Semiglutide 2.4 mg for Treatment of Obesity: Key Elements of the STEP Trials 1 to 5

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Overview

- Introduction
- Objective
- Methods
- Study Importance
- Future Implications

Introduction - Background

- Burden of Obesity
  - Obesity is chronic, relapsing, progressive disease
  - Many clinical complications
    - CVD, metabolic diseases, mechanical dysfunction, sleep apnea, and malignancy
- Treatment of Obesity
  - Lifestyle interventions
    - However, maintaining weight loss is inherently difficult due to counter-regulatory neuroendocrine pathways
  - Antiobesity medications (AOM) approved by US Food and Drug Administration

Introduction - Background

- Several trials that demonstrate promising effects of GLP-1s in general
- Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) trial
  - 3,731 individuals without diabetes showed weight loss maintained at 56 weeks with liraglutide 3.0 mg versus placebo ($p<0.001$)
  - 846 individuals with diabetes and obesity demonstrated reduction of initial body weight
- Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
  - > 8,000 individuals demonstrating weight management benefits at semaglutide 0.5 mg and 1.0 mg

Semaglutide Pharmacology

- Long-acting GLP-1 analogue that mimics effects of native GLP-1
  - Promotes weight loss by reducing energy intake, increasing satiety and satiation, reduces hunger, and enhances glycemic control
  - Many GLP-1s are approved for Type 2 Diabetes Mellitus
    - Only Liraglutide 3.0 mg daily has been approved for weight management
- Semaglutide is approved for treatment of diabetes at dosage of <1.0 mg once weekly subcutaneously or oral tablet of up to 14 mg
- Current phase 3 trials are investigating semaglutide as a weight loss medication
  - Observed greater weightless with semaglutide than with liraglutide

Semaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Program

- Objective
  - Investigate the effect of semaglutide versus placebo on weight loss, safety, and tolerability in adults with obesity or overweight
- Methods
  - Across five phase 3 trials, ~5,000 participants randomly assigned to receive semiglutide 2.4 mg once weekly subcutaneously versus placebo
  - *Results will be available in 2020/2021*
- Primary endpoint
  - Change from baseline to end of treatment in body weight

STEP Program: Population Characteristics

Trial population

- > 18 years of age
- BMI > 30 or BMI > 27 with presence of weight related complications (treated or untreated): HLD, obstructive sleep apnea, HTN, or CVD

Mean population characteristics

- Participants have a mean age of 46.2 to 55.3 years
- Mostly female (74.1-81.0%)
- BMI of 35.7 to 38.5
- Mean waist circumference of 113 cm to 115.7 cm

STEP Program

Exclusion criteria

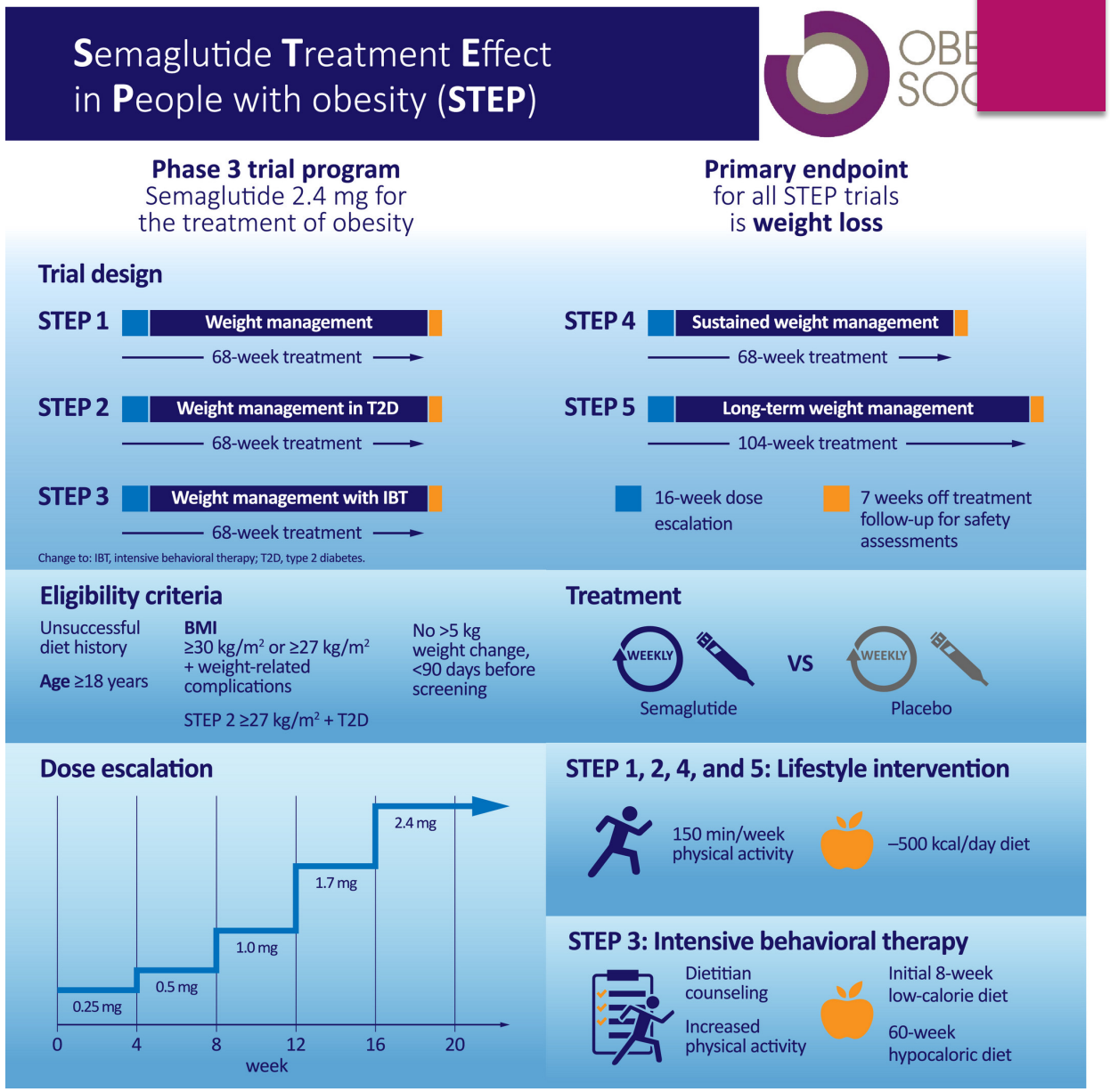
- Weight loss of > 5 kg within 90 days before screening
- Previous treatment with glucose-lowering agents or any AOM within the past 90 days before screening

General safety concerns during trials include:

- Calcitonin level > 100 ng/L
- Suspicions of pancreatitis
- Pregnancy or intention to become pregnant
- Participation in another clinical trial

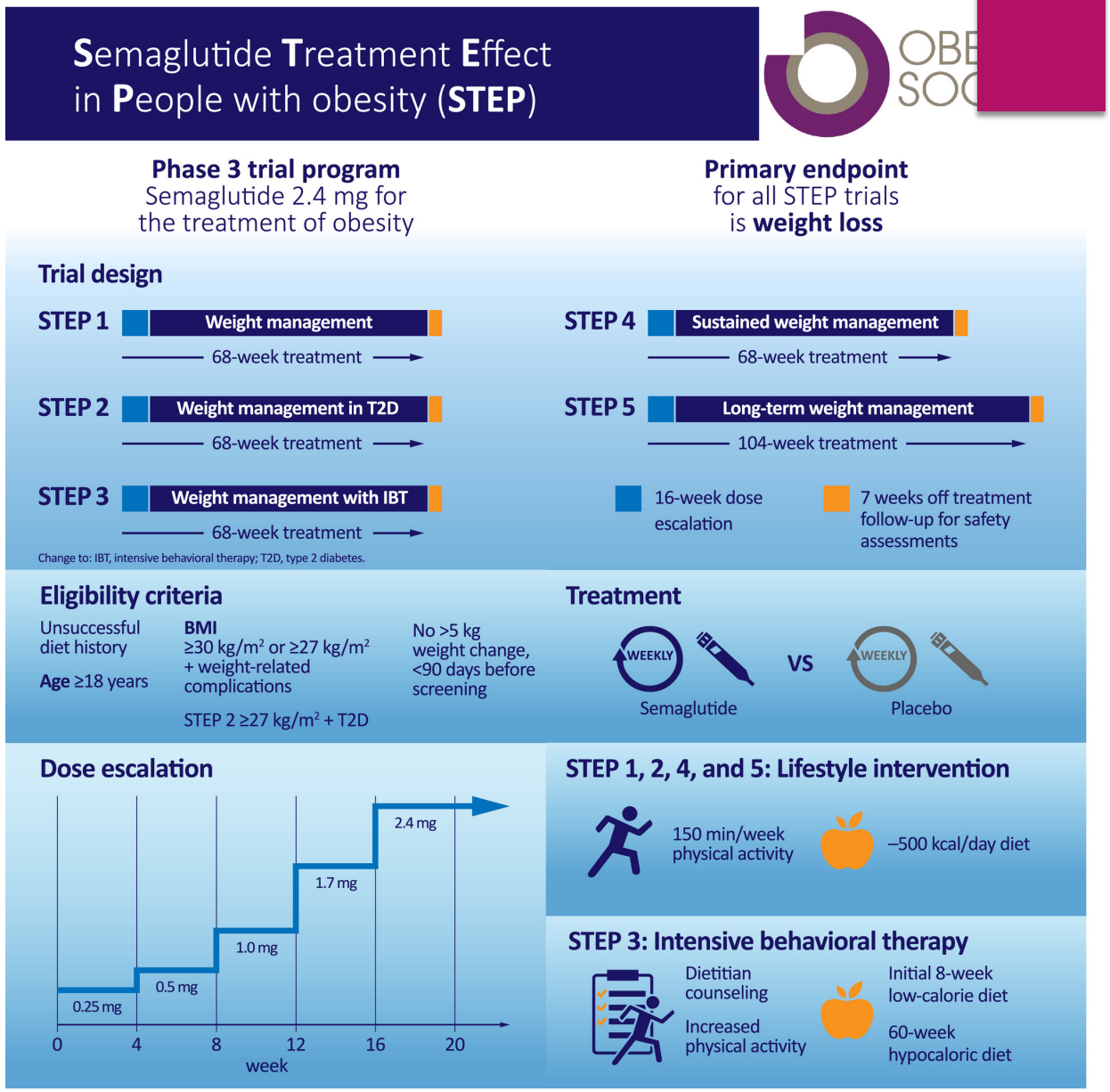
STEP Program

- STEP program evaluates efficacy and safety of semaglutide
- Trials will provide insights on weight management in people with obesity with and without type 2 diabetes along with long-term follow-up



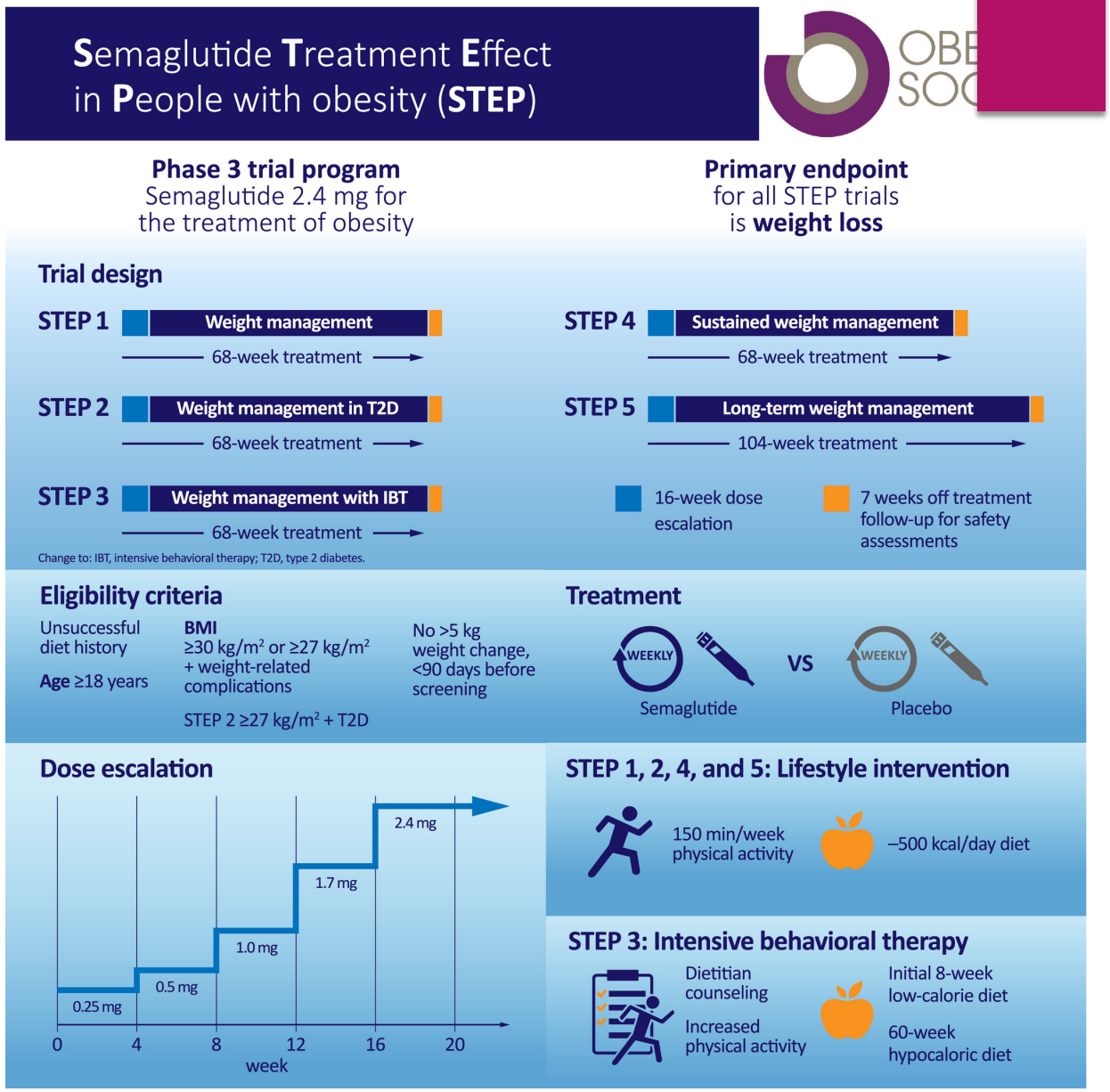
STEP Program

- STEP 1: 1,961 adults with obesity or overweight, without T2D, are being randomly assigned in a 2:1 manner to receive semaglutide 2.4 mg or placebo



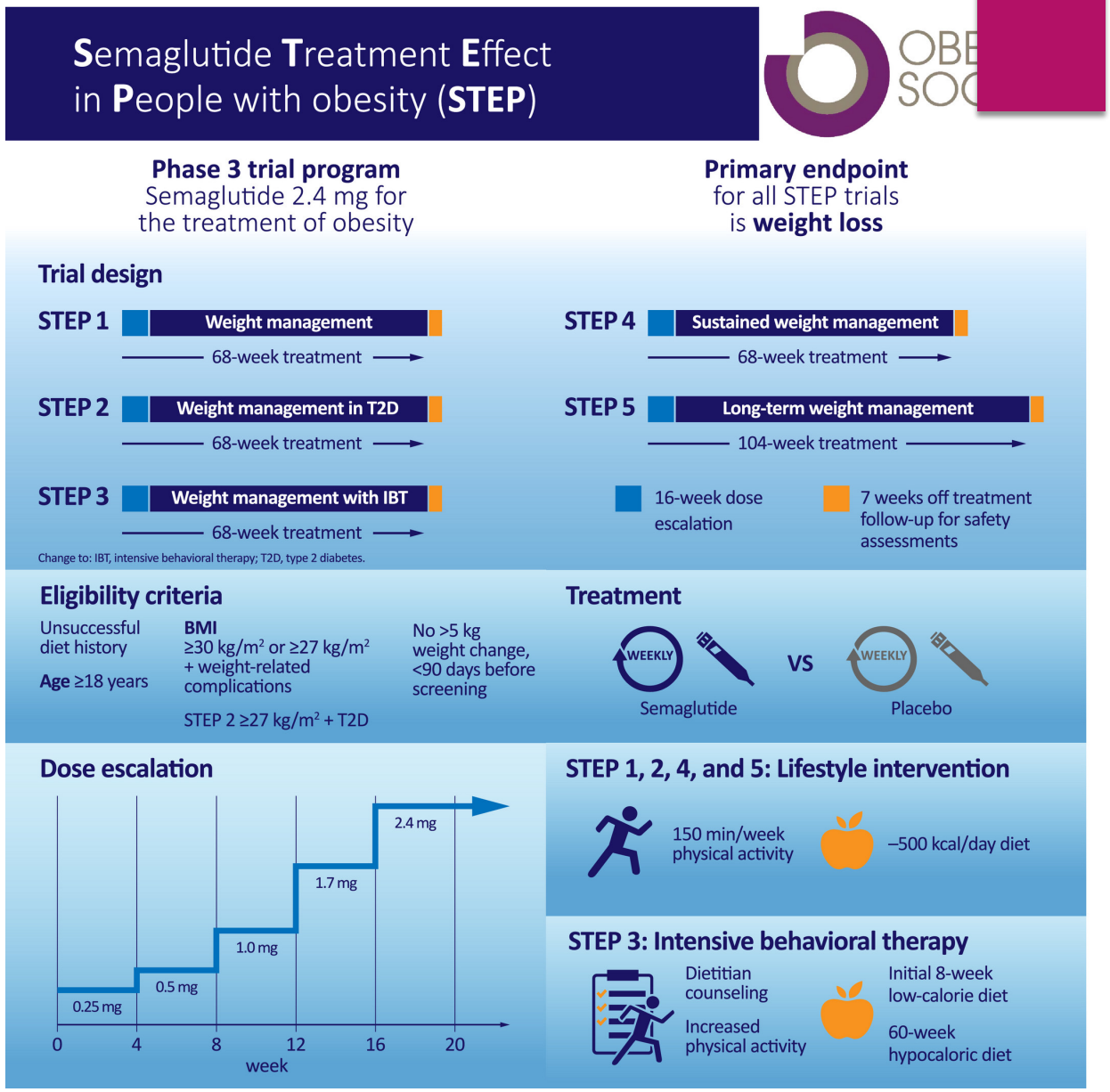
STEP Program

- STEP 2: 1,210 adults with obesity or overweight, and with T2D, are being randomly assigned 1:1:1 to receive either semaglutide 2.4 mg, semaglutide 1.0 mg once weekly, or placebo



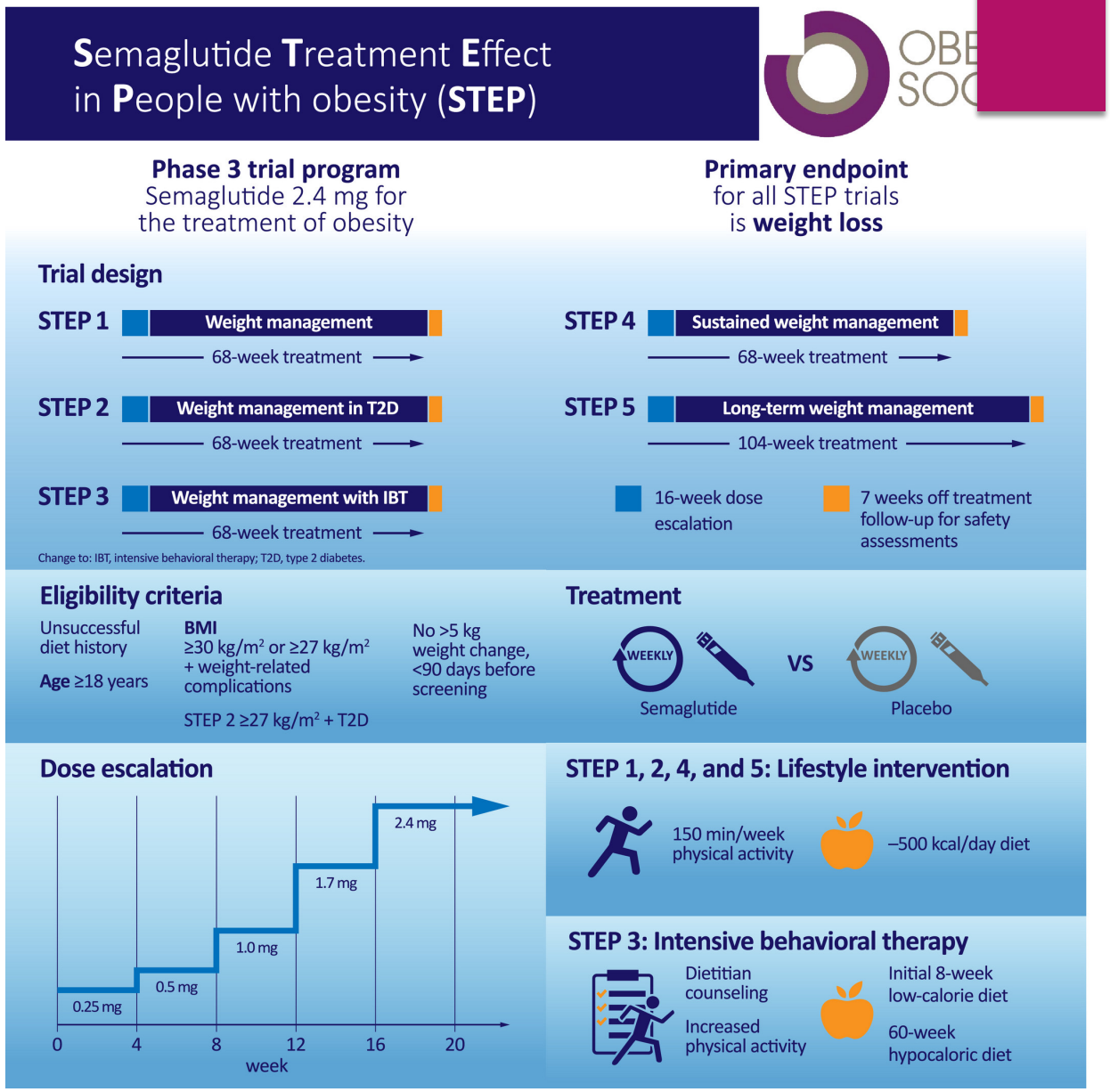
STEP Program

- STEP 3: 611 adults with obesity or overweight, without T2D, are being randomly assigned in a 2:1 manner to receive semaglutide 2.4 mg or placebo to assess WL. Treatment is administered as an adjunct to IBT, in addition to an initial 8-week, low-calorie diet, followed by 60 weeks of a hypocaloric diet and increased physical activity



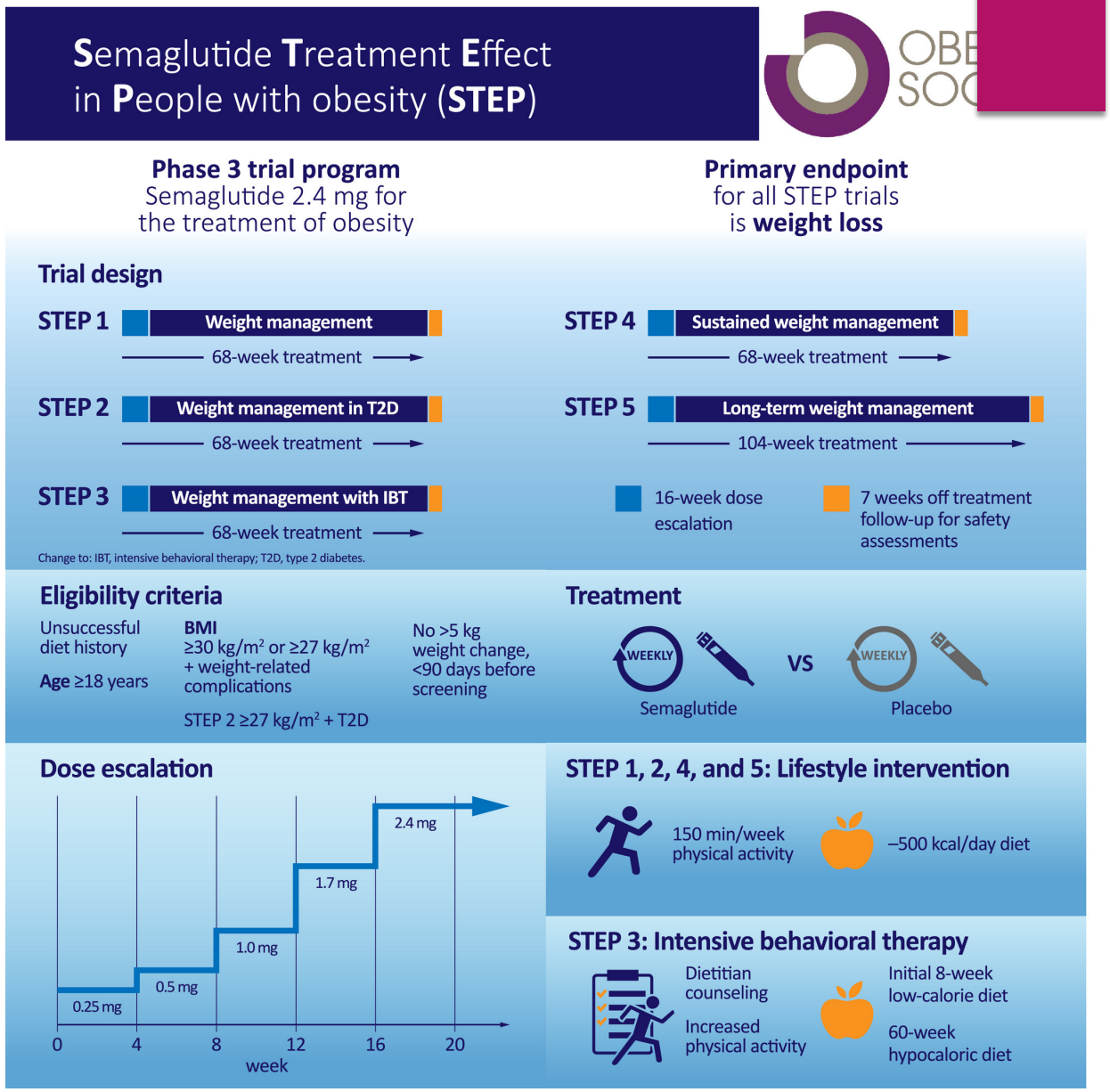
STEP Program

- STEP 4: 902 participants with obesity or overweight, without T2D, are being treated with semaglutide 2.4 mg once weekly. Those completing a 20-week run-in period are being randomly assigned in a 2:1 manner to receive continued semaglutide 2.4 mg or placebo for an additional 48 weeks to assess WL



STEP Program

- STEP 5: 304 participants with obesity or overweight, without T2D, are being randomly assigned in a 1:1 manner to receive semaglutide 2.4 mg or placebo to assess WL over a 2-year period.



STEP Program: Statistical Analysis

- Two-sided 95% CIs and corresponding p values with superiority defined at p values less than 5%
- Sample size provides effective power
  - 99% for STEP 1
  - 94% for STEP 2
  - 86% for STEP 3
  - 95% for STEP 4
  - 43% for STEP 5
- Continuous end points analysis using ANCOVA with randomized treatment as a factor and baseline end point value as covariate

STEP Program: Statistical Analysis

Serial Assessments

- Height
- Body weight
- Waist circumference
- Glucose metabolism
- Lipid panel
- Biomarkers
- Vital signs

Physical Functioning Assessments

- Short Form36v2 Health Survey
- Impact of Weight on Quality of Life
- Stanford Presenteeism Scale

STEP Program: Study Importance

- What is already known?
  - Lifestyle intervention often insufficient in treating obesity alone
    - However, when combined with pharmacological treatments, clinically relevant weight loss and amelioration of obesity complications can be achieved
  - GLP-1 receptor analogue agonist liraglutide is approved for treatment of people with obesity
    - Phase 2 trial with semaglutide suggested greater efficacy than liraglutide

STEP Program: Study Importance

- What does this study add?
  - One of the largest clinical trial programs for management of obesity to assess the efficacy and safety of semaglutide 2.4 mg subcutaneously once weekly
  - Designed to elucidate key aspects of medial management of obesity across various races and ethnicities including patients with or without diabetes, as an adjunct to intensive behavioral therapy plus low-calorie diet, and with longer term administration

Conclusion

- These pivotal trials will provide data on efficacy and safety of a new treatment (semaglutide) for obesity
  - Beyond safety and efficacy, provide a greater understanding of weight loss, weight loss maintenance, and tolerability in adults with obesity as an adjunct to lifestyle intervention
- Anticipation of trials to demonstrate that semaglutide represents a new and effective medication used to improve health and quality of life for patients with obesity

References

- Kushner RF, Calanna S, Davies M, et al. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. *Obesity (Silver Spring)*. 2020;28(6):1050-1061. doi:10.1002/oby.22794