# Stepping into Semaglutide: Dr. Patrick Pagador

**The “STEP” Trials 1-4**

Dr. Patrick Pagador

RIVERSIDE

# Semaglutide: an injectable GLP-1 Agonist

**Semaglutide**, sold under the brand name **Ozempic** among others, is an antidiabetic medication used for the treatment of type 2 diabetes and long-term weight management.

Semaglutide acts like human glucagon-like peptide-1 (GLP-1) in that it increases insulin secretion, thereby increasing sugar metabolism.

It appears to enhance growth of β cells in the pancreas, which are the sites of insulin production. It inhibits glucagon, which is a hormone that increases blood sugar. It reduces food intake by lowering appetite and slows down digestion in the stomach, helping to reduce body fat. Its half-life in the blood is about 7 days (165–184 hours).

# THE STEPS:

**Step 1**

Weight loss in obese non-diabetics VS. Placebo

**Step 2**

Weight loss in obese diabetics VS. Placebo

**Step 3**

Weight loss in obese non-diabetics VS. Intense Behavioral Therapy

**Step 4**

Weight loss after discontinuation of Semaglutide VS. Placebo

# STEP 1: Once Weekly Semaglutide in Adults with Overweight or Obesity:

## Clinical Question:

In patients with obesity, but without diabetes, does use of the GLP-1 agonist injected weekly, Semaglutide, result in significant weight loss?

# Success After Liraglutide

Obesity is an increasingly common condition associated with significant morbidity and mortality. Lifestyle modification is the mainstay of therapy as adjunctive pharmacologic therapies for weight loss are limited.

Among these is liraglutide, a GLP-1 receptor agonist administered as a daily subcutaneous injection, approved for weight management based on the SCALE trial.

Semaglutide is a GLP-1 analogue previously approved for treatment of type 2 diabetes, which has been associated with increased weight loss in diabetic patients compared to liraglutide.

# How’d They Do It?

**Inclusion Criteria: “Must Haves”**

- Age ≥18 years old
- BMI >30, or ≥27 with ≥1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)
- ≥1 self-reported unsuccessful dietary attempts to lose weight

# How’d They Do It?

**Exclusion Criteria: “Must Not Haves”**

- Diagnosis of type 1 or type 2 diabetes mellitus
- Glycolated hemoglobin (hemoglobin A1c) level ≥6.5% (≥48 mmol/mol)
- History of chronic pancreatitis or acute pancreatitis within 180 days before enrollment
- Previous or planned obesity treatment with surgery or weight-loss device (with exceptions for liposuction/abdominoplasty, lap banding, intragastric balloon, or duodenal-jejunal bypass sleeve *if* the intervention was removed or discontinued ≥1 year before screening)
- Use of an antiobesity or glucose-lowering medication within 90 days before enrollment
- Use of a GLP-1 agonist within 180 before enrollment

# Basically:

The Semaglutide Treatment Effect in People with Obesity (STEP) 1 trial enrolled non-diabetic obese patients (BMI ≥30) and overweight patients (BMI ≥27) with at least one cardiovascular risk factor (eg, hypertension or sleep apnea) to either semaglutide 2.4 mg once weekly or placebo for 68 weeks.

Individuals in both groups received counseling for lifestyle interventions including calorie reduction and physical activity.

# What Were the Interventions?

- Randomized to a group:
  - **Semaglutide** - 0.25 mg/weekly for 4 weeks. Dose increased q4wks until 2.4 mg/weekly by week 16. Lower doses were permitted for side effect control. Total duration was 68 weeks.
  - **Placebo**
- Both groups received a lifestyle intervention with individual counseling sessions q4wks, targeting -500 cal/day and 150 min/week of physical activity
- After 68 weeks, both groups underwent a 7 week washout with no semaglutide, placebo, or lifestyle intervention.

# What Were the Primary Outcomes?

**Primary Outcomes**

**Mean weight change from baseline to week 68**

-14.9% vs. -2.4% (ETD -12.4% with 95% CI -13.4% to -11.5%; P<0.001)

(Trial product estimand: -16.9% vs. -2.4% with ETD −14.4%; 95% CI −15.3% to −13.5%)

**Participants who achieved ≥5% weight reduction from baseline to week 68**

86.4% vs. 31.5% (OR 11.2; 95% CI of OR 8.9 to 14.2; P<0.001)

(Trial product estimand: 92.4% vs. 33.1% with OR 37; 95% CI of OR 28 to 49)

# What Were the Secondary Outcomes?

**Secondary Outcomes**

**Participants who achieved ≥10% weight reduction from baseline to week 68**

69.1% vs. 12% (OR 14.7; 95% CI of OR 11.1 to 19.4; P<0.001)

(Trial product estimand: 74.8% vs. 11.8% with OR 30; 95% CI of OR 22.5 to 40)

**Participants who achieved ≥15% weight reduction from baseline to week 68**

50.5% vs. 4.9% (OR 19.3; 95% CI of OR 12.9 to 28.8; P<0.001)

(Trial product estimand: 54.8% vs. 5.0% with OR 31.8; 95% CI of OR 21.0 to 48.3)

**Change in mean waist circumference from baseline to week 68**

-13.54 cm vs. -4.13 cm (ETD -9.42 cm with 95% CI -10.30 to -8.53; P<0.001)

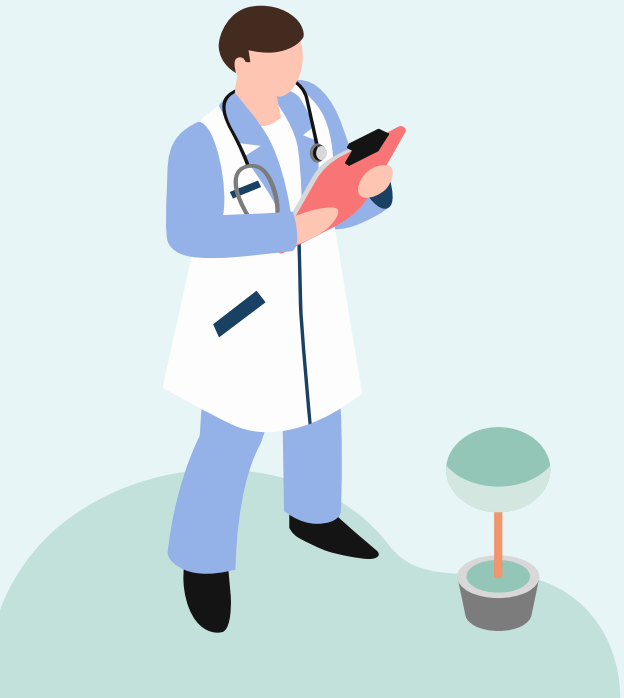
(Trial product estimand: -15.22 cm v.s -4.48 cm with ETD -10.75 cm; 95% CI -11.61 to -9.88)

**Change in systolic blood pressure from baseline to week 68**

-6.16 mmHg vs. -1.06 mmHg (ETD -5.10 mmHg with 95% CI -6.34 to -3.87)

(Trial product estimand: -7.08 mmHg vs. -1.14 mmHg with ETD -5.93 mmHg; 95% CI -7.19 to -4.68)

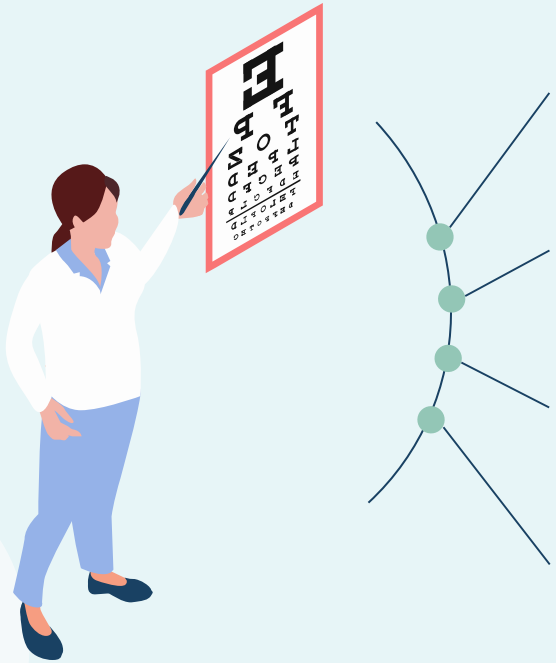
# What Ended Up Happening?



At the end of the study period, individuals in the semaglutide group experienced more weight loss as assessed in the coprimary endpoints of body weight change (-14.9% versus -2.4%) and proportion achieving ≥5% weight loss (86.4% versus 31.5%).

Secondary endpoints, which were not controlled for multiple comparisons, also favored the semaglutide group including improvement in blood pressure, waist circumference, hemoglobin A1c, CRP, lipid profiles, and quality of life scores.

# Downsides from the drug?



GI toxicity including nausea, diarrhea, vomiting, and constipation was more common in the semaglutide group (74.2% vs. 47.9%). Gallstones and pancreatitis were uncommon but were reported more commonly in the semaglutide group than in those receiving placebo.

# FDA Approval!

The FDA subsequently approved semaglutide for weight loss in this patient group, similar to the 2020 approval for liraglutide. The long-term benefits of these medical approaches are largely unknown given the relatively short study follow-up relative to cardiovascular disease complications and mortality which have a time horizon of many years.

# Any Criticism Of This Study?

- The trial population over-represented the female sex (73.1%) and white race (74.5%) compared to the US and global populations.
- Given the relatively short duration of the trial (68 weeks), the results may not generalize to long-term effects.
- The study used subcutaneous semaglutide rather than an oral formulation; the necessity of injections would likely reduce the number of patients willing to start use of this treatment or continue it in the long-term.
- Willingness to participate in a clinical trial may reflect a higher level of commitment to weight loss.

# Any More?

# STEP 2:

THE LANCET

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## Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial

Melanie Davies, MD • Louise Færch, MD • Ole K Jeppesen, MSc • Arash Pakseresht, MD • Sue D Pedersen, MD • Leigh Perreault, MD et al. Show all authors • Show footnotes

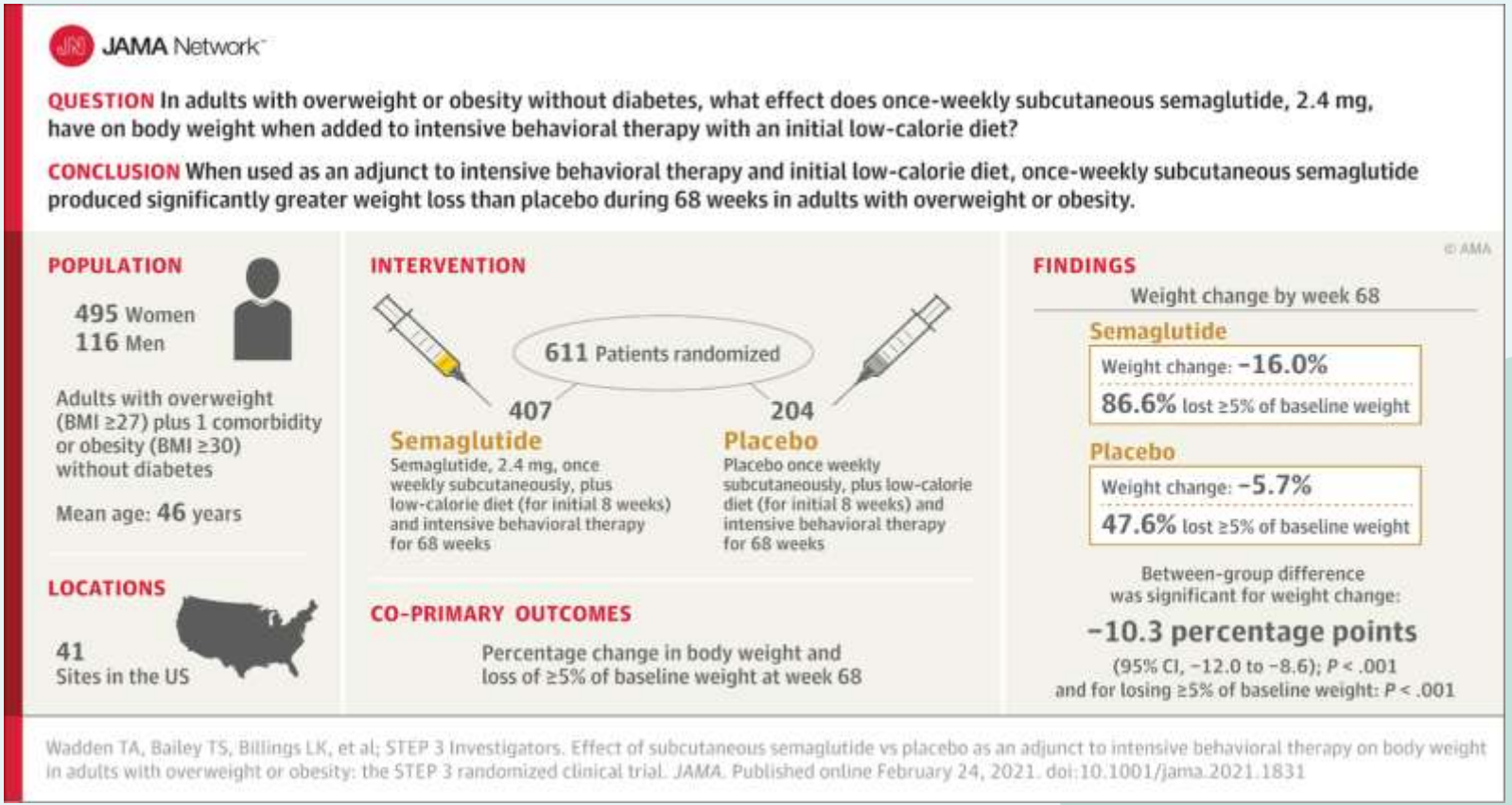
Published: March 02, 2021 • DOI: https://doi.org/10.1016/S0140-6736(21)00213-0 • Check for updates

# STEP 2

This trial, published in *The Lancet*, recruited 1210 participants **with type 2 diabetes and overweight or obesity** and tested the standard approved 1.0 mg dose versus the higher 2.4 mg dose and matched placebos over 68 weeks.

Average bodyweight reductions were 9.64%, 6.99%, and 3.42% with semaglutide 2.4 mg, 1.0 mg, and placebo, respectively. The higher dose also achieved slightly better glycemic control, reductions in cardiometabolic risk, and improved physical function relative to the standard dose.

# STEP 3:



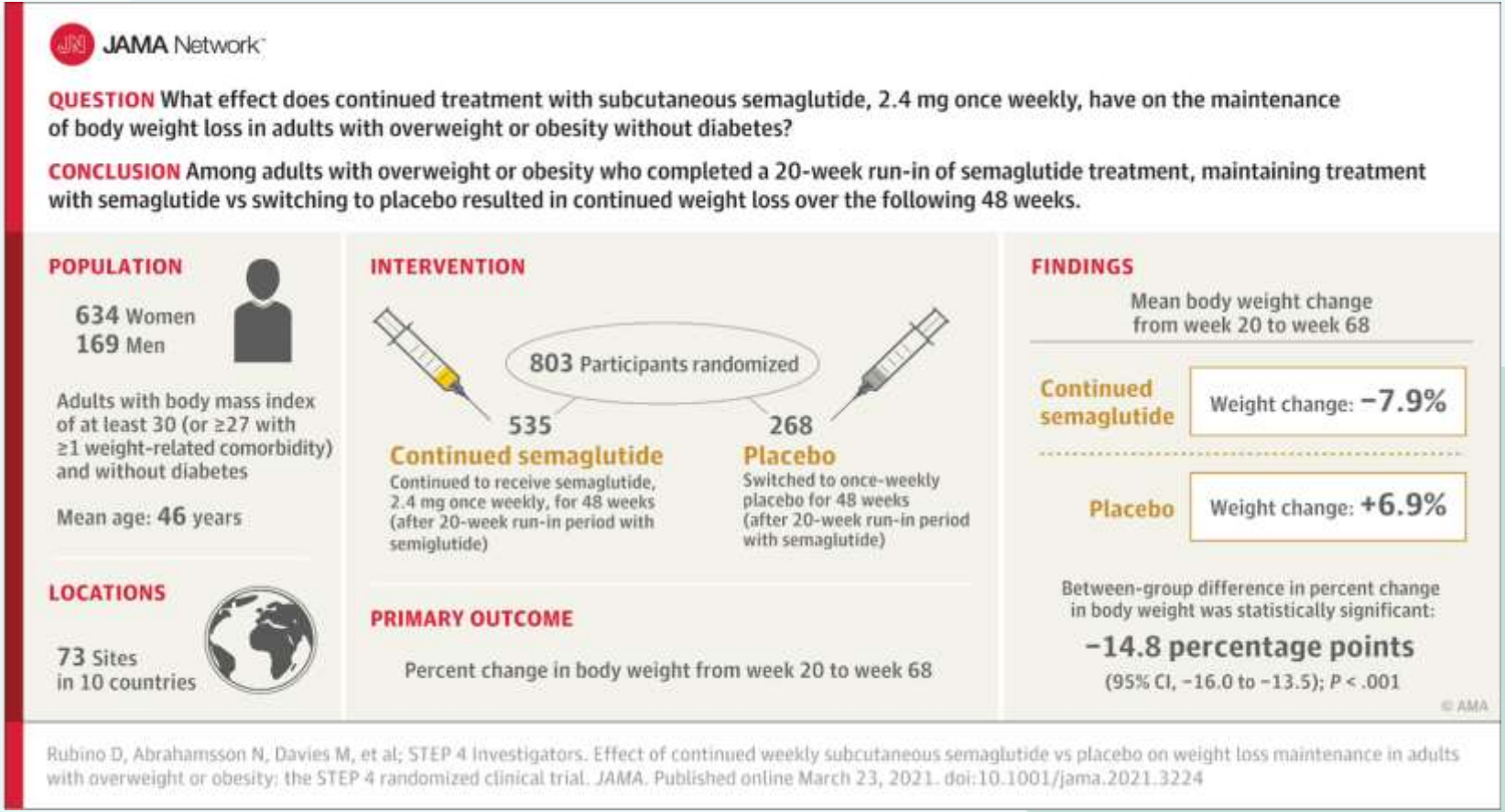

Wadden TA, Bailey TS, Billings LK, et al; STEP 3 Investigators. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. Published online February 24, 2021. doi:10.1001/jama.2021.1831

# STEP 3:

The 611 participants of STEP 3 were randomly assigned to receive semaglutide 2.4 mg or placebo in addition to intensive behavioral therapy to support them to adopt a healthier lifestyle.

As reported in *JAMA*, the average weight reduction after 68 weeks of treatment was 16.0% with semaglutide versus 5.7% with placebo. The co-primary endpoint of at least a 5% reduction in bodyweight was met by 86.6% versus 47.6%.

# STEP 4:




Rubino D, Abrahamsson N, Davies M, et al; STEP 4 Investigators. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. Published online March 23, 2021. doi:10.1001/jama.2021.3224

# STEP 4:

In this trial, the 902 participants all received semaglutide 2.4 mg for the first 20 weeks, after which they were randomly assigned to receive either semaglutide or placebo for the remaining 48 weeks.

The investigators reported in *JAMA* that participants who continued to take semaglutide after randomization lost an additional 7.9% of their bodyweight, on average, to give a total 17.4% weight loss over the whole trial, whereas those who switched to placebo regained an average 6.9%, giving a total weight loss of 5.0%.

# Biggest Barrier to Access? Cost.

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# Thanks!

Any Questions?