GLP1 Receptor agonists in treatment of obesity

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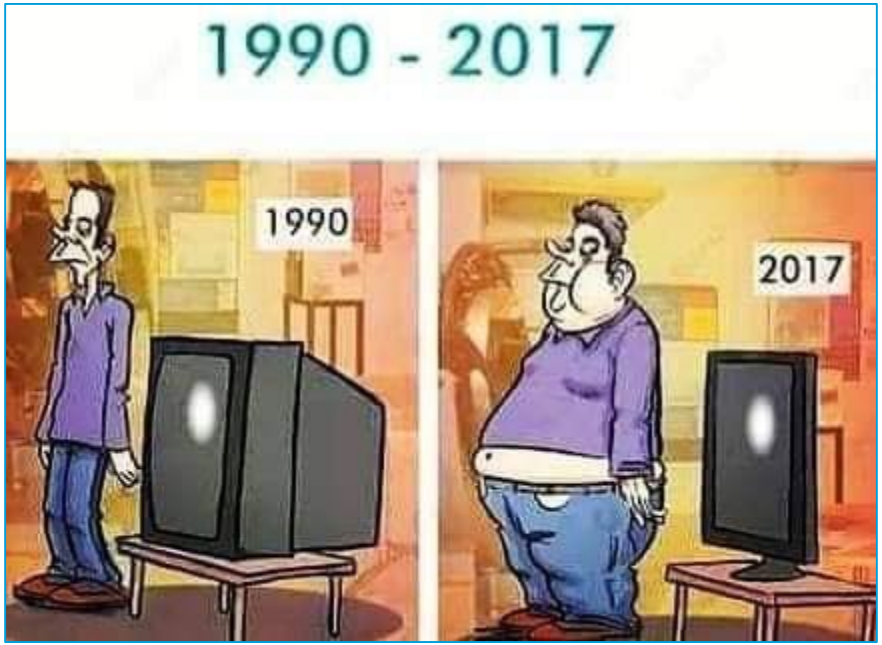
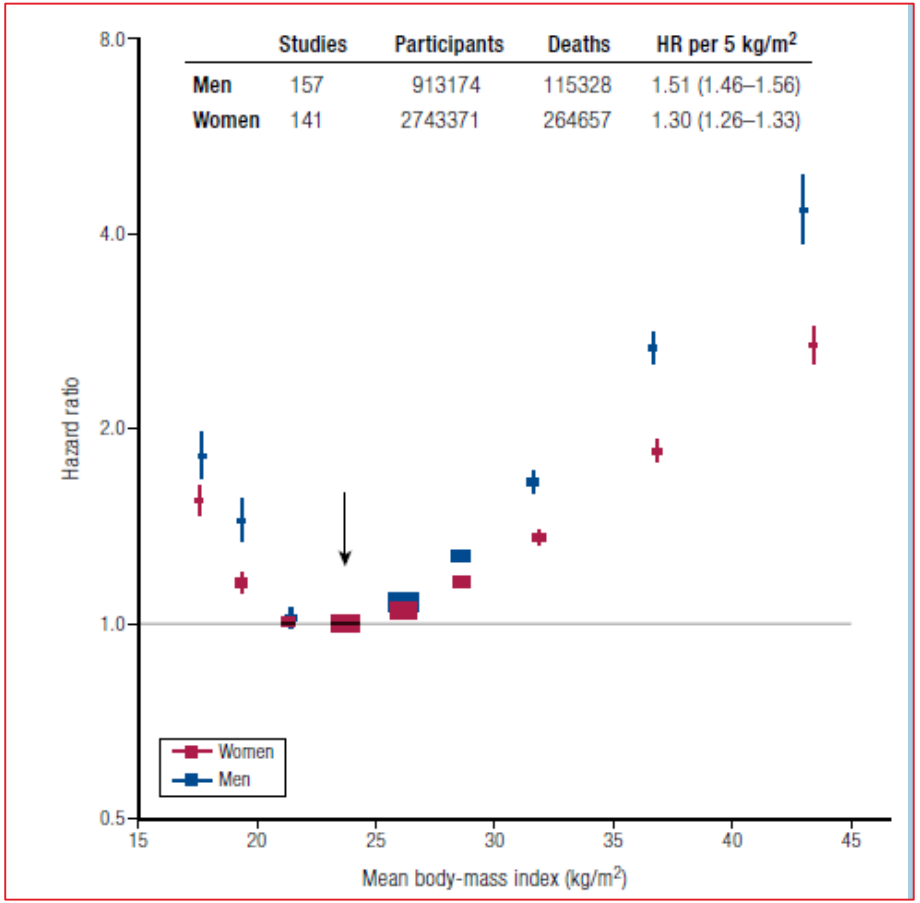


Agenda

- Introduction.
- Multiple direct effects of GLP1 agonists on human physiology.
- SCALE Obesity and Pre-diabetes.
- SCALE Maintenance.
- STEPS RCTs.
- Conclusions.

Introduction

- Obesity is a major global health challenge.
- A 5–10% reduction in body weight in overweight and obese improves several risk factors for cardiovascular disease .

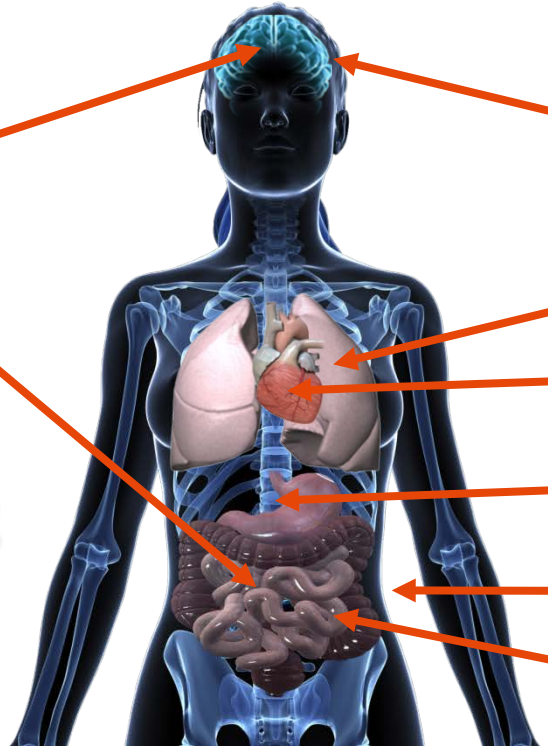


Endocrine Reviews, April 2018, 39(2):79–132

GLP-1 secretion and receptor expression

GLP-1 is secreted by:

- Neurons in hindbrain
- L-cells of the gut



GLP-1R is expressed in:

- Brain
- Lung
- Heart (AV node)
- Pancreas
- Kidney
- GI tract

Merchenthaler *et al. J Comp Neurol* 1999;403:261–80; Baggio, Drucker. *Gastroenterology* 2007;132:2131–57; Ban *et al. Circulation* 2008;117:2340–50; Vrang *et al. Prog Neurobiol* 2010;92:442–62; Pyke *et al. Endocrinology* 2014;155:1280–90

Multiple effects of GLP1 agonists on human physiology.

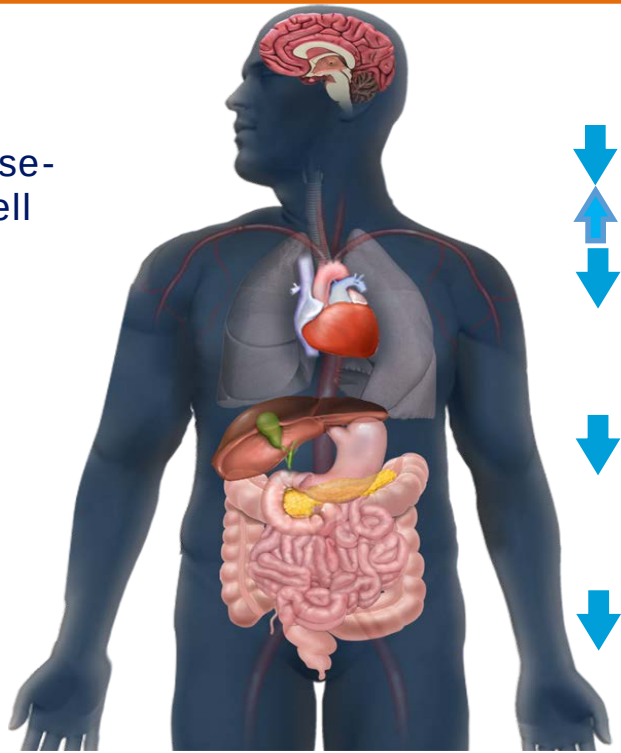
Pancreas

↑ Insulin secretion (glucose-dependent) and beta-cell sensitivity

Insulin synthesis

↑ Insulin synthesis

↓ Glucagon secretion (glucose-dependent)



Brain

↓ Body weight:

↑ Satiety

↓ Energy intake

Cardiovascular system

↓ Systolic blood pressure

Liver

↓ Hepatic glucose output

1. Holst *et al. Trends Mol Med* 2008;14:161–168; 2. Flint *et al. Adv Ther* 2011;28:213–226; 3. Degn *et al. Diabetes* 2004;53:1187–1194; 4. Baggio, Drucker. *Gastroenterology* 2007;132:2131–2157; 5. Horowitz *et al. Diabetes Res Clin Pract* 2012;97:258–266; 6. Vilsbøll *et al. BMJ* 2012;344:d7771; 7. Niswender *et al. Diabetes Obes Metab* 2013;15:42–54; 8. Fonseca *et al. Diabetes* 2010;59(suppl 1):A79 (296-OR)

Current GLP1 R.A

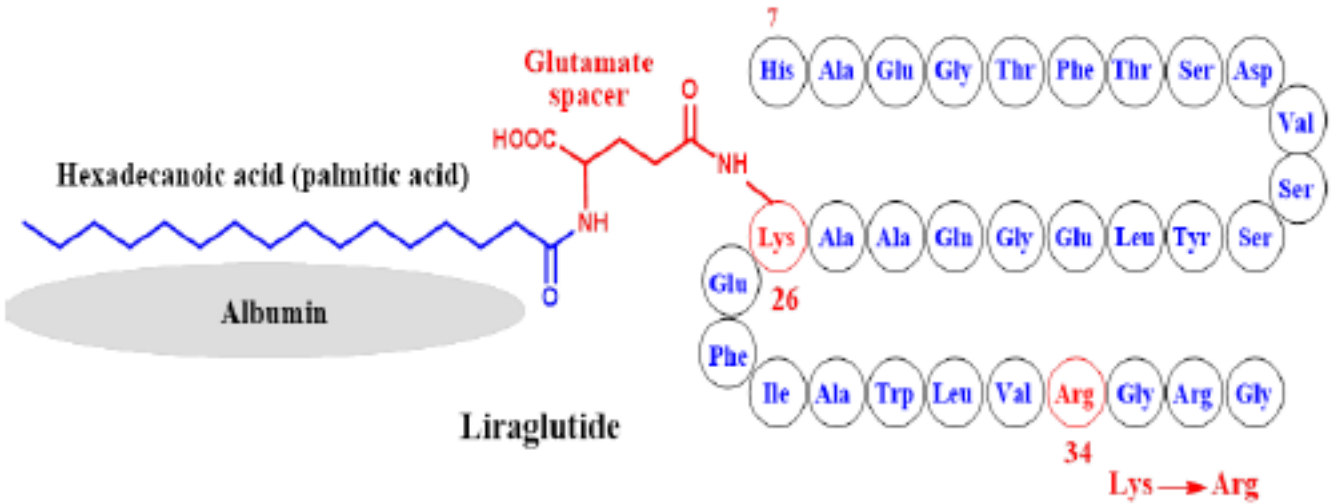
Drug	Dosing	Half-life	Duration of Action
Exenatide BID	5 to 10 mcg SC twice daily	2.4 hours	Short-acting
Lixisenatide	10 to 20 mcg SC daily	3 hours	Short-acting
Liraglutide	0.6 to 1.8 mg SC once daily	13 hours	Long-acting
Dulaglutide	0.75 to 1.5 mg SC once weekly	4.5 to 4.7 days	Long-acting
Exenatide ER	2 mg SC once weekly	Extended-release formulation	Long-acting
Semaglutide QW	0.25 mg SC weekly × 4 weeks; 0.5 mg weekly × 4 weeks; 1 mg once weekly if needed	~ 1 week	Long-acting
Semaglutide oral	3 mg once daily × 30 days; increase to 7 mg once daily	~ 1 week	Short-acting

GLP1 Receptor agonists in treatment of obesity

liraglutide 3 mg was approved by the FDA in 2014 for the treatment of adult obesity and in 2020 for obesity in adolescents aged 12–17 years.

On 4 June 2021, FDA approved **semaglutide** 2.4 mg for chronic weight management in adults with obesity or overweight with at least one weight-related condition (such as high blood pressure or cholesterol, or T2D).

Liraglutide



SCALE Obesity and Pre-diabetes.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2015 VOL. 373 NO. 1

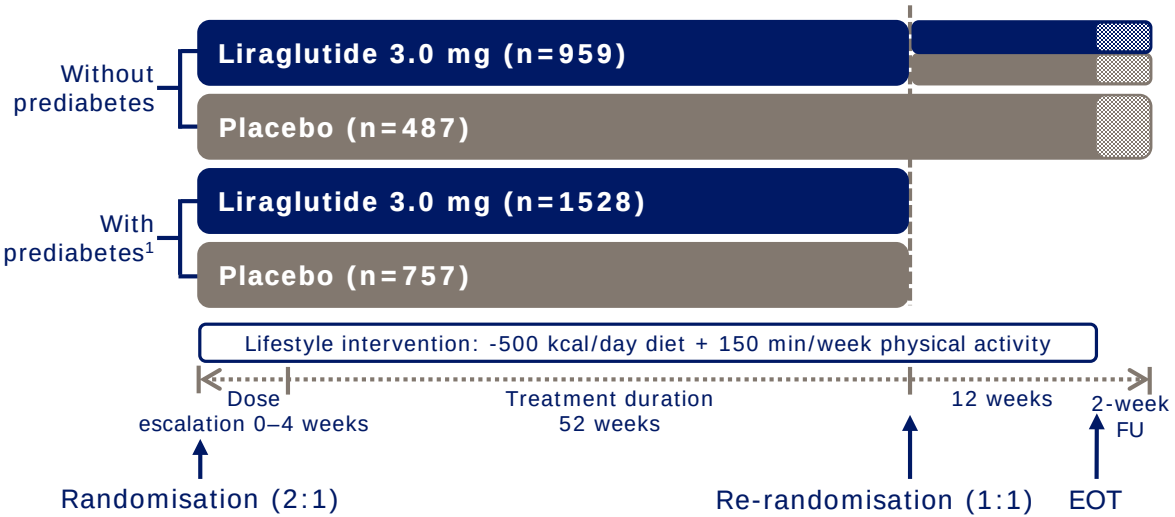
A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Xavier Pi-Sunyer, M.D., Arne Astrup, M.D., D.M.Sc., Ken Fujioka, M.D., Frank Greenway, M.D., Alfredo Halpern, M.D., Michel Krempf, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Rafael Violante Ortiz, M.D., Christine Bjørn Jensen, M.D., Ph.D., and John P.H. Wilding, D.M., for the SCALE Obesity and Prediabetes NN8022-1839 Study Group*

Pi-Sunyer *et al*. *N Engl J Med* 2015;373:11–22

Trial design

3731 participants
- ≥18 years
- Stable BW
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 + comorbidities



Trial information
- June 2011 to March 2013
- Randomised controlled double-blind study
- 191 sites in 27 countries
- Duration: 56 weeks (with prediabetes), 68 weeks (without prediabetes)

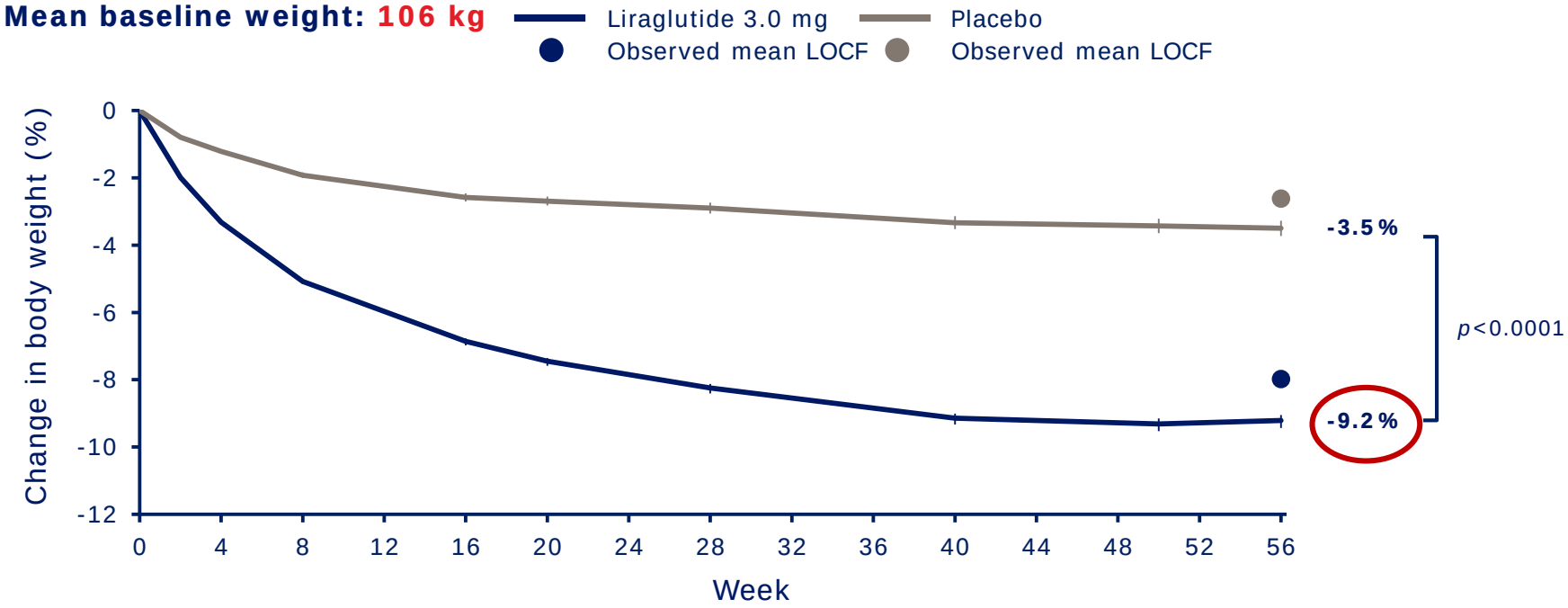
Trial objective
- Efficacy and safety of liraglutide 3.0 mg, as adjunct to D&E, in participants with obesity or overweight plus comorbidities, without diabetes

Key endpoints
- Three co-primary: BW change, 5% or 10% BW loss
- Secondary: Changes from baseline in BMI, WC, glycaemic control variables, cardiometabolic risk factors, and HRQoL

Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22

Change in body weight (%)
0–56 weeks

Mean baseline weight: 106 kg

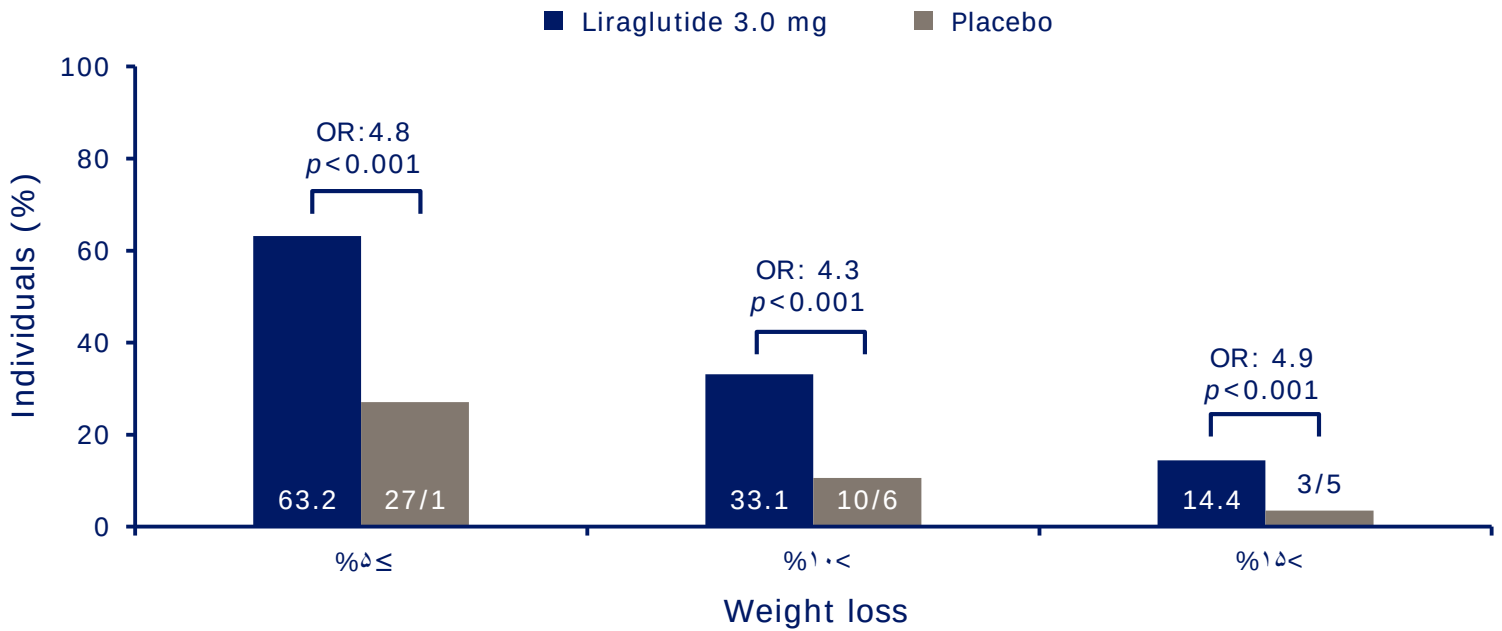


Pi-Sunyer *et al. Diabetologia* 2014;57(Suppl. 1): Abstract 73-OR

Categorical weight loss

At week 56

Mean baseline weight: 106.2 kg



Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22

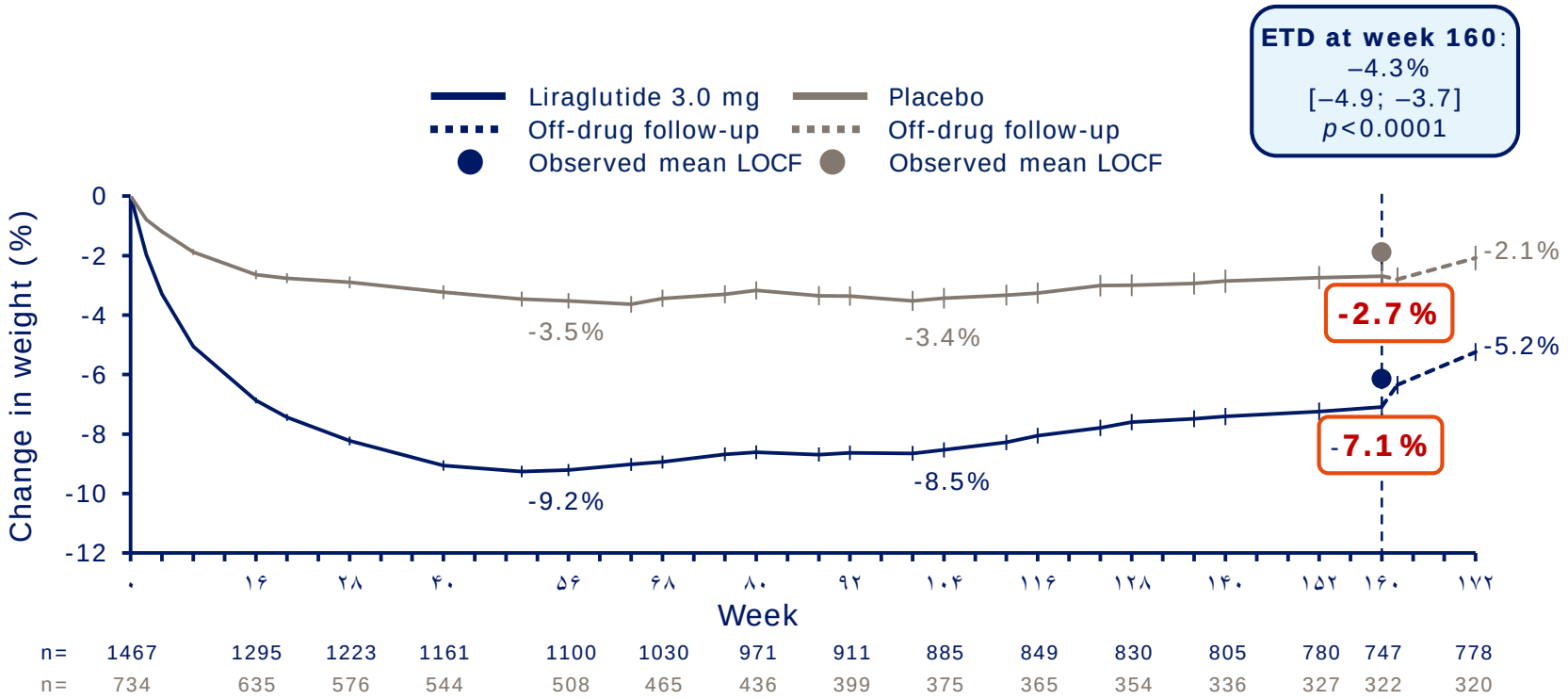
3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial

*Carel W le Roux, Arne Astrup, Ken Fujioka, Frank Greenway, David C W Lau, Luc Van Gaal, Rafael Violante Ortiz, John P H Wilding, Trine V Skjøth, Linda Shapiro Manning, Xavier Pi-Sunyer, for the SCALE Obesity and Prediabetes NN8022-1839 Study Group**

le Roux *et al*. *Lancet* 2017;389:1399–409

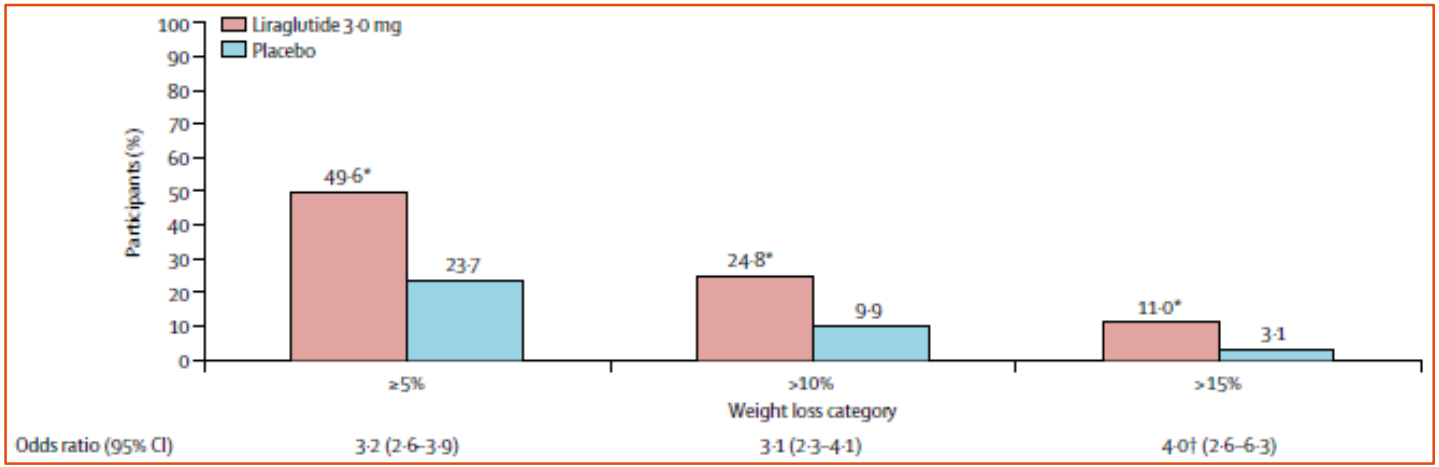
Change in body weight (%)

0–172 weeks



le Roux *et al*. *Lancet* 2017;389:1399–409

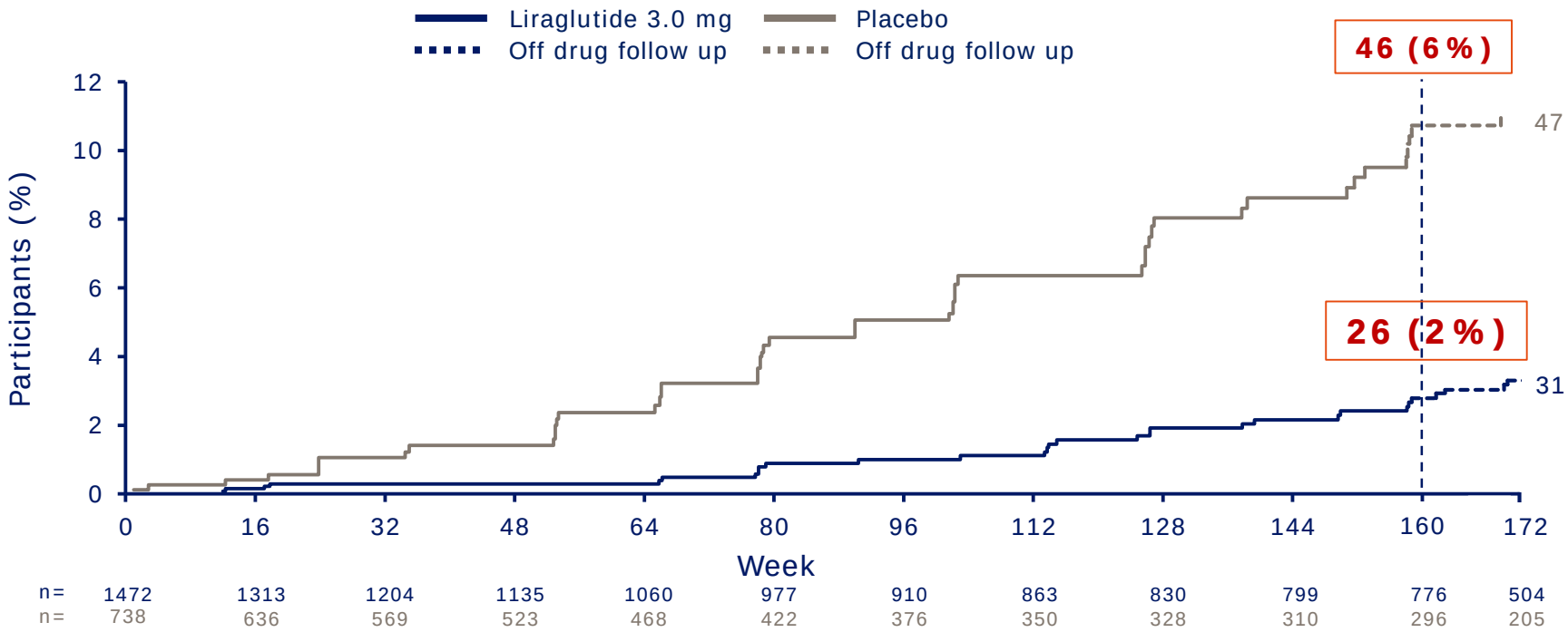
The proportion of participants who lost at least 5%, more than 10%, and more than 15% of their baseline bodyweight at week 160.



le Roux *et al*. *Lancet* 2017;389:1399–409

Participants diagnosed with T2D over time

0–172 weeks



le Roux *et al*. *Lancet* 2017;389:1399–409

SCALE Maintenance

International Journal of Obesity (2013) **37**, 1443–1451

www.nature.com/ijo

ORIGINAL ARTICLE

Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study

This article has been corrected since online publication and an erratum is also printed in this issue

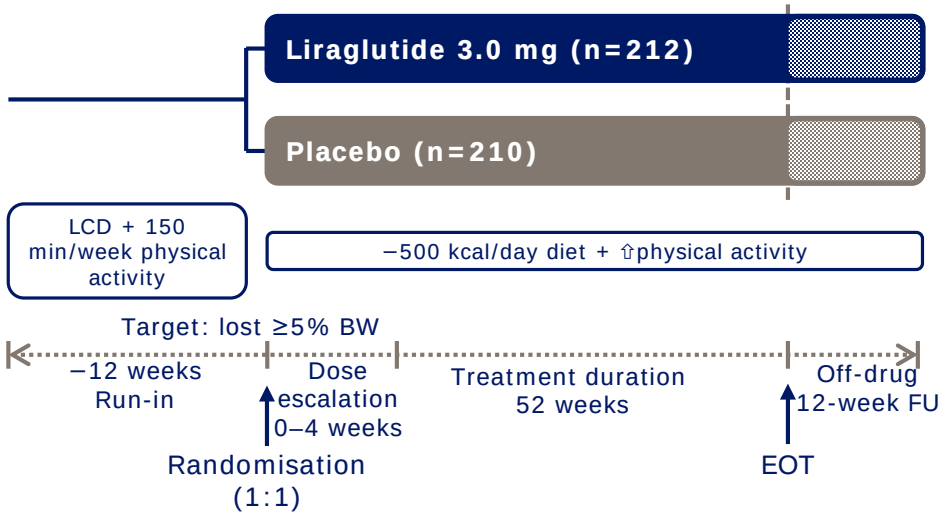
TA Wadden[1], P Hollander[2], S Klein[3], K Niswender[4], V Woo[5], PM Hale[6] and L Aronne[7] on behalf of the NN8022-1923 Investigators[8]

Trial design: SCALE Maintenance

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

551 participants

- ≥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)

Trial objective

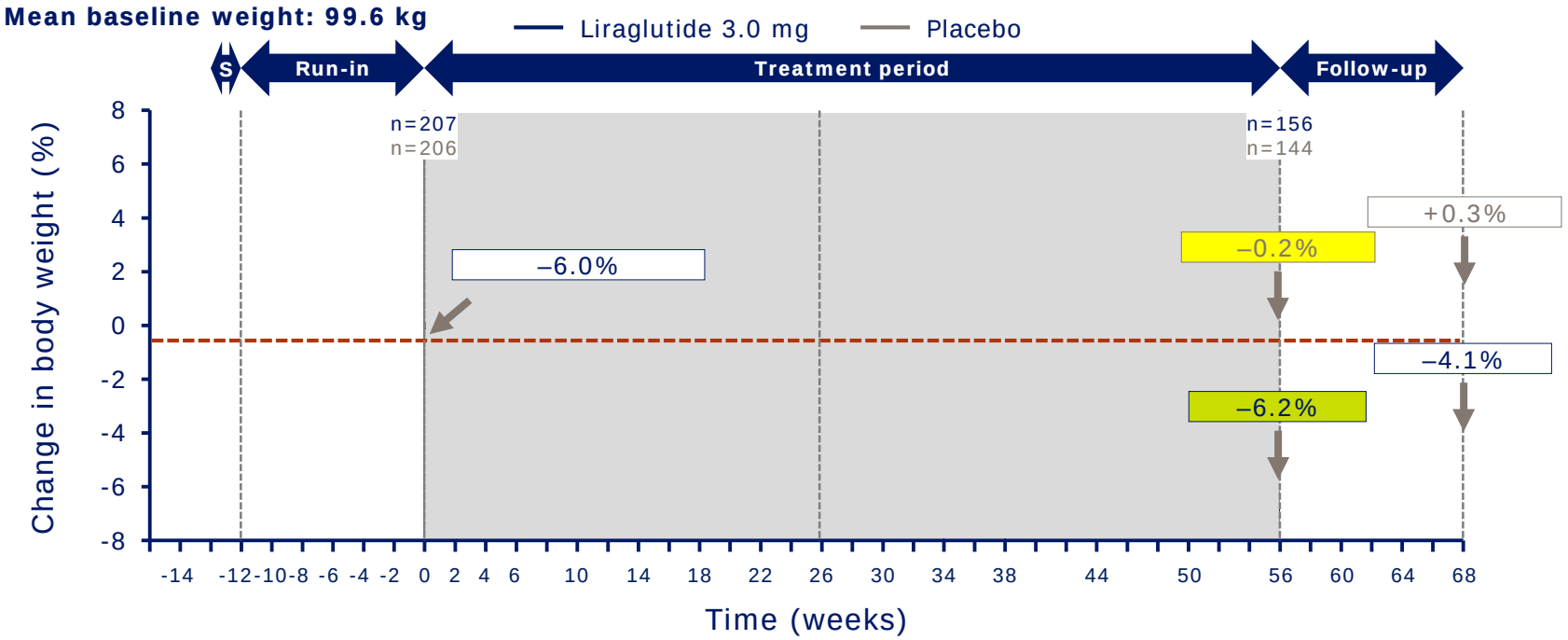
- Efficacy of liraglutide 3.0 mg in maintaining weight loss achieved with a LCD (1200–1400 kcal/diet) and increased physical activity (150 min/week) during run-in

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

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

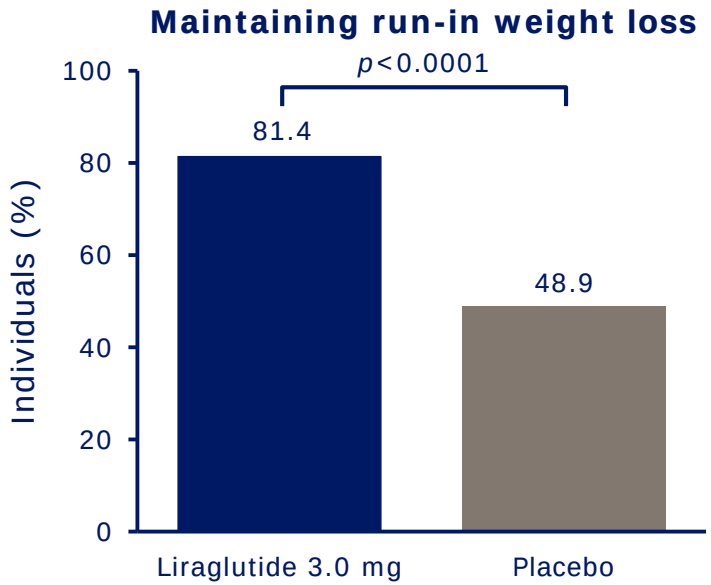
Change in body weight (%)

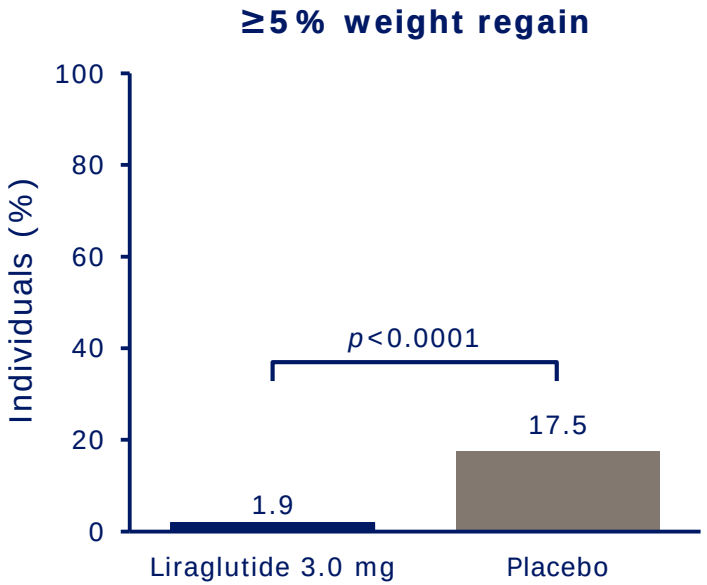


Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51

Individuals maintaining or regaining weight loss
At week 56

Mean baseline weight: 99.6 kg

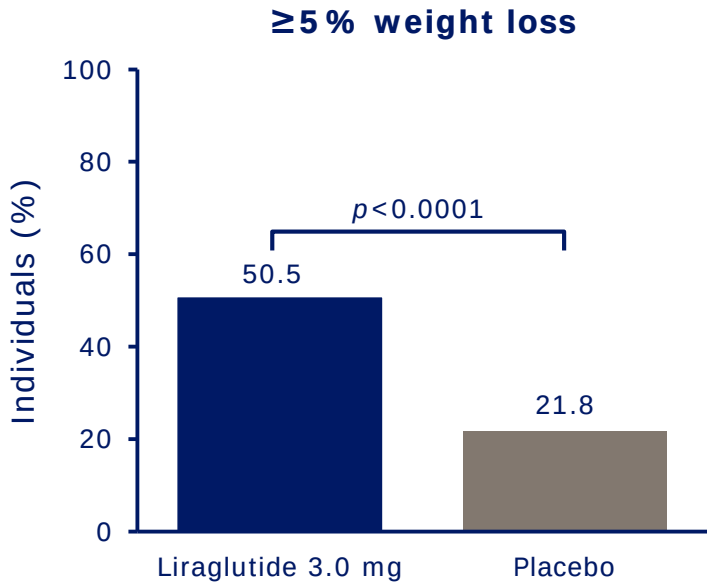


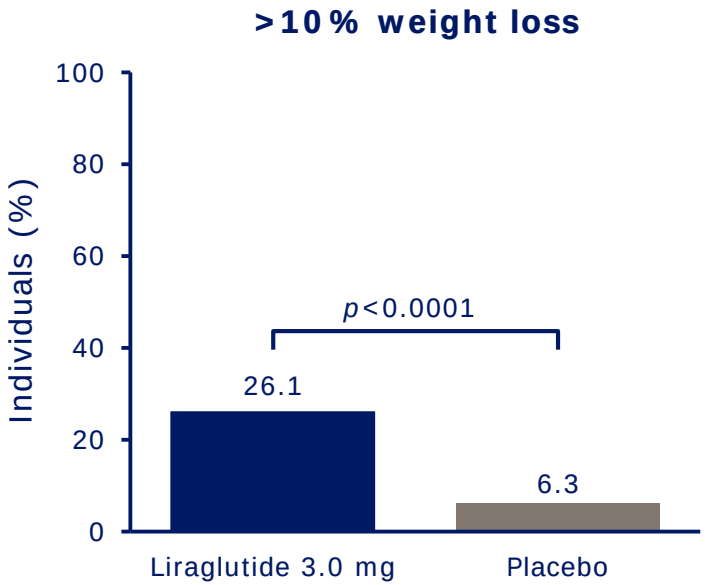


Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51

Individuals achieving additional weight loss
At week 56

Mean baseline weight: 99.6 kg





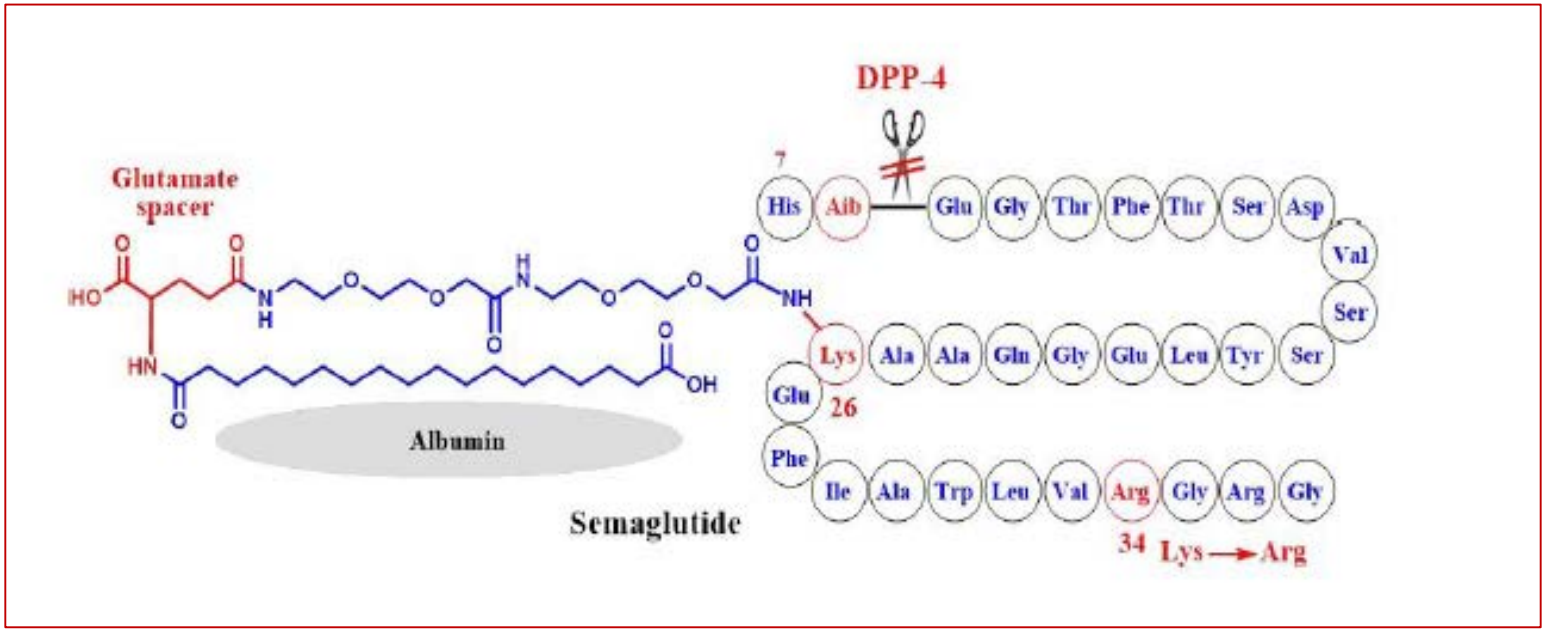
Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51

SCALE Maintenance
Summary

- Following low-calorie diet-induced weight loss ≥5%, liraglutide 3.0 mg treatment of 56 weeks:
  - Induced additional weight loss of **6.2%** (6.0 kg).
  - 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.
- 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

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

Semaglutide



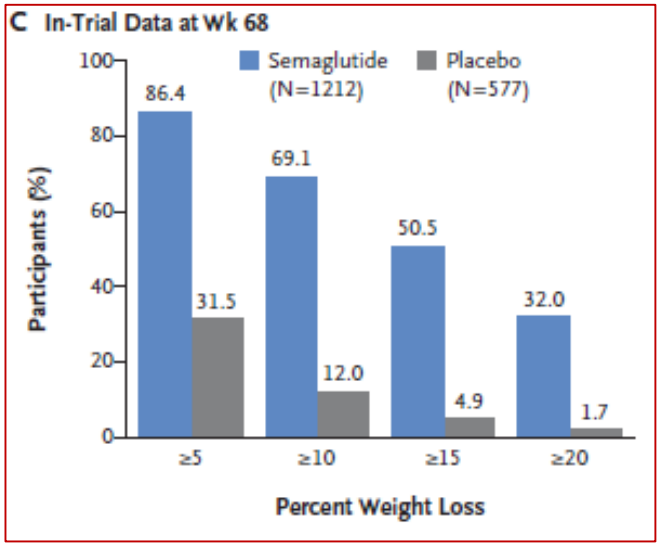
The NEW ENGLAND JOURNAL of MEDICINE

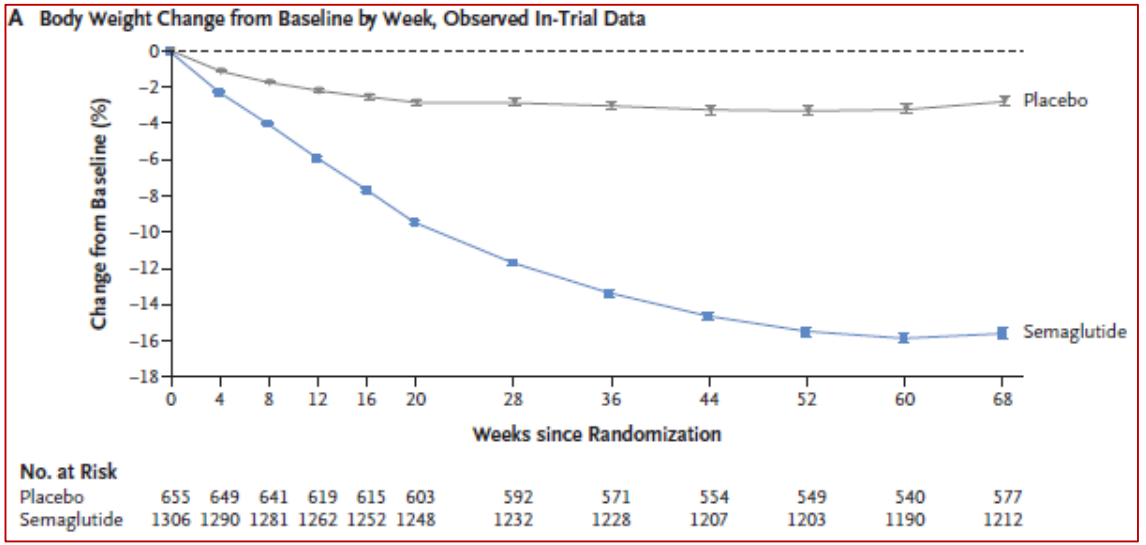
ESTABLISHED IN 1812 MARCH 18, 2021 VOL. 384 NO. 11

Once-Weekly Semaglutide in Adults with Overweight or Obesity

METHOD

Double-blind trial, 1961 adults with a body-mass index of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have Diabetes randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention.





The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo

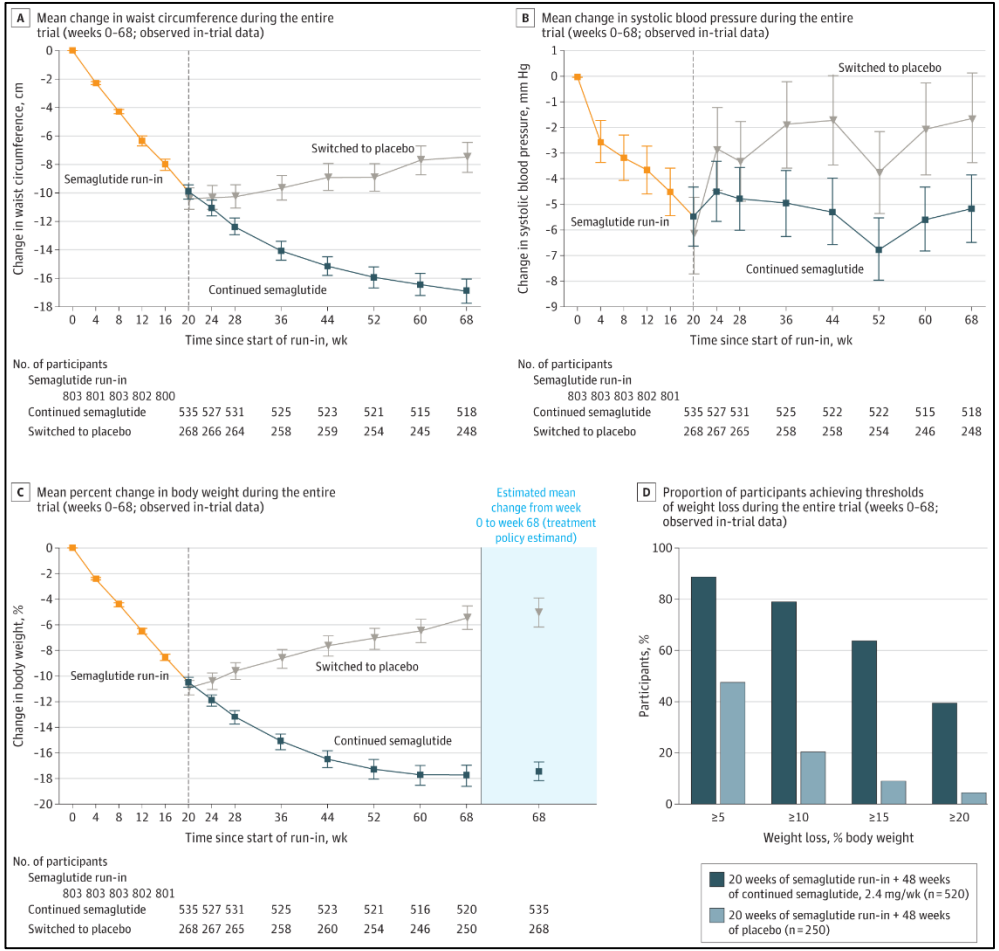
Original Investigation
March 23, 2021

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or ObesityThe STEP 4 Randomized Clinical Trial

Domenica Rubino, MD[1]; Niclas Abrahamsson, MD[2]; Melanie Davies, MD[3,4]; et al

Method: Randomized clinical trial of adults with overweight or obesity, 803 participants completed a 20-week run-in of weekly treatment with subcutaneous semaglutide, 2.4 mg, with a mean weight loss of 10.6%, and were randomized to continued treatment with subcutaneous semaglutide vs placebo for an additional 48 weeks.

Rubino D et al JAMA. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224



Rubino D et al JAMA. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224

Results

- With continued semaglutide, mean body weight change from week 20 to week 68 was **−7.9% vs +6.9%** with the switch to placebo (*P* < .001).

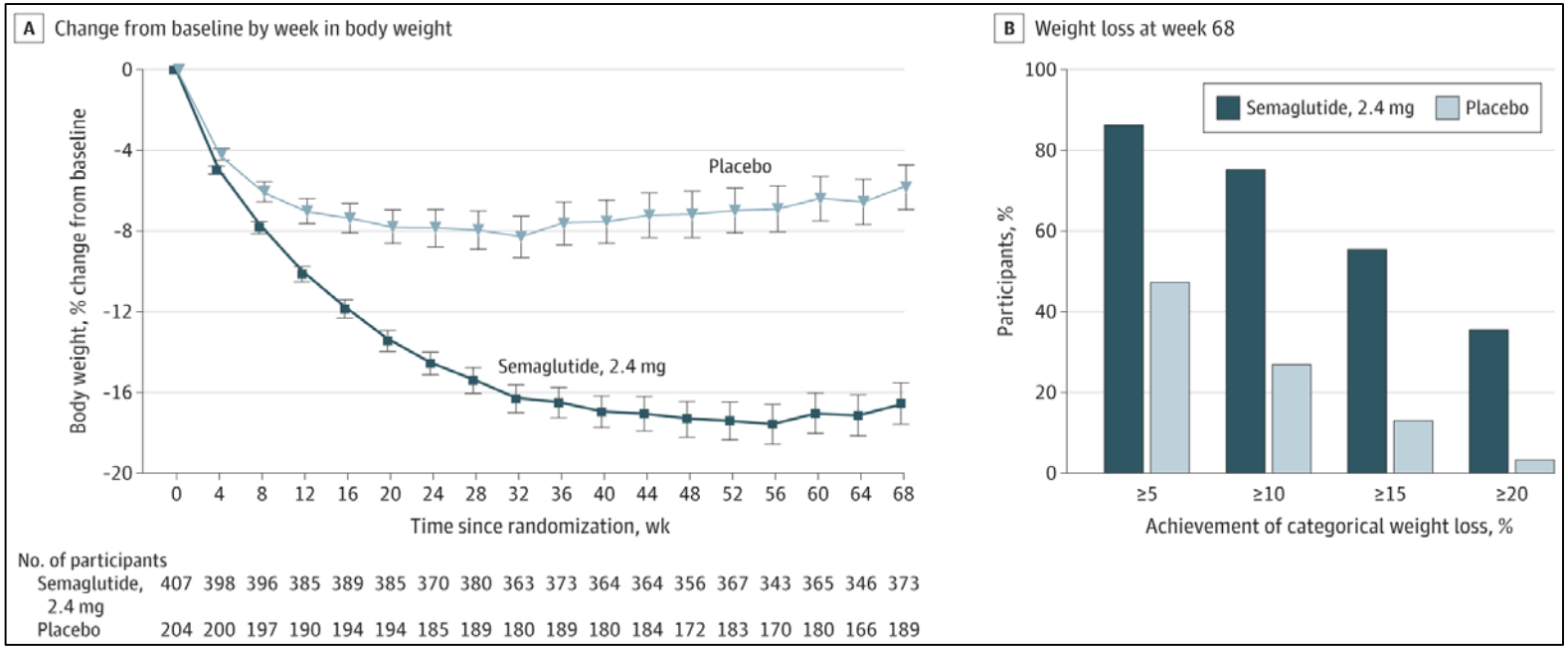
- Waist circumference (**−9.7 cm** [95% CI, −10.9 to −8.5 cm]), systolic blood pressure (−3.9 mm Hg [95% CI, −5.8 to −2.0 mm Hg]), also improved with continued subcutaneous semaglutide vs placebo (all *P* < .001).

Rubino D et al JAMA. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224

Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial

JAMA. 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831

Method :Randomized clinical trial that included 611 adults with overweight or obesity, 68 weeks' treatment with once-weekly subcutaneous semaglutide vs placebo, combined with intensive behavioral therapy (and a low-calorie diet for the initial 8 weeks)



Wadden TA et al JAMA. 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831

Results

- At week 68, the estimated mean body weight change from baseline was **–16.0%** for semaglutide vs **–5.7%** for placebo (*P* < .001).
- More participants treated with semaglutide vs placebo lost at least 5% of baseline body weight (**86.6% vs 47.6%,** respectively; *P* < .001).
- A higher proportion of participants in the semaglutide vs placebo group achieved weight losses of at least 10% or 15% (**75.3% vs 27.0%** and 55.8% vs 13.2%, respectively; *P* < .001)

Wadden TA et al JAMA. 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831

Key massage

Across the trials, weight loss was **5.7–9.2%** with liraglutide 3.0mg **and 12–14.9**% with Semaglutide which **more than two third of** the individuals achieved a clinically meaningful weight loss of **at least 5%**, which is associated with a variety of health benefits and improvements in obesity-related comorbidities such as diabetes and hypertension.

GLP1 Ras , improve weight maintenance and induce additional reductions in CVD risk factors, including waist circumference, FPG,SBP and hsCRP.

Maintaining long-term weight loss is the Achilles' heel of obesity therapy