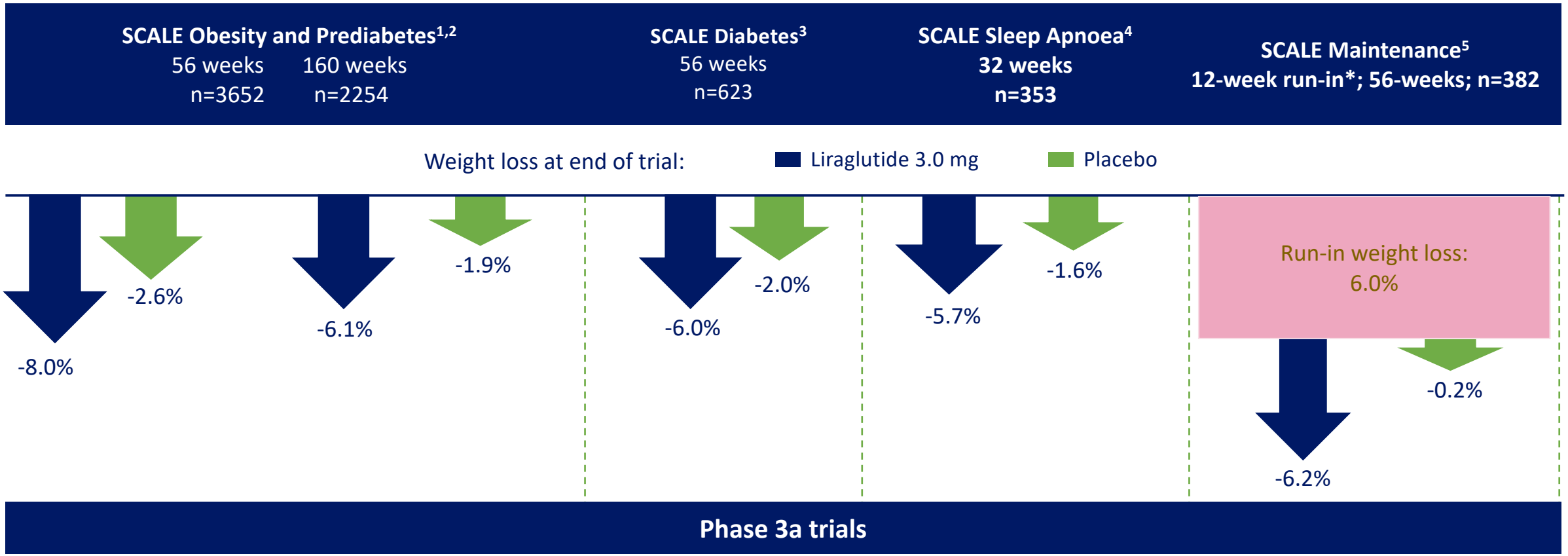


Figure 2 **(A)** Mean absolute weight loss, **(B)** mean percent weight loss, and **(C)** proportion achieving ≥5% or >10% weight loss for ≥6-month (n=145), All Subjects (n=203), and ≥4-month (n=187) persistence cohorts. Error bars represent ± SD. *Significant change in weight ($P<0.05$).

Weight loss across Phase 3a trials



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Categorical weight loss across Phase 3a trials

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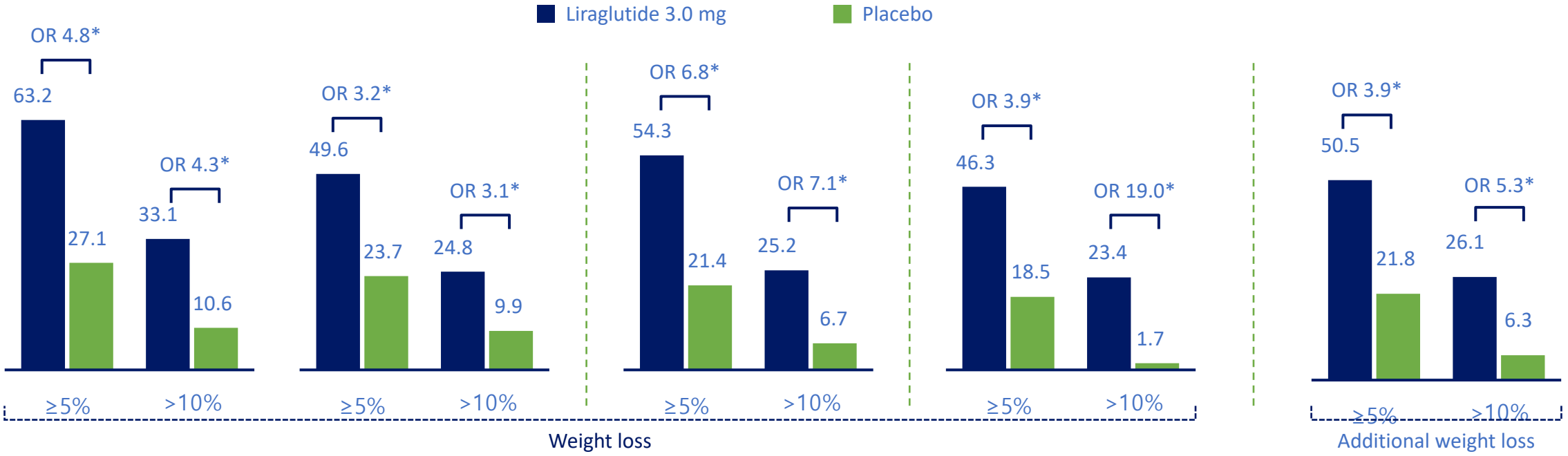

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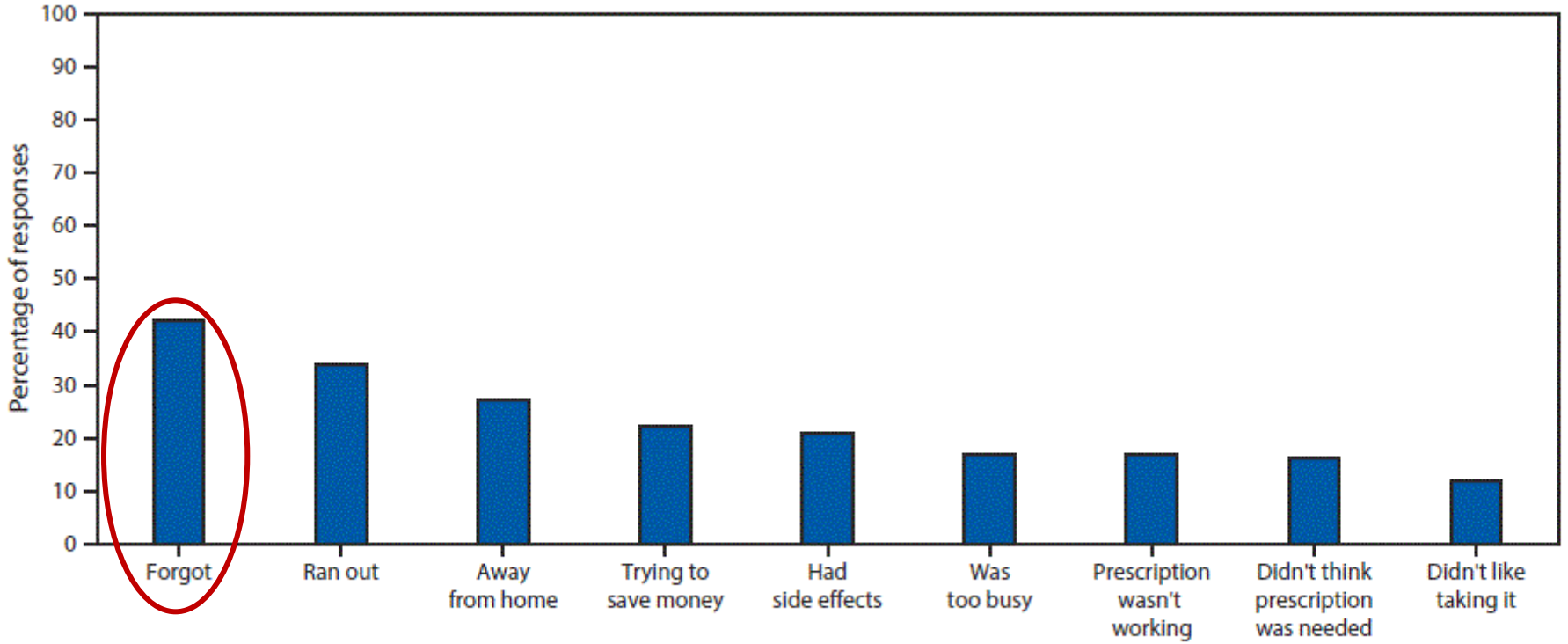
Contents

Non-adherences

FIGURE. Self-reported reasons* for nonadherence to recommended medication regimens — United States, 2013



Source: Medication Adherence in America: A National Report Card, 2013. Adapted with permission.
https://www.ncpanet.org/pdf/reportcard/AdherenceReportCard_Abridged.pdf .

Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

SNUH

Improving Adherence to Weight-Loss Medication (Liraglutide 3.0 mg) Using Mobile Phone Text Messaging and Healthcare Professional Support

Ang Li [1,2], *Michelle Cunich*[1,2], *Nicholas Fuller*[1], *Katrina Purcell*[3], *Allanah Flynn*[3], *and Ian Caterson*[1]

Background: Adherence to weight-loss medication is suboptimal, leading to poor health outcomes. Short message service (SMS) can potentially improve adherence.

Methods: A total of 3,994 participants with overweight or obesity in Australia receiving Saxenda® (liraglutide 3.0 mg) were enrolled from September 1, 2017, to February 28, 2018, through doctors, pharmacists, or websites and were randomly assigned to receive none, three, or five SMS per week. Participants were additionally offered a face-to-face consultation with a diabetes educator or a call from a dietitian. Medication adherence was measured as whether the total scripts claimed were at least as many as the total claims expected by March 31, 2018, and was modeled adjusting for age, sex, baseline BMI, residential region, enrolment channel, the total number of SMS, and additional patient support.

Results: Participants receiving five SMS (OR, 6.25; 95% CI: 4.28-9.12) had greater adherence than those receiving three SMS (OR, 3.67; 95% CI: 2.67-5.03) or zero SMS per week. The effectiveness of SMS on adherence decreased as participants received more SMS over time. Moreover, the odds of adhering to liraglutide were higher for participants enrolled with pharmacists compared with those enrolled with doctors (OR, 2.28; 95% CI: 1.82-2.86) and for participants who received a face-to-face consultation (OR, 3.10; 95% CI: 1.82-5.29) or a call (OR, 1.31; 95% CI: 1.02-1.68) compared with those who received no extra support.

Study Importance

What is already known?

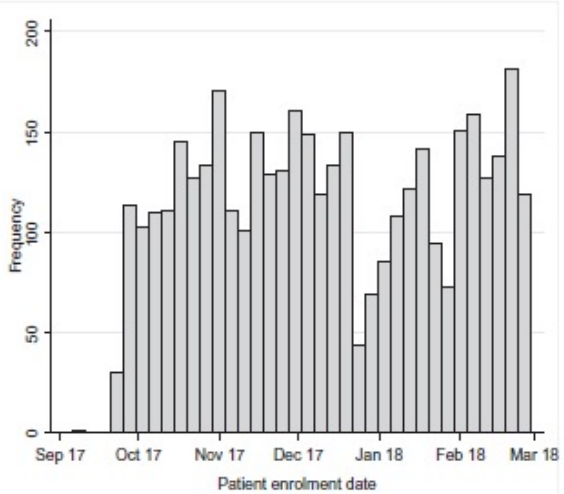
- One of the major causes of treatment failure is patient noncompliance.
- The use of SMS increases medication adherence and treatment effectiveness for a range of chronic diseases.

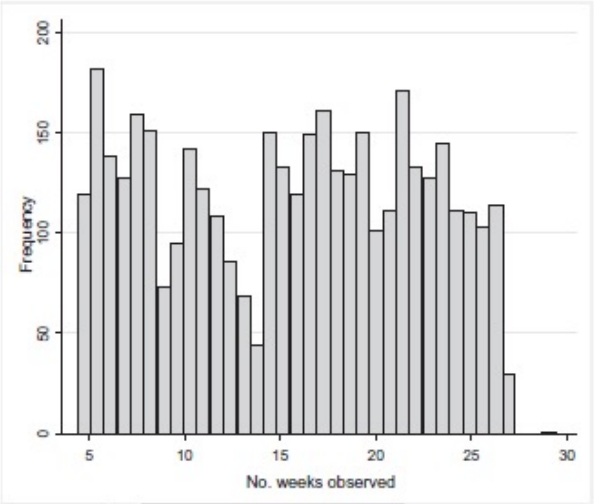
What does this study add?

- SMS reminders can improve medication adherence of participants with overweight or obesity prescribed weight-loss medication (liraglutide 3.0 mg), with five SMS per week leading to a better improvement than three SMS per week.
- The effectiveness of SMS reminders on medication adherence decreased as the number of text messages received increased over time.
- Participants who received face-to-face consultations or phone calls had greater medication adherence. Participants who unsubscribed from SMS reminders showed increased adherence with face-to-face consultations.

Obesity, Volume28, Issue10, Pages 1889-1901

3,994 patients enrolled into SaxendaCare® PSP
1 Sep 2017 - 28 Feb 2018 (prescription followed until 31 Mar 2018)
received weekly support emailsand had access to SaxendaCare ® patient website





1,604 registered via prescribing doctors

1,739 registered via Saxenda® network pharmacists

651 registered via SaxendaCare® patient website

1,308 randomised to 0 SMS
1,357 randomised to 3 SMS
1,329 randomised to 5 SMS

86 received a one-hour face-to-face consultation with a HCP (diabetes educator)

284 received an outbound call from a dietitian

1,234 did not receive any additional support

297 received an outbound call from a dietitian

1,442 did not receive any additional support

No additional support made available

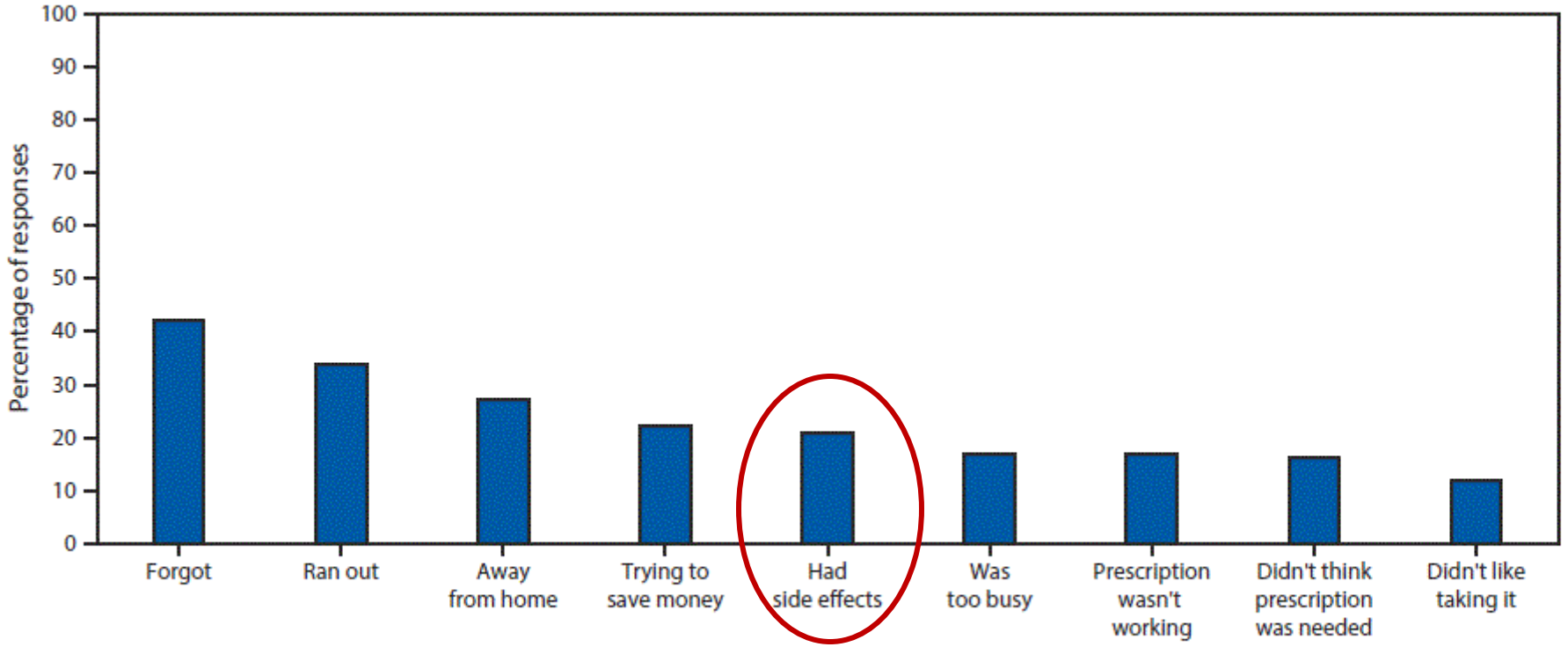
TABLE 3 Odds ratio estimates on effectiveness of SMS by enrollment channel and patient support

	All patients	Enrollment channel			Patient support type		
		Doctors	Saxenda network pharmacist	Saxenda patient website	Face-to-face consultation with a HCP	Phone call from a dietitian	No extra support
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
SMS (base: 0 SMS)							
3 SMS	**3.67** (2.67-5.03)	**3.36** (2.30-4.90)	**3.40** (2.06-5.63)	**4.77** (2.76-8.24)	1.12 (0.27-4.53)	**2.83** (1.57-5.11)	**3.92** (2.81-5.48)
5 SMS	**6.25** (4.28-9.12)	**6.91** (4.50-10.62)	**4.44** (2.62-7.52)	**6.96** (3.81-12.70)	**6.28** (1.77-22.31)	**6.86** (3.70-12.72)	**5.98** (4.03-8.86)
Enrollment (base: doctor)							
Saxenda network pharmacist	**2.28** (1.82-2.86)	NA	NA	NA	NA	1.15 (0.72-1.84)	**2.79** (2.16-3.60)
Saxenda patient website	1.42 (0.96-2.09)	NA	NA	NA	NA	NA	**1.54** (1.04-2.29)
Patient support (base: no extra support)							
Face-to-face consultation with a HCP	**3.10** (1.82-5.29)	**3.32** (1.94-5.69)	NA	NA	NA	NA	NA
Phone call from a dietitian	**1.31** (1.02-1.68)	**1.76** (1.30-2.39)	0.74 (0.48-1.13)	NA	NA	NA	NA
No observations				2,354			

Logit models performed adjusting for age, sex, BMI class, residential states/territories, and total number of SMS received. Odds ratios and 95% CIs reported. Estimates in bold indicate significance at 5% level.
NA, not applicable.

Non-adherences

FIGURE. Self-reported reasons* for nonadherence to recommended medication regimens — United States, 2013



Source: Medication Adherence in America: A National Report Card, 2013. Adapted with permission.
https://www.ncpanet.org/pdf/reportcard/AdherenceReportCard_Abridged.pdf .

SCALE Safety Summary

Key safety outcomes with liraglutide 3.0 mg

SNUH

GI adverse events

68%[1], 62%[5] and 71%[6] events

vs. 39%[1], 47%[5] and 49%[6] in placebo. Severe events were <5%[1,5,6]

Pancreatitis

10 events

vs. 2 events with placebo were recorded over 172 wks[2]

Breast neoplasms

10 events

vs. 0 events with placebo were recorded over 172 wks[2]

MTC

0 events

of MTC or confirmed C-cell hyperplasia with liraglutide or placebo[2]

MACE

1.54 events

per 1000 years observation vs. 3.65 events of adjudication-confirmed MACE with placebo. HR, 0.42 (95% CI 0.17-1.08)[3]

Neuro-psychiatric

Similar rates vs. placebo

observed in the SCALE programme[4]

gallbladder events

2.9 events

PYO vs. 1.2 events PYO[2]
3 events vs. 2 events[6]
2 events vs. 1 event[5]

GI, gastrointestinal; HR, hazard ratio; MACE, major adverse cardiac events; MTC, medullary thyroid carcinoma;

1. Novo Nordisk Briefing Document: Liraglutide 3.0 mg for weight management NDA 206-321. FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. September 11, 2014; 2. le Roux et al. Lancet 2017;389:1399–4092. 3. Davies et al. Diabetes Obes Metab 2018; 20(3): 734-739; 4. O'Neil et al. Diabetes Obes Metab 2017; 19(11): 1529-1536; 5. Garvey et al. Diabetes Care 2020; 43(5): 1085-1093 ; 6. Wadden et al. Obesity (Silver Spring) 2020; 28(3): 529-536

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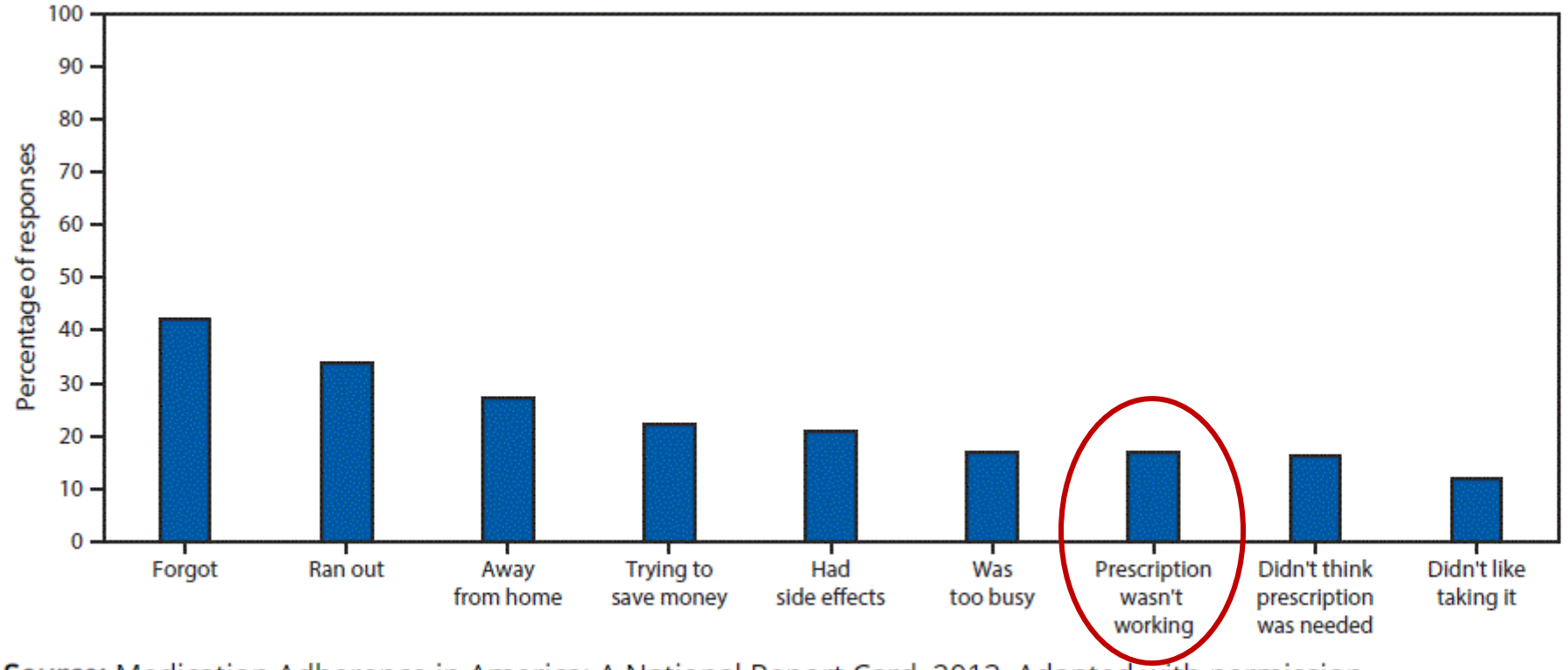

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Contents

SCALE Phase 3a trials

SNUH

SCALE Obesity and Prediabetes
56 weeks

The NEW ENGLAND JOURNAL of MEDICINE

SCALE Obesity and Prediabetes
160 weeks

THE LANCET

SCALE Diabetes

JAMA The Journal of the American Medical Association

SCALE Maintenance

International Journal of Obesity

SCALE Sleep Apnoea

International Journal of Obesity

Hyperlinked to Medical toolbox publication decks; PDF images are linked to published article PDFs in the Medical toolbox

Trial design: SCALE Maintenance

Weight maintenance with liraglutide 3.0 mg after LCD-induced weight loss

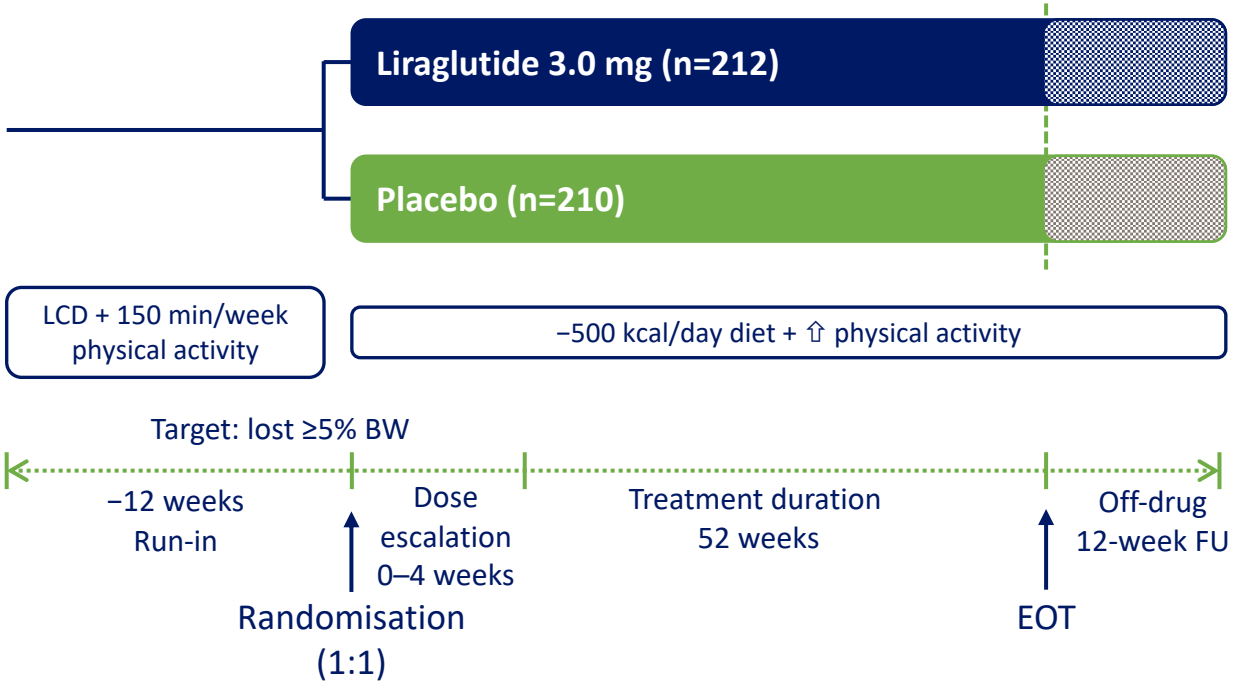
SNUH

Trial objective

Efficacy of liraglutide 3.0 mg in maintaining weight loss achieved with a LCD (1200–1400 kcal/day) and increased physical activity (150 min/week) during run-in

Inclusion criteria

- ≥18 years
- Stable BW
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 + comorbidities



Trial information

- October 2008 to January 2009
- Randomised controlled double-blind study
- 36 sites (US and Canada)

BW, body weight; EOT, end of treatment; FPG, fasting plasma glucose; FU, follow-up; LCD, low-calorie diet; WL, weight loss

Wadden et al. Int J Obes (Lond) 2013;37:1443–51

Trial design: SCALE Maintenance

Weight maintenance with liraglutide 3.0 mg after LCD-induced weight loss

Inclusion criteria

- ≥18 years
- Stable BW
- BMI ≥30 kg/m^2
  or
  ≥27 kg/m^2 + comorbidities

Key endpoints

- Three co-primary: change in BW; maintenance of ≥5% WL from LCD run-in; ≥5% WL after randomisation
- Secondary: weight change; >10% WL; maintenance >50% and >75% of WL achieved during LCD run-in period

BW, body weight; EOT, end of treatment; FPG, fasting plasma glucose; FU, follow-up; LCD, low-calorie diet; WL, weight loss
Wadden et al. Int J Obes (Lond) 2013;37:1443–51

Subject characteristics at randomisation

SCALE Maintenance

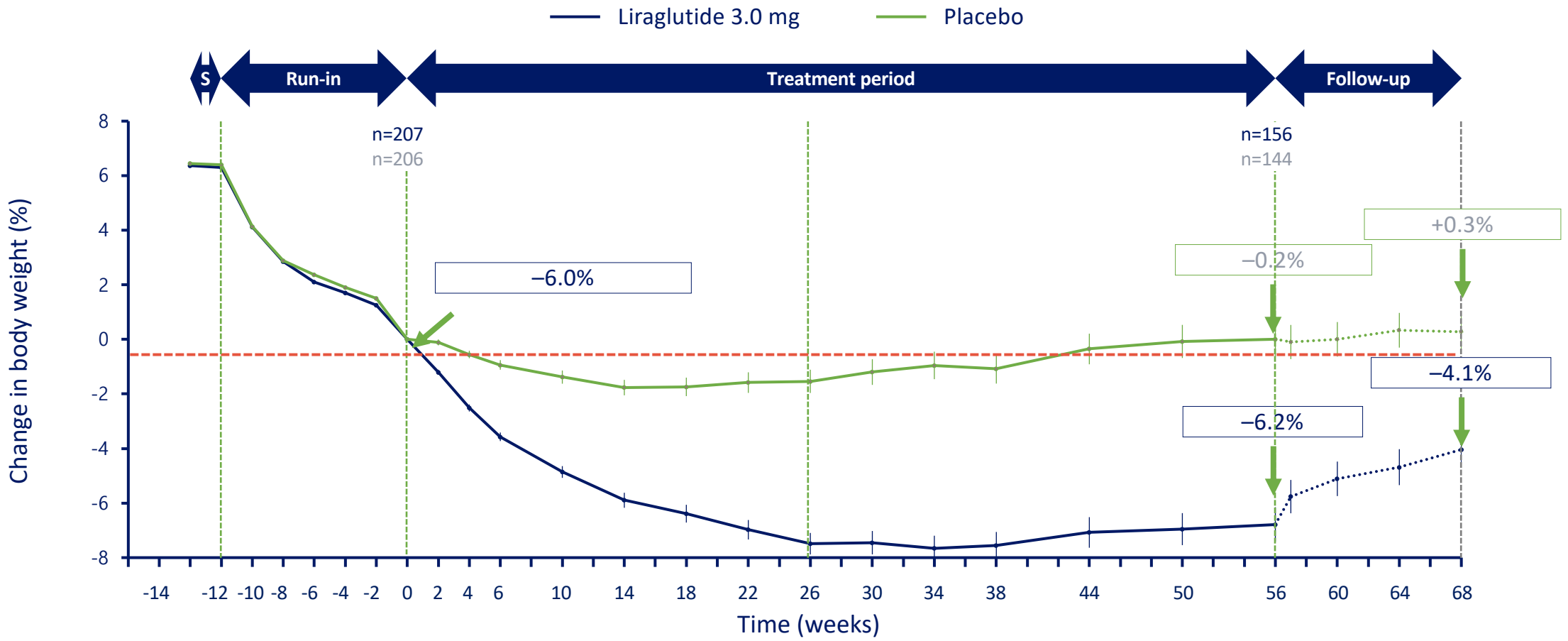
	Liraglutide 3.0 mg n=212		Placebo n=210	
	n	(%/SD)	n	(%/SD)
Age, years (SD)	45.9	(11.9)	46.5	(11)
Men/women	34/178	(16/84)	44/166	(21/79)
Race				
White, n (%)	170	(80)	185	(88)
Black or African-American, n (%)	32	(15)	24	(11)
Asian or other, n (%)	10	(5)	1	(1)
Comorbidities present, n (%)	94	(44)	96	(46)
Hypertension, n (%)	71	(33)	61	(29)
Dyslipidaemia, n (%)	59	(28)	65	(31)
Weight, kg (SD)	100.4	(20.8)	98.7	(21.2)
BMI, kg/m² (SD)	36.0	(5.9)	35.2	(5.9)
Waist circumference, cm (SD)	109.4	(15.3)	107.8	(15.2)

Data are means. Full analysis set
BMI, body mass index; SD, standard deviation
Wadden et al. Int J Obes (Lond) 2013;37:1443–51

Change in body weight (%)

SCALE Maintenance

Mean baseline weight: 99.6 kg



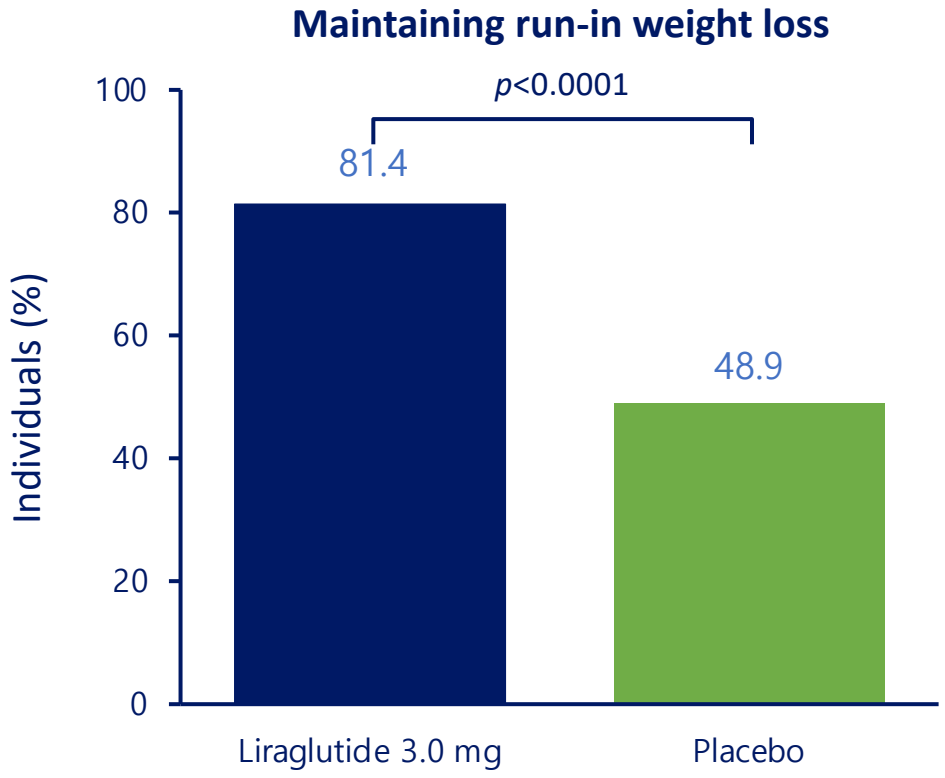
Total
-12.2%

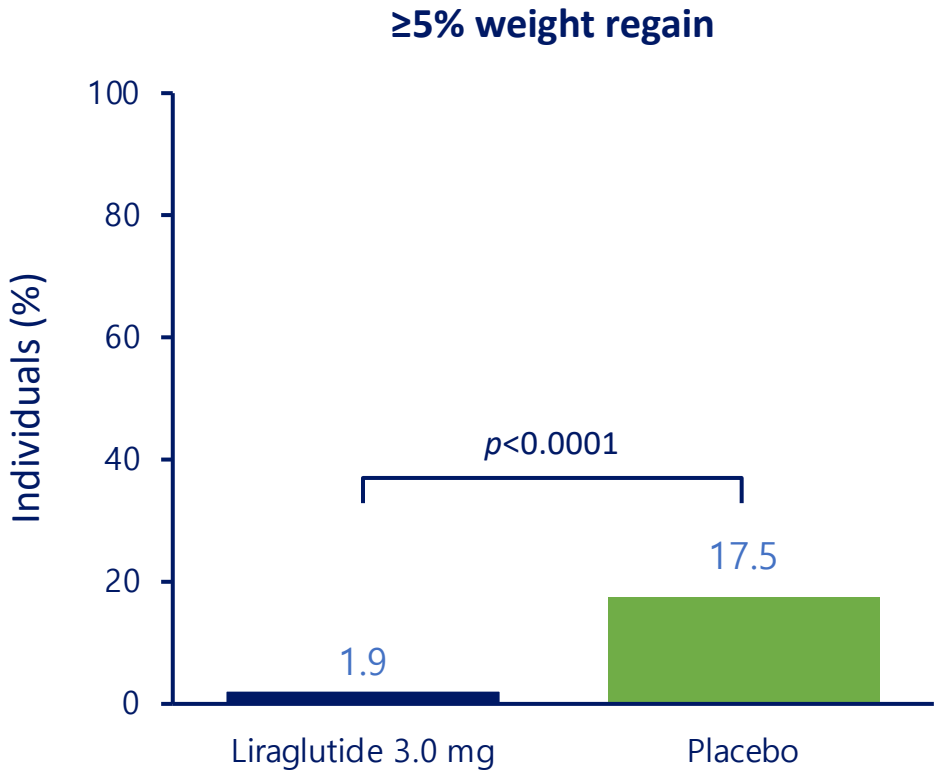
Mean (±SD); Full analysis set. S, screening period; SD, standard deviation
Wadden et al. Int J Obes (Lond) 2013;37:1443–51

Individuals maintaining or regaining weight loss

SCALE Maintenance: At week 56

Mean baseline weight: 99.6 kg



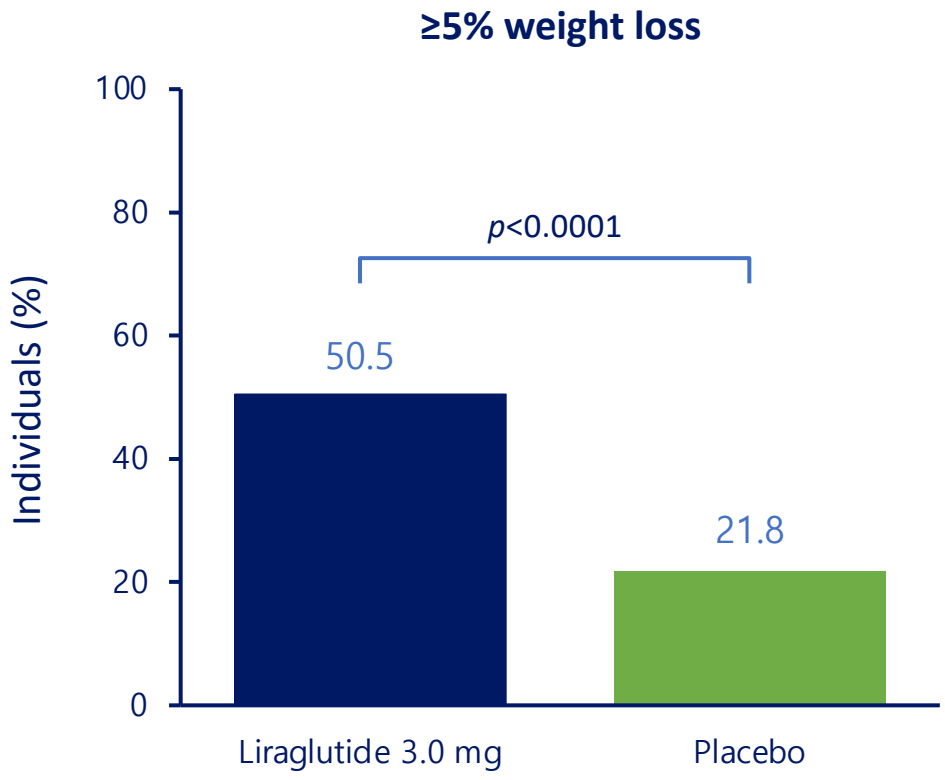


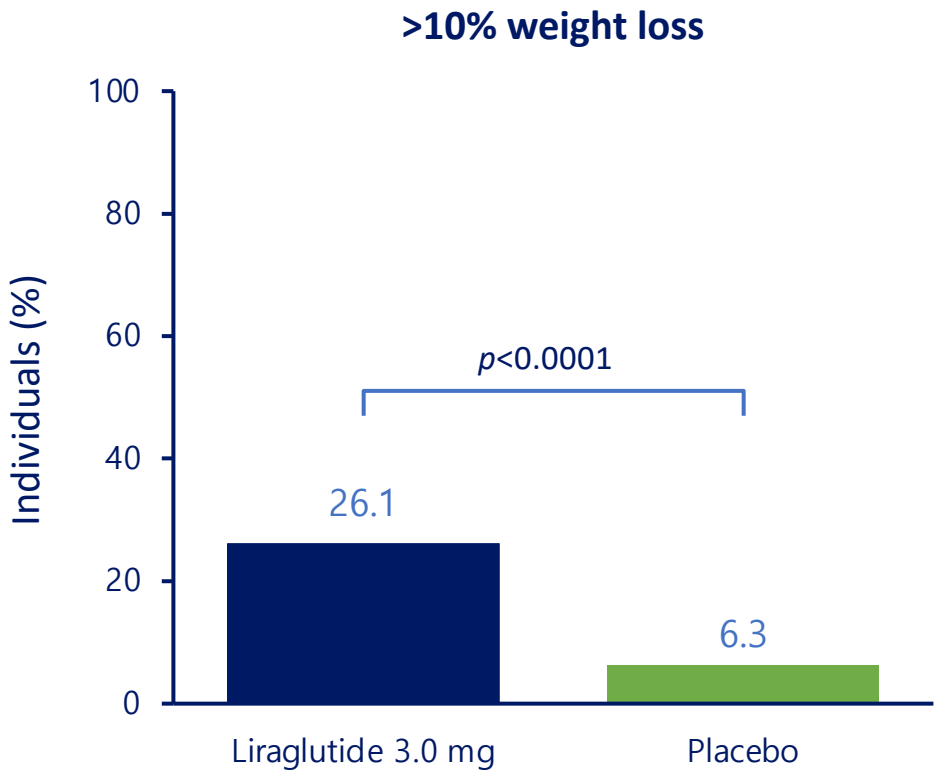
Full analysis set; LOCF at week 56. LOCF, last observation carried forward
Wadden et al. Int J Obes (Lond) 2013;37:1443–51

Individuals achieving additional weight loss

SCALE Maintenance: At week 56

Mean baseline weight: 99.6 kg





Full analysis set; LOCF at week 56
Wadden et al. Int J Obes (Lond) 2013;37:1443–51

Summary
SCALE Maintenance

Clinical Efficacy

From randomization to week 56, weight decreased an additional mean 6.2% with liraglutide and 0.2% with placebo

Risk factors

- Maintained diet-induced weight loss in 81% of subjects
- Induced additional ≥5% body weight loss in 51% of subjects and an additional >10% body weight loss in 26% of subjects

Safety profile

Liraglutide 3.0 mg was well tolerated, with few withdrawals

- Nausea was the most common GI AE in both groups but was of mild to moderate severity and generally transient

AE, adverse event; GI, gastrointestinal
Wadden et al. Int J Obes (Lond) 2013;37:1443–51

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined

Julie R. Lundgren, M.D., Ph.D., Charlotte Janus, Ph.D., Simon B.K. Jensen, M.Sc., Christian R. Juhl, M.D., Lisa M. Olsen, M.Sc., Rasmus M. Christensen, B.Sc.Med., Maria S. Svane, M.D., Ph.D., Thomas Bandholm, Ph.D., Kirstine N. Bojsen-Møller, M.D., Ph.D., Martin B. Blond, M.D., Ph.D., Jens-Erik B. Jensen, M.D., Ph.D., Bente M. Stallknecht, M.D., D.M.Sc., Jens J. Holst, M.D., D.M.Sc., Sten Madsbad, M.D., D.M.Sc., and Signe S. Torekov, Ph.D.

N Engl J Med 2021;384:1719-30

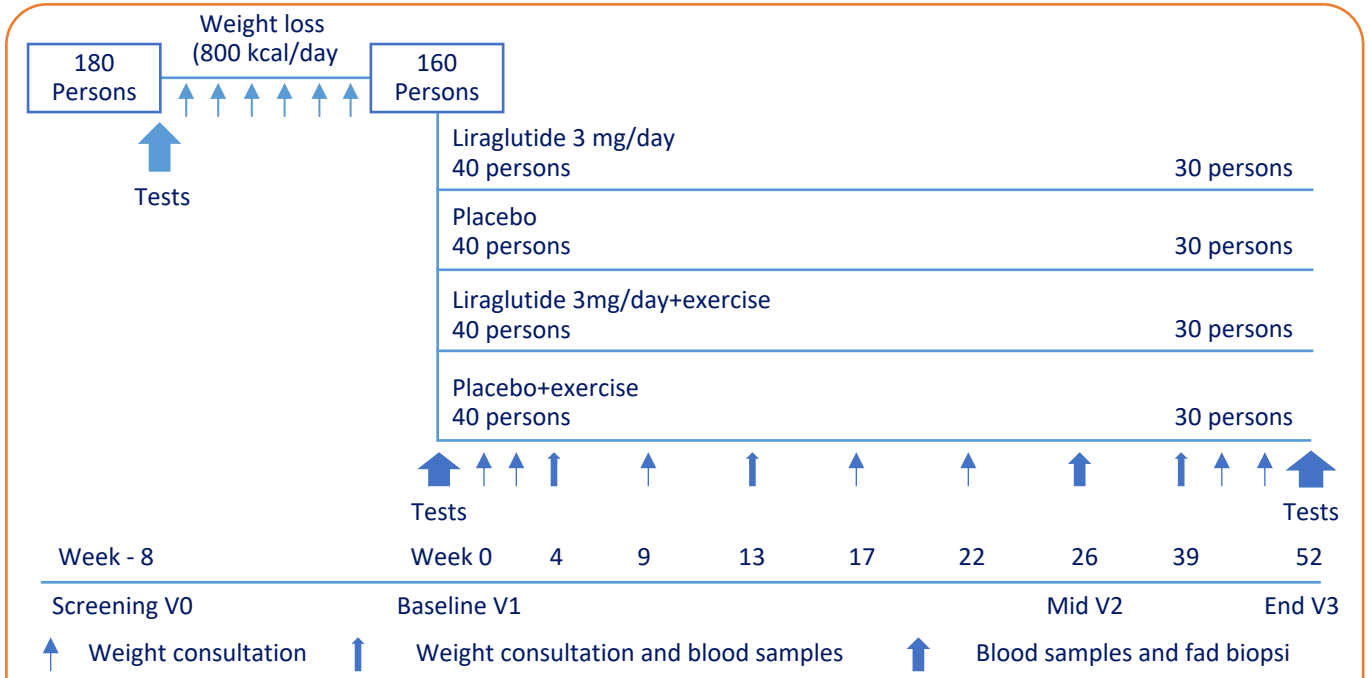
Study design

Key inclusion criteria

- Age >18 years < 65 years
- BMI >32 kg/m^2 and < 40 kg/m^2 *
- Safe contraceptive method

Key exclusion criteria

- Serious chronic illness including type 1 or 2 diabetes (or a randomly measured fasting plasma glucose > 7 mmol/l)
- Angina pectoris, coronary heart disease, congestive heart failure (NYHA III-IV)
- Severe renal impairment (creatinine clearance (GFR) <30 mL/min)
- Severe hepatic impairment
- Psychiatric disease, a history of major depressive or other severe psychiatric disorders
- The use of medications that cause clinically significant weight gain or loss



Trial information

- Randomized, double-blind, controlled parallel groups study conducted in Denmark
- 200 Participants were recruited in the study

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Study intervention: Liraglutide or placebo intervention

- Liraglutide (at a concentration of 6 mg per milliliter) or volume-matched placebo was injected subcutaneously
- Starting dose was of 0.6 mg per day, with supervised weekly increments of 0.6 mg per day; the dose was intended to eventually reach 3.0 mg per day
- Participants who had unacceptable adverse effects at a given dose received the maximum dose at which they did not have such effects

Lundgren et al. N Engl J Med. 2021 May 6;384(18):1719-1730

Study intervention: Exercise intervention

- The exercise program was designed to meet the World Health Organization (WHO) recommendations on physical activity for health
  - A minimum of 150 minutes per week of moderate-intensity aerobic physical activity, or 75 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination of both
- Each participant was **assigned to an instructor** who planned and monitored individualized programs.
- After an initial 6-week ramp-up phase, per week participants were encouraged to attend 2 supervised **group exercise sessions** and 2 sessions of moderate-to vigorous– intensity exercise carried out **individually.**
- The exercise program was structured and flexible to substitute group exercise with individual exercise or vice versa; or to reduce exercise frequency if duration was prolonged or the intensity was increased.
- Participants randomized to the placebo or liraglutide group were instructed to maintain usual physical activity.

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Primary endpoints

- Change in body weight (in kilograms) from randomization to week 52

Secondary endpoint

- Change in the percentage of body fat (calculated as the fat mass [in kilograms] divided by the body weight [in kilograms], times 100) from randomization to week 52

Pre-specified metabolic health related endpoints

changes from randomization to week 52 in

- fat mass
- lean mass
- cardiorespiratory fitness
- glycated hemoglobin level
- indexes of insulin
- resistance during fasting (liver insulin resistance, as assessed by the homeostatic model assessment of insulin resistance [HOMA-IR]) and during meal intake (whole-body insulin resistance, as assessed by the Matsuda index28)
- lipid levels
- quality of life
- waist and hip circumferences
- waist-to-hip ratio, blood pressure
- resting heart rate

Lundgren et al. N Engl J Med. 2021 May 6;384(18):1719-1730

Baseline demographics and clinical characteristics

	Placebo (n = 49)	Exercise (n = 48)	Liraglutide (n = 49)	Exercise + liraglutide (n = 49)
Men/women, n (%)	18/31 (37/63)	17/31 (35/65)	18/31 (37/63)	18/31 (37/63)
Age, years	43±12	43±12	43±12	42±12
Weight, kg	96.7±12.7	96.8±13.2	95.1±12.8	98.3±11.5
BMI, kg/m2	32.3±3.0	32.7±3.0	32.7±3.1	32.8±2.4
Body fat percentage, percentage	37.9±7.1	37.8±7.0	39.3±6.7	39.5±6.7
Fat mass, kg	37.0±6.8	37.1±8.8	37.7±6.9	39.0±6.2
Lean mass, kg	61.5±12.6	61.0±10.5	58.9±11.9	60.5±11.6
Waist circumference, cm	99.6±10.4	99.0±9.0	100.7±11.8	102.0±8.3
Hip circumference, cm	112.6±6.9	114.1±8.8	113.5±6.9	115.4±6.3
Waist/Hip Ratio	0.89±0.10	0.87±0.09	0.89±0.11	0.89±0.09
Cardiorespiratory fitness mL/min/kg †	24.9±5.6	26.6±6.1	24.6±4.7	23.5±4.6
Glycated hemoglobin, mmol/mol	34±4	34±4	34±4	34±3
Systolic blood pressure, mmHg	122±15	122±14	122±12	122±13
Diastolic blood pressure, mmHg	79±7	78±8	79±8	79±9
Resting heart rate, beats per minute	71±12	66±12	69±9	70±12

Plus–minus values are observed means±SD. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.
†Cardiorespiratory fitness was assessed as the peak oxygen consumption (in milliliters of oxygen per minute per kilogram of body weight). ‡ The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the fasting insulin level (in milliunits per milliliter) times the fasting glucose level (in millimoles per liter), divided by 22.5. The conversion factor used for insulin was 1 μU/mL = 6.00 pmol/L and the conversion factor used for glucose was 1 mg/dL = 0.05551 mmol/L. § The Matsuda index was calculated as 10,000 divided by the square root of the following value: the fasting glucose level times the fasting insulin level times the mean glucose level times the mean insulin level. ¶ Scores on each domain of the RAND 36-Item Health Survey (RAND-36) range from 0 to 100, with higher scores indicating better health.
Lundgren et al. N Engl J Med. 2021 May 6;384(18):1719-1730

Baseline demographics and clinical characteristics

	Placebo (n = 49)	Exercise (n = 48)	Liraglutide (n = 49)	Exercise + liraglutide (n = 49)
HOMA-IR ‡	2.0±1.4	1.5±0.8	1.5±0.7	1.9±0.9
Matsuda Index §	4.3±1.6	5.7±2.7	5.5±3.4	4.5±2.5
Total cholesterol, mmol/L	4.1±0.8	4.0±0.8	4.3±0.8	3.8±0.9
Cholesterol LDL, mmol/L	2.5±0.6	2.4±0.8	2.8±0.8	2.2±0.8
Cholesterol HDL, mmol/L	1.2±0.2	1.2±0.3	1.1±0.3	1.1±0.3
Triglycerides, mmol/L	1.1±0.5	1.0±0.3	1.0±0.3	1.1±0.5
General health perception, RAND-36 score	82±14	77±18	78±14	79±14
Physical functioning, RAND-36 score	92±11	92±10	88±13	90±8
Emotional well-being, RAND-36 score	86±11	83±13	83±11	83±11

Plus–minus values are observed means±SD. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.
†Cardiorespiratory fitness was assessed as the peak oxygen consumption (in milliliters of oxygen per minute per kilogram of body weight). ‡ The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the fasting insulin level (in milliunits per milliliter) times the fasting glucose level (in millimoles per liter) divided by 22.5. The conversion factor used for insulin was 1 μU/mL = 6.00 pmol/L and the conversion factor used for glucose was 1 mg/dL = 0.05551 mmol/L. § The Matsuda index was calculated as 10,000 divided by the square root of the following value: the fasting glucose level times the fasting insulin level times the mean glucose level times the mean insulin level. ¶ Scores on each domain of the RAND 36-Item Health Survey (RAND-36) range from 0 to 100, with higher scores indicating better health.
Lundgren et al. N Engl J Med. 2021 May 6;384(18):1719-1730

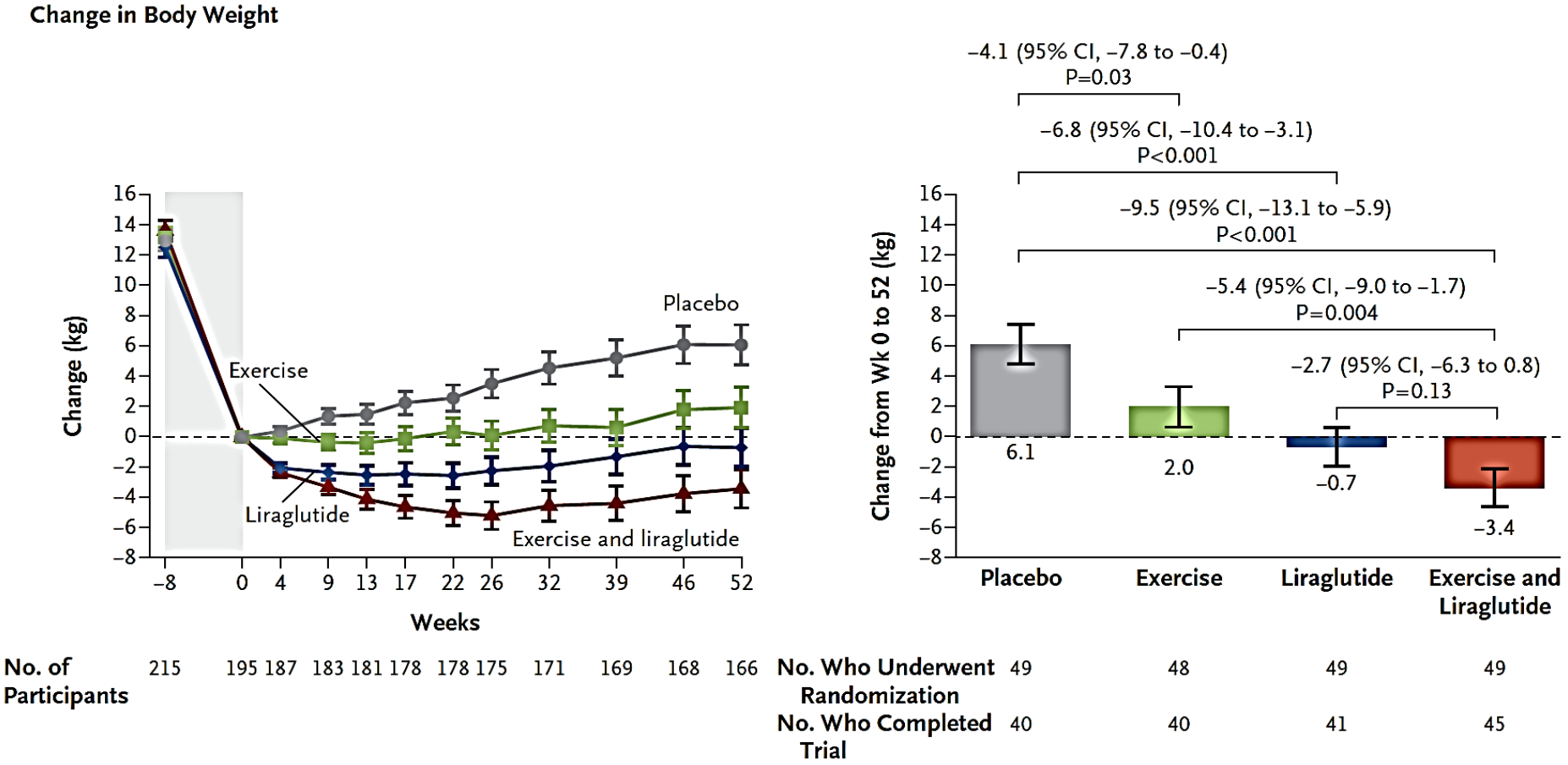
Characteristics before and after 8 Weeks of a LCD

Characteristic	Before Low-Calorie Diet (N = 215)	After Low-CalorieDiet, at Randomization (N = 195)
Sex – no. (%)		
Male	80 (37)	71 (36)
Female	135 (63)	124 (64)
Age ō5 yr	42±12	43±12
Body weight — kg	109.7±14.9	96.7±12.5
Body-mass index	37.0±2.9	32.6±2.9
Body-fat percentage — %	41.1±6.1	38.6±6.9
Fat mass — kg	44.9±7.2	37.7±7.2
Lean mass — kg	65.3±12.9	60.4±11.6
Waist circumference — cm	110.6±11.3	100.3±10.0
Hip circumference — cm	121.4±7.5	113.9±7.3
Waist-to-hip ratio	0.91±0.10	0.88±0.10
Cardiorespiratory fitness — ml/min/kg†	22.9±4.2	24.9±5.4
Glycated hemoglobin — mmol/mol	36±4	34±3

Characteristic	Before Low-Calorie Diet (N = 215)	After Low-CalorieDiet, at Randomization (N = 195)
Blood pressure — mm Hg		
Systolic	132±16	122±13
Diastolic	86±10	79±8
Resting heart rate — beats/min	73±10	69±12
HOMA-IR‡	3.9±2.4	1.7±1.0
Matsuda index§	2.7±1.8	4.9±2.7
Cholesterol — mmol/liter		
Total	5.0±1.0	4.1±0.8
Low-density lipoprotein	3.1±0.8	2.5±0.8
High-density lipoprotein	1.3±0.3	1.1±0.3
Triglycerides — mmol/liter	1.5±0.9	1.1±0.4
RAND-36 score		
General health perception	71±16	79±15
Physical functioning	86±13	91±11
Emotional well-being	81±12	84±11

- *Plus–minus values are observed means ±SD. Among the 215 enrolled participants who began the low-calorie diet, those who had a weight loss at 8 weeks of at least 5% of their baseline body weight (195 participants) underwent randomization. The estimated mean changes (with 95% confidence intervals) during the low-calorie diet are shown in Table S2. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. † Cardiorespiratory fitness was assessed as the peak oxygen consumption (in milliliters of oxygen per minute per kilogram of body weight). ‡ The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the fasting insulin level (in milliunits per milliliter) times the fasting glucose level (in millimoles per liter) divided by 22.5. The conversion factor that was used for insulin was that 1 μU per milliliter was equal to 6.00 pmol per liter. The conversion factor that was used for glucose was that 1 mg per deciliter was equal to 0.05551 mmol per liter. § The Matsuda index was calculated as 10,000 divided by the square root of the following value: the fasting glucose level times the fasting insulin level times the mean glucose level times the mean insulin level. ¶ Scores on each domain of the RAND 36-Item Health Survey (RAND-36), range from 0 to 100, with higher scores indicating better health.*
- *Lundgren et al. N Engl J Med. 2021 May 6;384(18):1719-1730*

Primary endpoint: Mean changes in Bwt



No. of Participants	215	195	187	183	181	178	178	175	171	169	168	166

No. Who Underwent Randomization	49	48	49	49
No. Who Completed Trial	40	40	41	45

Shown are the mean changes in body weight (primary end point; during a low-calorie diet (weeks −8 to 0, shaded area) and during 1 year of subsequent treatment (from randomization [week 0] to week 52). All the means were estimated from a repeated measures linear regression model with time, group, sex, age, and a time–group interaction as explanatory variables in the intention-to treat population. I bars indicate the standard error, and the dashed lines indicate baseline at randomization (week 0). The results from the prespecified hypotheses of changes in body weight from week 0 to 52 are shown in the bar charts as estimated mean differences with 95% confidence intervals. (See the Hypothesis: Analysis Results and Claims section in the Supplementary Appendix.)
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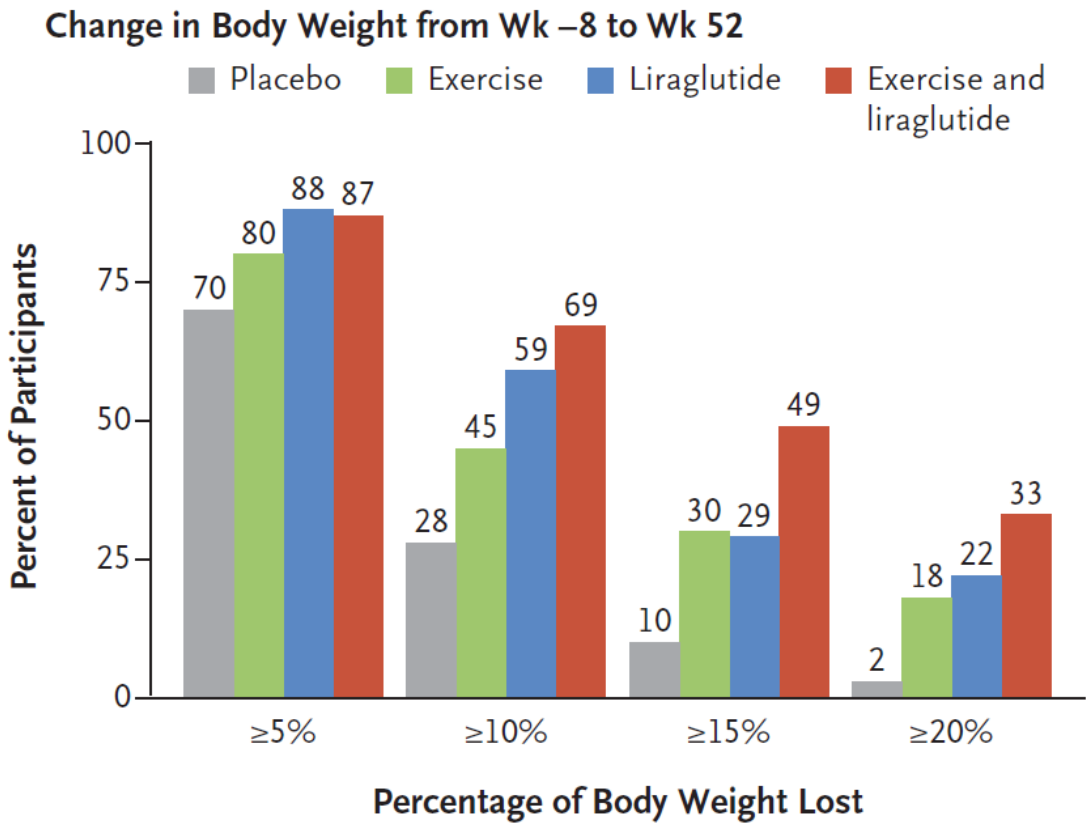
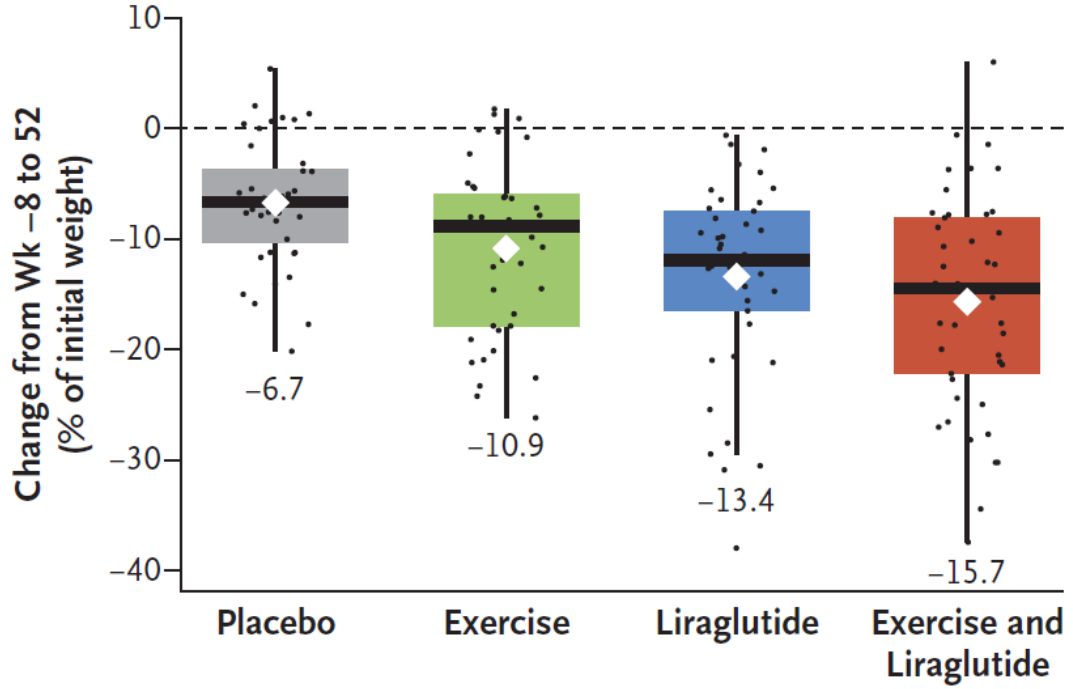
Change in body weight from wk −8 to wk 52





bar chart of the percentages of participants in each trial group who had a total weight loss from baseline at enrollment (week −8) to the end of the trial (week 52) of at least 5%, 10%, 15%, and 20% of the initial body weight (left graph) and also shows a box plot of the percentage weight loss from baseline (dashed line) to the end of the trial in each group (right graph). In the box plot, the diamonds indicate means; the black horizontal bars medians; the tops and bottoms of the boxes the upper and lower quartiles, respectively; and the whiskers ±1.5 times the interquartile range or the smallest or highest observation. Dots indicate individual observations

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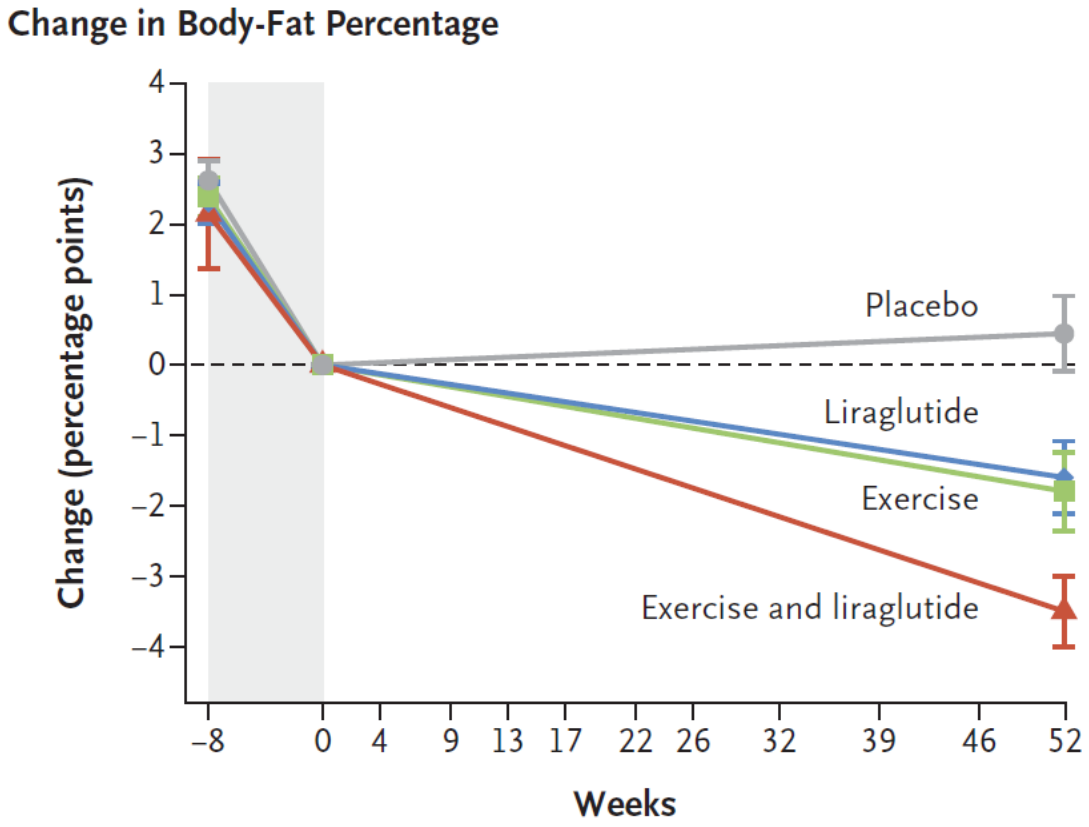
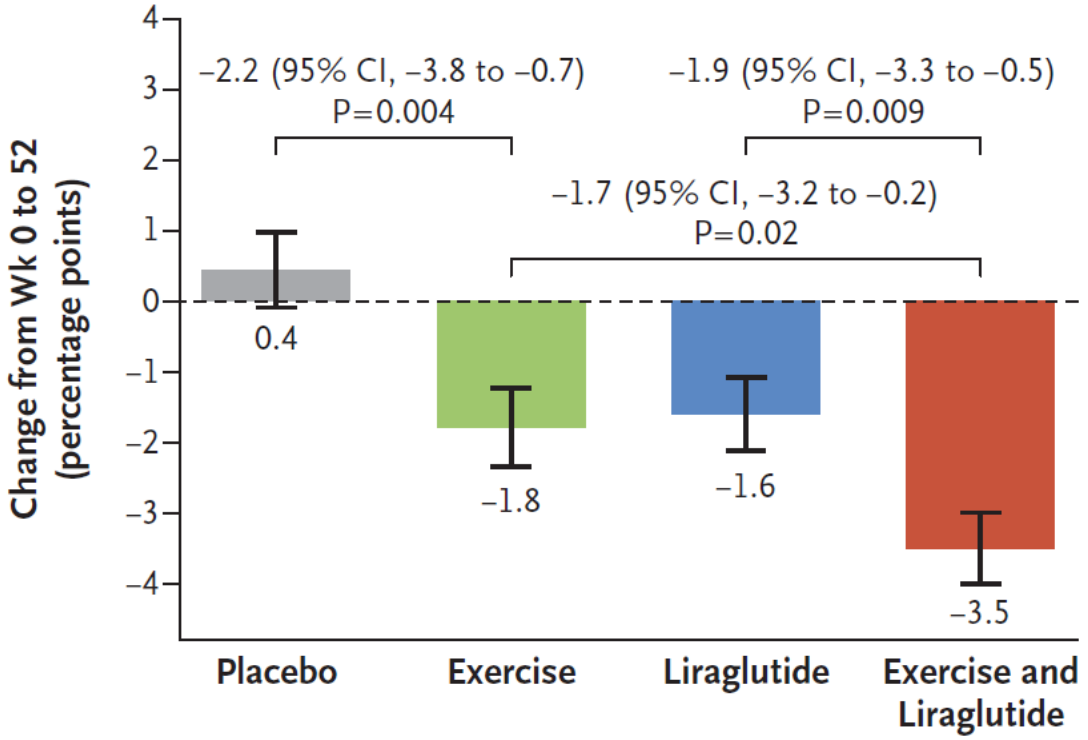
Secondary end point: Changes in BFP change





Shown are the mean changes in body fat percentage (secondary end point; during a low-calorie diet (weeks −8 to 0, shaded area) and during 1 year of subsequent treatment (from randomization [week 0] to week 52). All the means were estimated from a repeated measures linear regression model with time, group, sex, age, and a time–group interaction as explanatory variables in the intention-to treat population. I Bars indicate the standard error, and the dashed lines indicate baseline at randomization (week 0). The results from the prespecified hypotheses of changes in body fat percentage from week 0 to 52 are shown in the bar charts as estimated mean differences with 95% confidence intervals. (See the Hypothesis: Analysis Results and Claims section in the Supplementary Appendix.)
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Conclusions

- Diet-induced weight loss was maintained with exercise or liraglutide and weight was further reduced with the co mbined treatment
- After the 8-week low-calorie diet, 195 participants had a mean decrease in body weight of 13.1 kg. At 1 year, all the active-treatment strategies led to greater weight loss than placebo: difference in the exercise group, −4.1 kg (95% confidence interval [CI], −7.8 to −0.4; P = 0.03); in the liraglutide group, −6.8 kg (95% CI, −10.4 to −3.1; P <0.001); and in the combination group, −9.5 kg (95% CI, −13.1 to −5.9; P<0.001).
- The combination strategy led to greater weight loss than exercise (difference, −5.4 kg; 95% CI, −9.0 to −1.7; P = 0.004) but not liraglutide (−2.7 kg; 95% CI, −6.3 to 0.8; P = 0.13). The combination strategy decreased body-f at percentage by 3.9 percentage points, which was approximately twice the decrease in the exercise group (−1.7 percentage points; 95% CI, −3.2 to −0.2; P = 0.02) and the liraglutide group (−1.9 percentage points; 95% CI, − 3.3 to −0.5; P = 0.009).
- Only the combination strategy was associated with improvements in the glycated hemoglobin level, insulin sensi tivity, and cardiorespiratory fitness.
- Increased heart rate and cholelithiasis were observed more often in the liraglutide group than in the combinatio n group.

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Contents

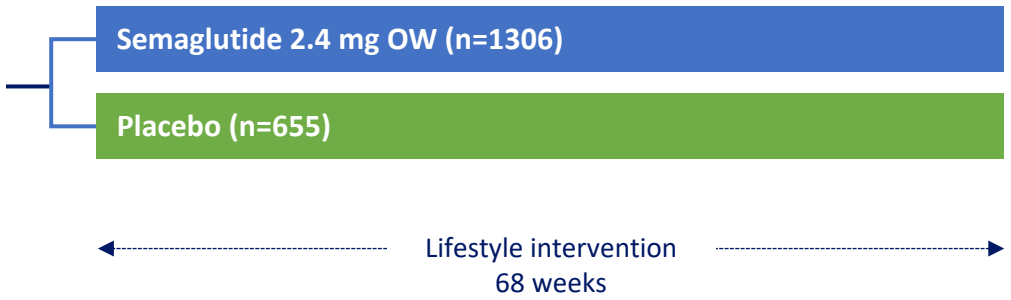
STEP programme: Four pivotal trials at a glance

Semaglutide 2.4 mg is not approved for weight management in Korea

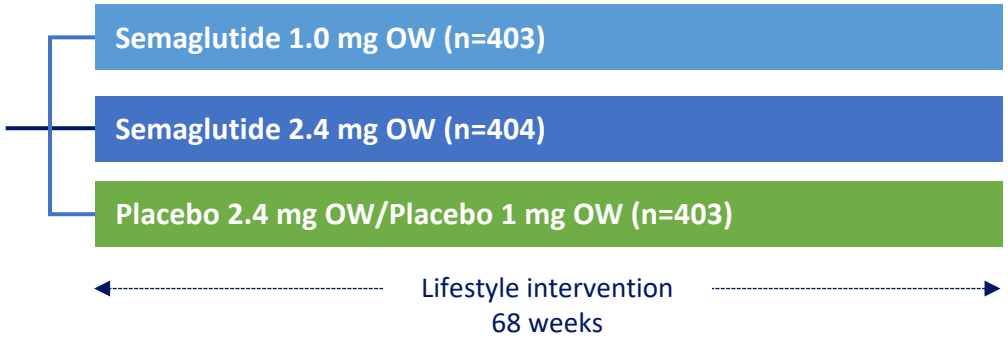
SNUH

4,700 PATIENTS IN TOTAL

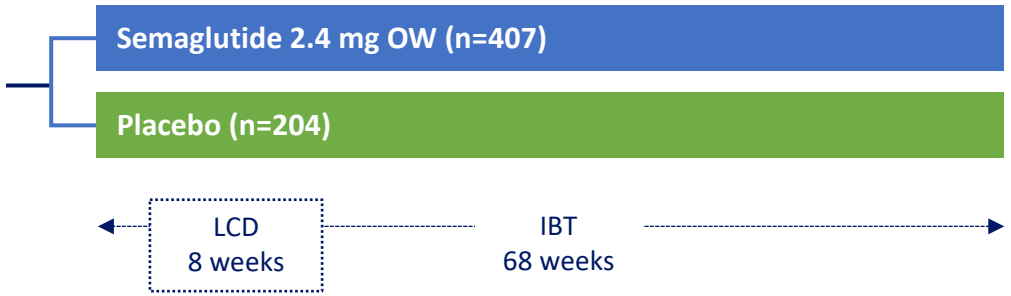
STEP 1: Weight Management



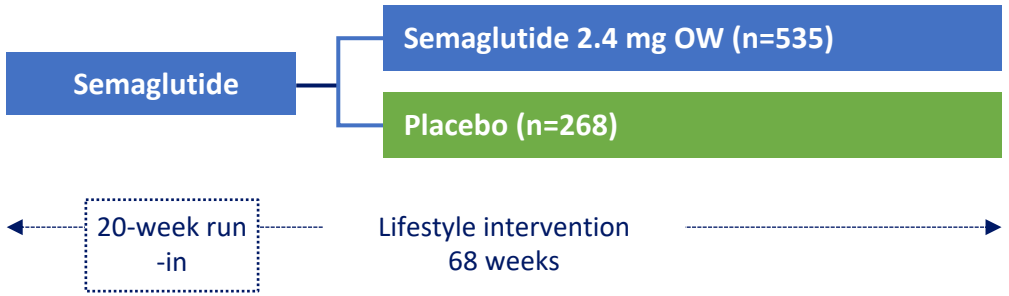
STEP 2: Weight Management in T2D



STEP 3: Weight Management with IBT



STEP 4: Sustained Weight Management

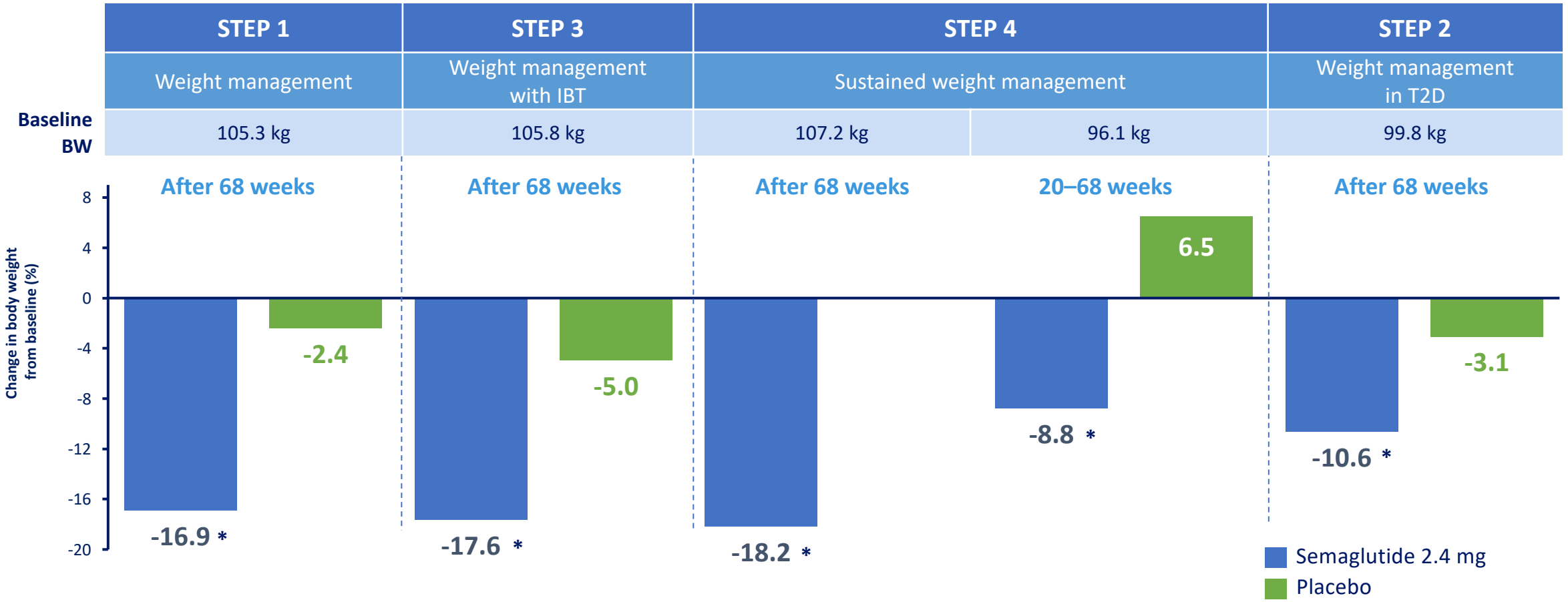


Lifestyle intervention: –500 kcal/day diet + 150 min/week physical activity. IBT, intensive behavioural therapy; LCD, low-calorie diet; OW, once weekly; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes.
Kushner et al. Obesity (Silver Spring) 2020;28:1050–61.

STEP 1–4: Mean weight loss

Semaglutide 2.4 mg is not approved for weight management in Korea

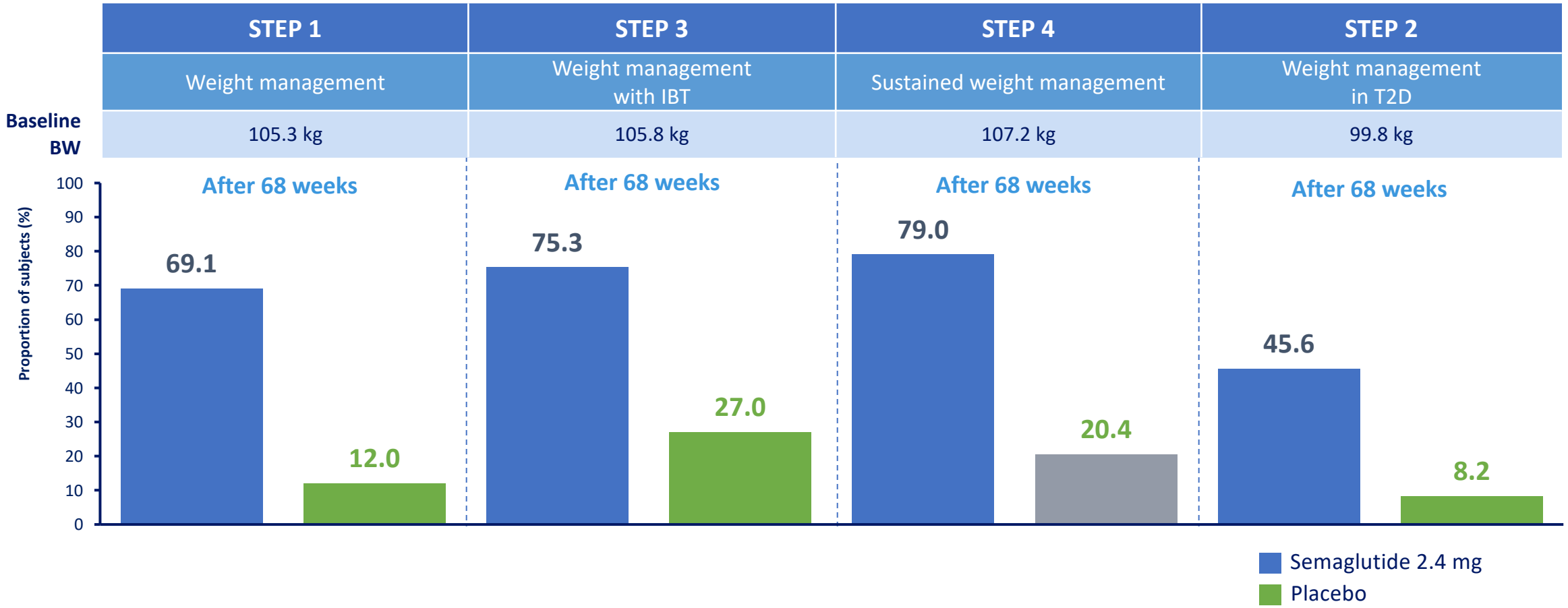
SNUH



*Trial product estimand data. *Statistically significant vs placebo. BW, body weight; IBT, intensive behavioural therapy.*
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. JAMA. 2021;325(14):1414–1425

STEP 1–4: Subjects achieving ≥10% weight loss

Semaglutide 2.4 mg is not approved for weight management in Korea



Proportions are based observed (in trial) data. BW, body weight; IBT, intensive behavioural therapy.

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. JAMA. 2021;325(14):1414–1425

Key findings from STEP 1–4

Semaglutide 2.4 mg is not approved for weight management in Korea

SNUH

68 weeks of treatment with once weekly s.c. semaglutide 2.4 mg resulted in:

Substantial and clinically meaningful weight loss of **17–18%* on average in people with overw eight or obesity** and **10% in those with T2D**

Increased number of patients meeting categorical weight-loss targets vs placebo

Improvements in **physical functioning** and **cardiometabolic risk factors**

*when treatment was taken as intended

s.c., subcutaneous; T2D, type 2 diabetes; Wilding et al. N Engl J Med 2021 doi: 10.1056/NEJMoa2032183 [Epub]; Wadden et al. JAMA 2021 doi:10.1001/jama.2021.1831 [Epub]; Davies et al. Lancet 2021 doi: 10.1016/S0140-6736(21)00213-0 [Epub]; Kushner et al. Obesity (Silver Spring) 2020;28:1050–61; Wing et al. Diabetes Care 2011;34:1481–6; Rubino DM et al. Rubino DM et al. JAMA. 2021;325(14):1414–1425

Tirzepatide

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide Once Weekly for the Treatment of Obesity

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Glucagon-like Peptide-1 Receptor Agonism

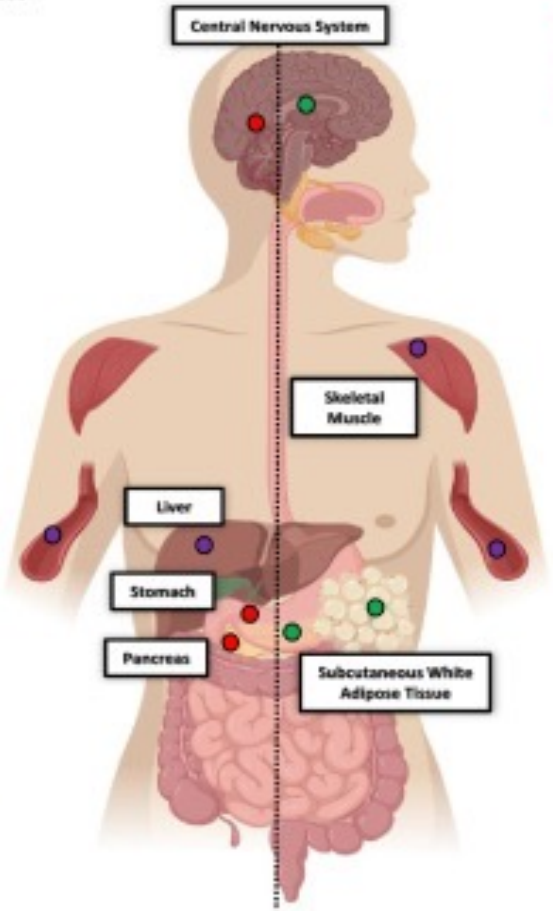
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
Glucagon-like Peptide 1 Receptor Agonism
Indirect Action

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

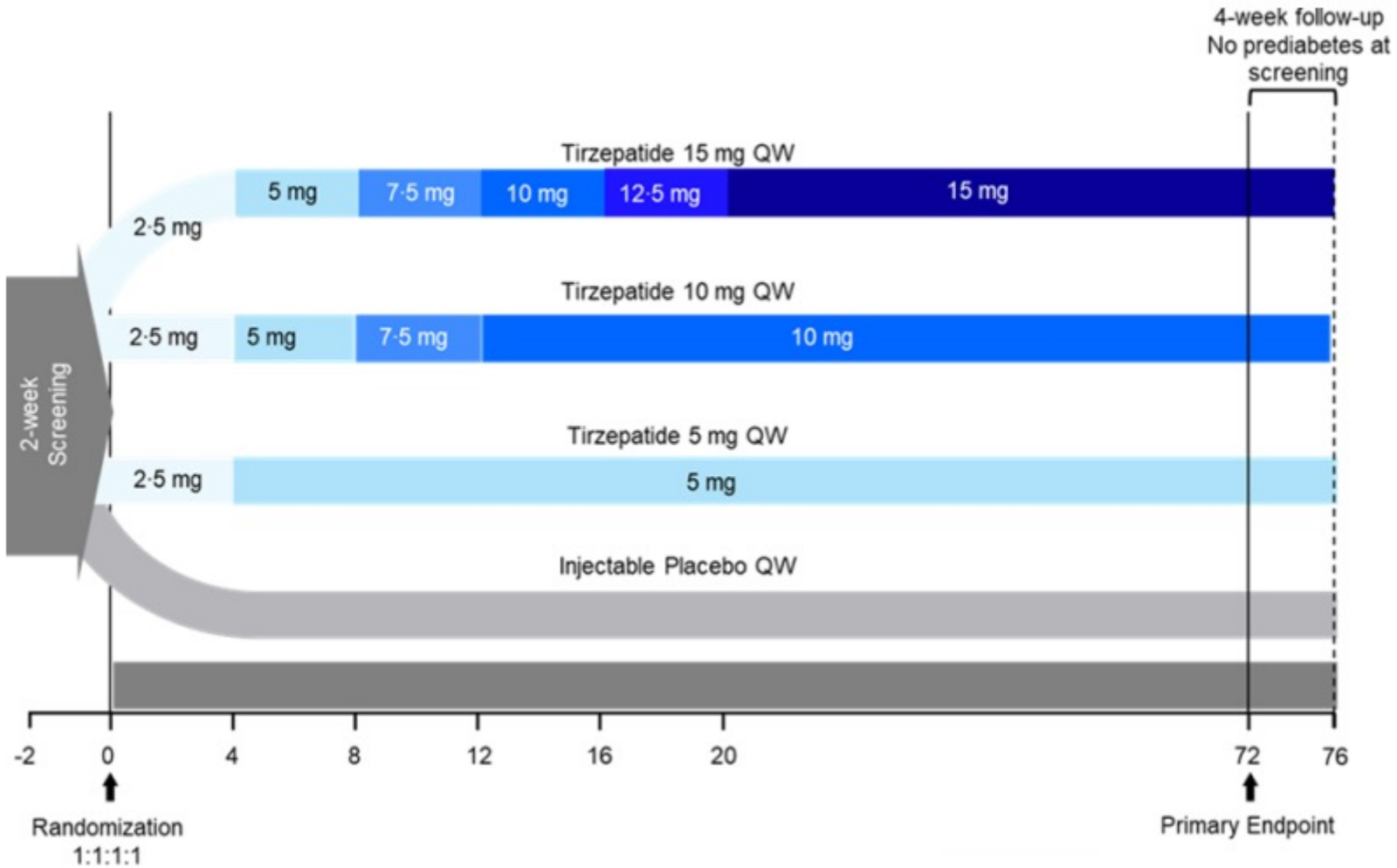
Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

Trends in Endocrinology & Metabolism


4-week follow-up
No prediabetes at screening
Tirzepatide 15 mg QW
5 mg
7·5 mg
10 mg
12·5 mg
15 mg
2·5 mg
Tirzepatide 10 mg QW
2·5 mg
5 mg
7·5 mg
10 mg
2-week Screening
Tirzepatide 5 mg QW
2·5 mg
5 mg
Injectable Placebo QW
-2
0
4
8
12
16
20
72
76
Randomization
1:1:1:1
Primary Endpoint

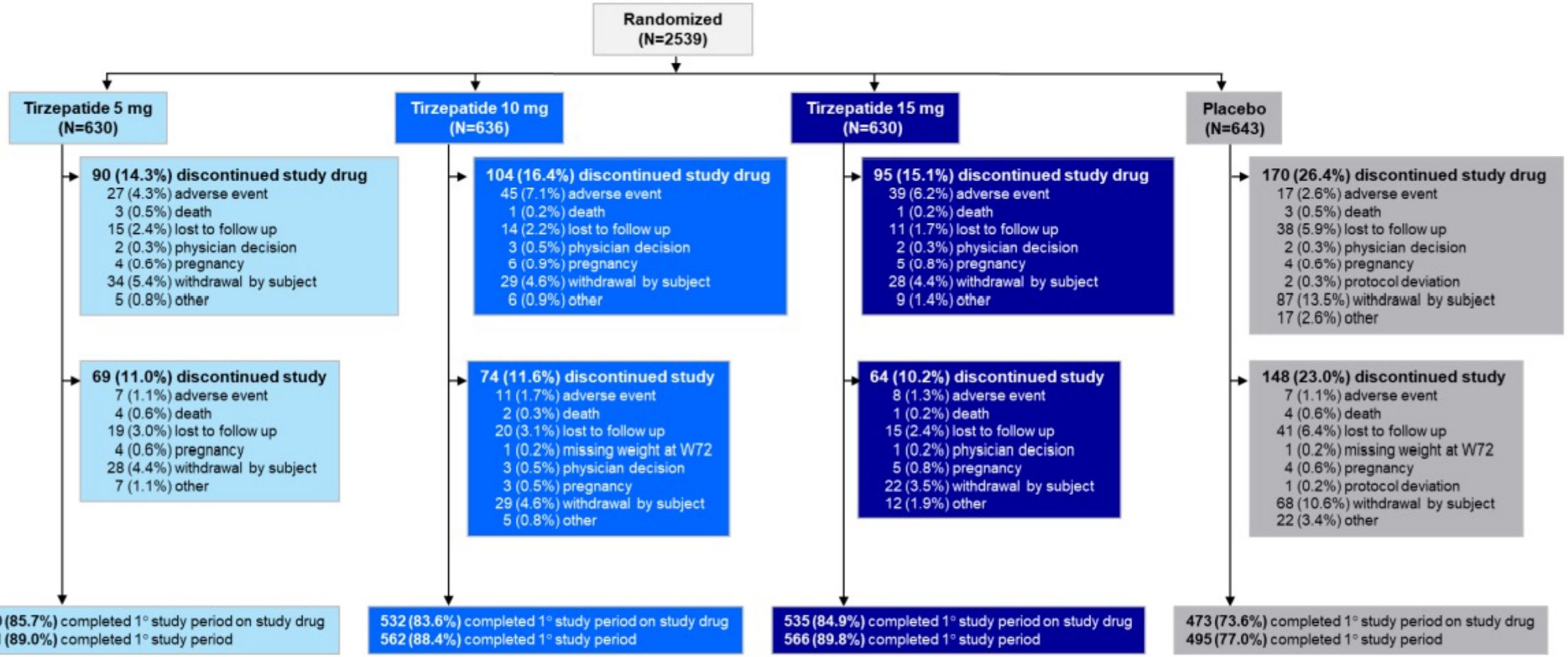
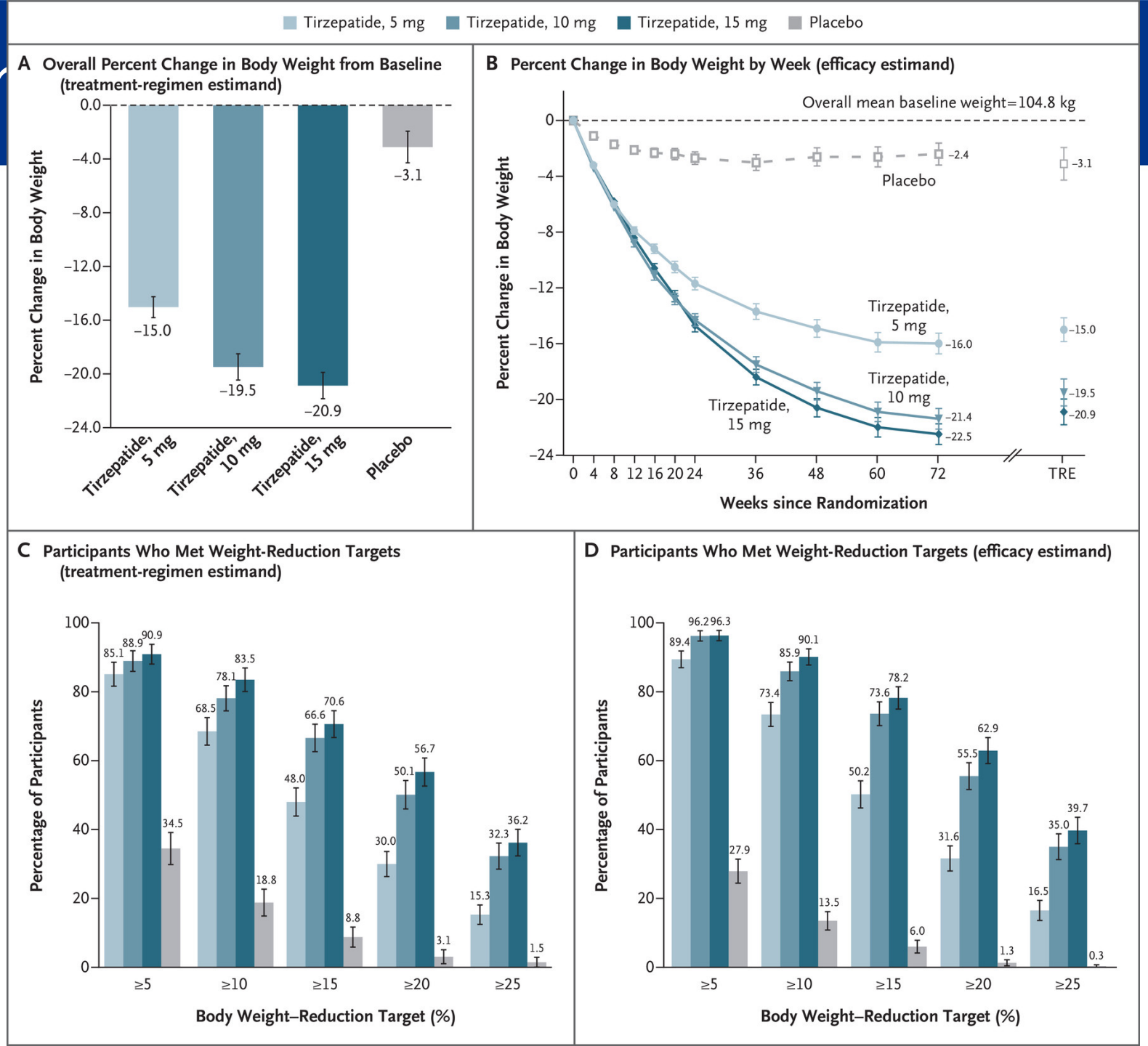


Figure S2. Participant disposition from randomization to primary endpoint. Mean duration of follow-up in the study was 72.3 to 72.7 weeks across tirzepatide groups and 69.2 weeks in the placebo group. Mean duration of follow-up on treatment was 65.4 to 66.8 weeks across tirzepatide groups and 61.9 weeks in the placebo group.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)	Total (N=539)
Age — yr	45.6±12.7	44.7±12.4	44.9±12.3	44.4±12.5	44.9±12.5
Female sex — no. (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	56 (8.9)	58 (9.1)	59 (9.4)	58 (9.0)	231 (9.1)
Asian	68 (10.8)	71 (11.2)	66 (10.5)	71 (11.0)	276 (10.9)
Black or African American	48 (7.6)	47 (7.4)	51 (8.1)	55 (8.6)	201 (7.9)
White	447 (71.0)	452 (71.1)	443 (70.3)	450 (70.0)	1792 (70.6)
Native Hawaiian or other Pacific Islander	2 (0.3)	2 (0.3)	3 (0.5)	2 (0.3)	9 (0.4)
Multiple	9 (1.4)	6 (0.9)	8 (1.3)	7 (1.1)	30 (1.2)
Hispanic or Latino — no. (%)	308 (48.9)	297 (46.7)	299 (47.5)	310 (48.2)	1214 (47.8)
Duration of obesity — yr	14.0±10.81	14.7±11.05	14.8±10.75	14.0±10.71	14.4±10.83
Body weight — kg	102.9±20.71	105.8±23.32	105.6±22.92	104.8±21.37	104.8±22.12
Mean body-mass index	37.4±6.63	38.2±7.01	38.1±6.69	38.2±6.89	38.0±6.81
Body-mass index category — no. (%)					
<30	38 (6.0)	38 (6.0)	40 (6.3)	24 (3.7)	140 (5.5)
≥30 to <35	241 (38.3)	209 (32.9)	199 (31.6)	227 (35.3)	876 (34.5)
≥35 to <40	174 (27.6)	187 (29.4)	179 (28.4)	180 (28.0)	720 (28.4)
≥40	177 (28.1)	202 (31.8)	212 (33.7)	212 (33.0)	803 (31.6)
Waist circumference — cm	113.2±14.25	114.8±15.80	114.4±15.59	114.0±14.92	114.1±15.16
Blood pressure — mm Hg					
Systolic	123.6±12.45	123.8±12.77	123.0±12.94	122.9±12.77	123.3±12.73
Diastolic	79.3±8.14	79.9±8.32	79.3±8.23	79.6±7.95	79.5±8.16
Pulse — beats per min	72.3±9.60	71.8±9.57	72.5±9.95	72.9±9.27	72.4±9.60
Lipid levels — geometric mean mg/dl (coefficient of variation, %)					
Total cholesterol	187.1 (21.1)	190.7 (19.9)	187.4 (19.9)	186.4 (20.3)	187.9 (20.3)
HDL cholesterol	47.6 (26.6)	47.5 (26.1)	47.5 (25.5)	46.5 (26.9)	47.3 (26.3)
LDL cholesterol	108.7 (30.2)	111.5 (30.3)	109.5 (30.0)	108.4 (30.5)	109.5 (30.2)
Triglycerides	128.9 (51.7)	126.5 (51.5)	127.9 (47.5)	130.5 (49.2)	128.4 (50.0)
Estimated GFR — ml/min/1.73 m^2 ‡	97.6±17.87	98.3±18.26	98.2±17.67	98.1±18.28	98.1±18.02
Prediabetes, n (%)	247 (39.2)	262 (41.2)	253 (40.2)	270 (42.0)	1032 (40.6)
Glycated hemoglobin — %	5.6±0.36	5.6±0.37	5.6±0.41	5.6±0.38	5.6±0.38
Fasting glucose — mg/dl	95.4±9.7	95.5±10.7	95.3±10.3	95.7±9.5	95.5±10.1
Fasting insulin — mIU/liter	13.6±10.0	14.1±12.2	14.4±9.3	14.3±9.9	14.1±10.4
SF-36 physical function score	49.6±8.3	49.6±7.5	49.6±7.8	49.7±7.7	49.6±7.8

* Plus–minus values are mean±SD. GFR denotes glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, and SF-36 Short Form Health Survey, version 2, acute form.
† Race or ethnic group was reported by the participants.
‡ The estimated GFR was calculated with use of the serum creatinine–based Chronic Kidney Disease Epidemiology Collaboration equation.


Tirzepatide, 5 mg
Tirzepatide, 10 mg
Tirzepatide, 15 mg
Placebo
A Overall Percent Change in Body Weight from Baseline (treatment-regimen estimand)
Percent Change in Body Weight
0.0
−4.0
−8.0
−12.0
−16.0
−20.0
−24.0
−15.0
−19.5
−20.9
−3.1
Tirzepatide, 5 mg
Tirzepatide, 10 mg
Tirzepatide, 15 mg
Placebo
B Percent Change in Body Weight by Week (efficacy estimand)
Overall mean baseline weight=104.8 kg
Placebo
−2.4
−3.1
Tirzepatide, 5 mg
−16.0
−15.0
Tirzepatide, 10 mg
−21.4
−19.5
Tirzepatide, 15 mg
−22.5
−20.9
0 4 8 12 16 20 24 36 48 60 72 TRE
Weeks since Randomization
C Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)
Percentage of Participants
85.1 88.9 90.9 34.5
68.5 78.1 83.5 18.8
48.0 66.6 70.6 8.8
30.0 50.1 56.7 3.1
15.3 32.3 36.2 1.5
≥5 ≥10 ≥15 ≥20 ≥25
Body Weight–Reduction Target (%)
D Participants Who Met Weight-Reduction Targets (efficacy estimand)
Percentage of Participants
89.4 96.2 96.3 27.9
73.4 85.9 90.1 13.5
50.2 73.6 78.2 6.0
31.6 55.5 62.9 1.3
16.5 35.0 39.7 0.3
≥5 ≥10 ≥15 ≥20 ≥25
Body Weight–Reduction Target (%)

Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial

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See Comment page 1687

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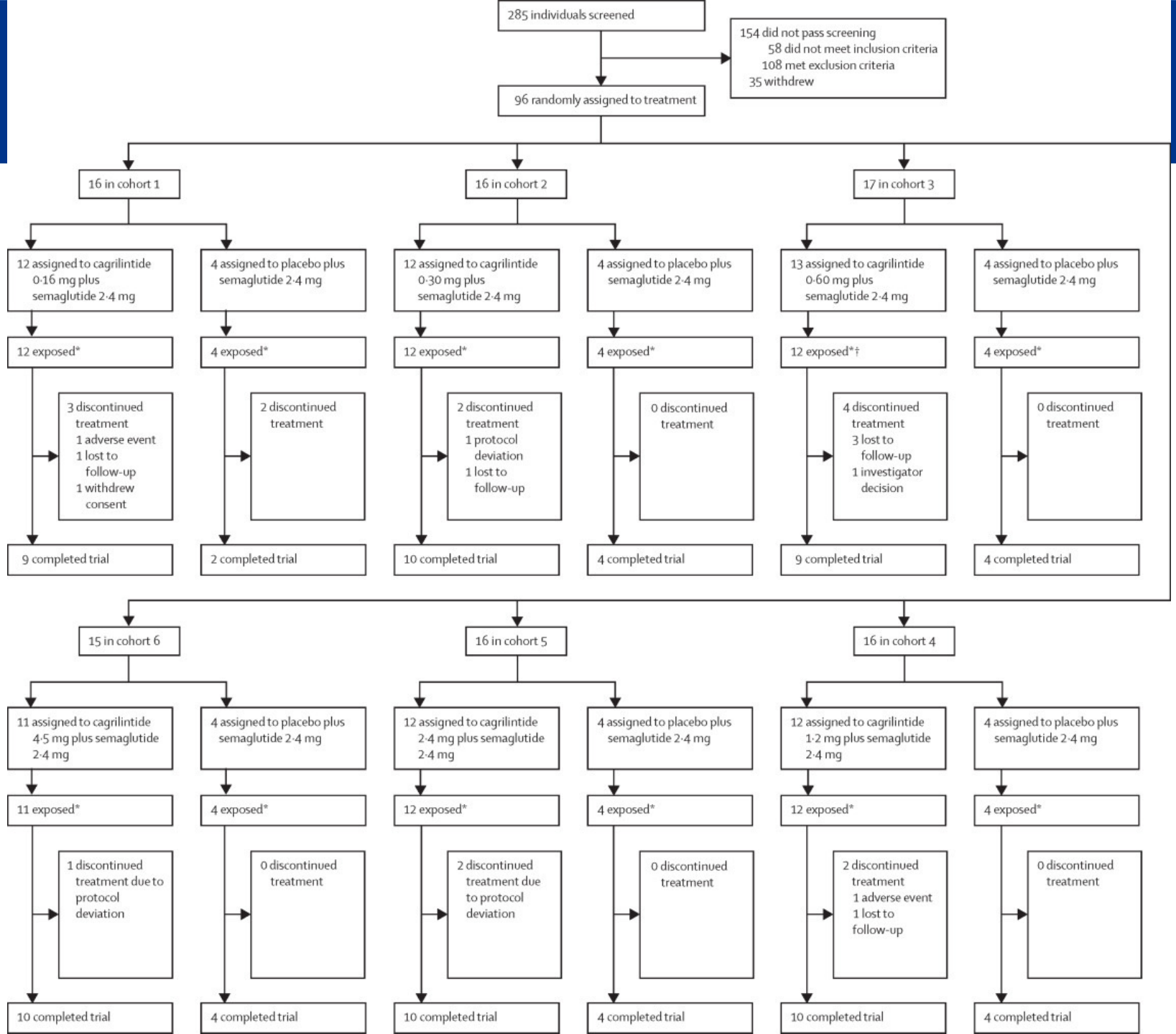
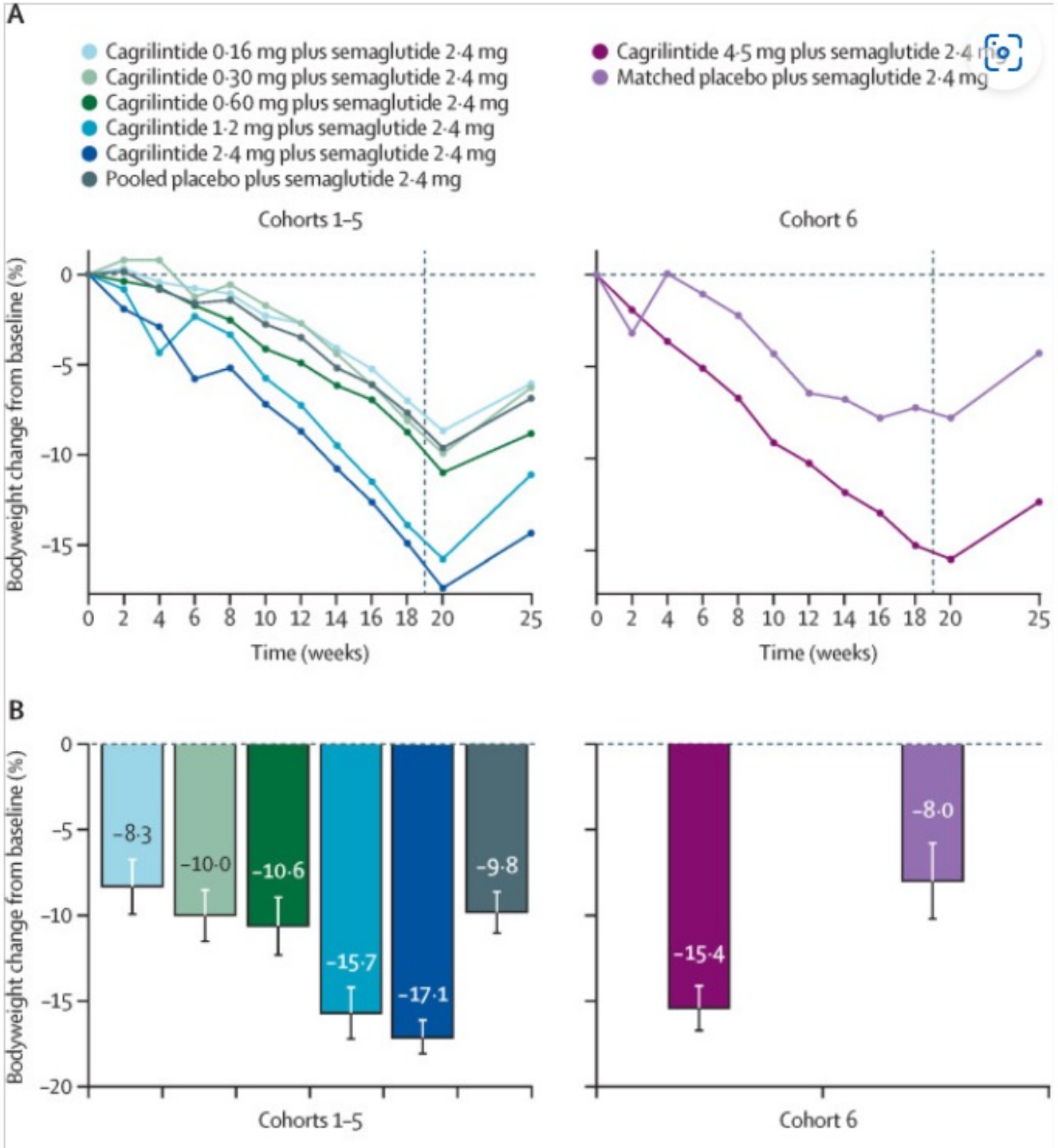
Summary

Background Cagrilintide, a long-acting amylin analogue, and semaglutide 2·4 mg, a glucagon-like peptide-1 analogue, are both being investigated as options for weight management. We aimed to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of this drug combination.

Methods In this randomised, placebo-controlled, multiple-ascending dose, phase 1b trial, individuals aged 18–55 years with a body-mass index 27·0–39·9 kg/m² and who were otherwise healthy were recruited from a single centre in the USA. The trial included six sequential overlapping cohorts, and in each cohort eligible participants were randomly assigned (3:1) to once-weekly subcutaneous cagrilintide (0·16, 0·30, 0·60, 1·2, 2·4, or 4·5 mg) or matched placebo, in combination with once-weekly subcutaneous semaglutide 2·4 mg, without lifestyle interventions. In each cohort, the doses of cagrilintide and semaglutide were co-escalated in 4-week intervals to the desired dose over 16 weeks, participants were treated at the target dose for 4 weeks, and then followed up for 5 weeks. Participants, investigators, and the sponsor were masked to treatment assignment. The primary endpoint was number of treatment-emergent adverse events from baseline to end of follow-up. Secondary pharmacokinetic endpoints assessed from day of last dose (week 19) to end of treatment (week 20) were area under the plasma concentration-time curve from 0 to 168 h ($AUC_{0-168\ h}$) and maximum concentration [C_{max}] of cagrilintide and semaglutide; exploratory pharmacokinetic endpoints were half-life, time to C_{max} [t_{max}], plasma clearance, and volume of distribution of cagrilintide and semaglutide; and exploratory pharmacodynamic endpoints were changes in bodyweight, glycaemic parameters, and hormones. Safety, pharmacokinetic, and pharmacodynamic endpoints were assessed in all participants who were exposed to at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03600480, and is now complete.

Lancet 2021; 397: 1736–48


285 individuals screened
154 did not pass screening
58 did not meet inclusion criteria
108 met exclusion criteria
35 withdrew
96 randomly assigned to treatment
16 in cohort 1
12 assigned to cagrilintide 0·16 mg plus semaglutide 2·4 mg
12 exposed*
3 discontinued treatment
1 adverse event
1 lost to follow-up
1 withdrew consent
9 completed trial
4 assigned to placebo plus semaglutide 2·4 mg
4 exposed*
2 discontinued treatment
2 completed trial
16 in cohort 2
12 assigned to cagrilintide 0·30 mg plus semaglutide 2·4 mg
12 exposed*
2 discontinued treatment
1 protocol deviation
1 lost to follow-up
10 completed trial
4 assigned to placebo plus semaglutide 2·4 mg
4 exposed*
0 discontinued treatment
4 completed trial
17 in cohort 3
13 assigned to cagrilintide 0·60 mg plus semaglutide 2·4 mg
12 exposed*†
4 discontinued treatment
3 lost to follow-up
1 investigator decision
9 completed trial
4 assigned to placebo plus semaglutide 2·4 mg
4 exposed*
0 discontinued treatment
4 completed trial
15 in cohort 6
11 assigned to cagrilintide 4·5 mg plus semaglutide 2·4 mg
11 exposed*
1 discontinued treatment due to protocol deviation
10 completed trial
4 assigned to placebo plus semaglutide 2·4 mg
4 exposed*
0 discontinued treatment
4 completed trial
16 in cohort 5
12 assigned to cagrilintide 2·4 mg plus semaglutide 2·4 mg
12 exposed*
2 discontinued treatment due to protocol deviation
10 completed trial
4 assigned to placebo plus semaglutide 2·4 mg
4 exposed*
0 discontinued treatment
4 completed trial
16 in cohort 4
12 assigned to cagrilintide 1·2 mg plus semaglutide 2·4 mg
12 exposed*
2 discontinued treatment
1 adverse event
1 lost to follow-up
10 completed trial
4 assigned to placebo plus semaglutide 2·4 mg
4 exposed*
0 discontinued treatment
4 completed trial


A
Cagrilintide 0·16 mg plus semaglutide 2·4 mg
Cagrilintide 0·30 mg plus semaglutide 2·4 mg
Cagrilintide 0·60 mg plus semaglutide 2·4 mg
Cagrilintide 1·2 mg plus semaglutide 2·4 mg
Cagrilintide 2·4 mg plus semaglutide 2·4 mg
Pooled placebo plus semaglutide 2·4 mg
Cagrilintide 4·5 mg plus semaglutide 2·4 mg
Matched placebo plus semaglutide 2·4 mg
Cohorts 1–5
Cohort 6
Bodyweight change from baseline (%)
0
−5
−10
−15
0 2 4 6 8 10 12 14 16 18 20 25
Time (weeks)
B
Bodyweight change from baseline (%)
0
−5
−10
−15
−20
−8·3
−10·0
−10·6
−15·7
−17·1
−9·8
−15·4
−8·0
Cohorts 1–5
Cohort 6

Take Home Message

- Liraglutide showed moderate efficacy in various clinical trials

- We can maximize its clinical value by
  - Increasing compliance
  - Reducing adverse effect
  - Adding intensive LSM

- Other good GLP-1 agonists are coming!

Contents