Medical Information Response

Wegovy® (semaglutide) injection vs. Placebo – Sustained Weight Management (STEP 4)

STEP 4

STEP 4 was a 68-week, Phase 3a, randomized, placebo-controlled, double-blind, multicenter, multinational trial that consisted of a 20-week run-in period with a total of 902 patients followed by a 48-week randomized period with 803 patients.[1] Enrolled patients were ≥18 years of age, had a body mass index (BMI) of ≥30 kg/m^2 (obesity) or ≥27 kg/m^2 (overweight) with at least 1 weight-related comorbidity (e.g., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), had a glycosylated hemoglobin level of <6.5%, and a stable body weight within 90 days prior to screening. As shown in **Figure 1**, all 902 patients received treatment with Wegovy® during the 20-week run-in period. A once-weekly dose of 0.25 mg was initiated at Week 0 and followed a fixed dose-escalation regimen every 4 weeks until the 2.4 mg maintenance dose was achieved. The 803 patients receiving Wegovy® 2.4 mg at Week 20 were then randomized in a 2:1 ratio to continue treatment with once-weekly Wegovy® 2.4 mg or be switched to placebo for 48 weeks. Throughout the 68-week trial, all patients underwent lifestyle interventions (reduced calorie diet and increased physical activity) as an adjunct to treatment; the study included a 7-week off-treatment follow-up period for all patients from Week 68 to Week 75. Key trial endpoints evaluated the treatment differences during the randomized period from Week 20 to Week 68 using the treatment policy estimand with effects assessed regardless of treatment discontinuation or rescue medication use. Please reference **Table 1** for key trial endpoints, while key safety data are summarized for the run-in and randomized periods, respectively, in **Table 2** and **Table 3**.

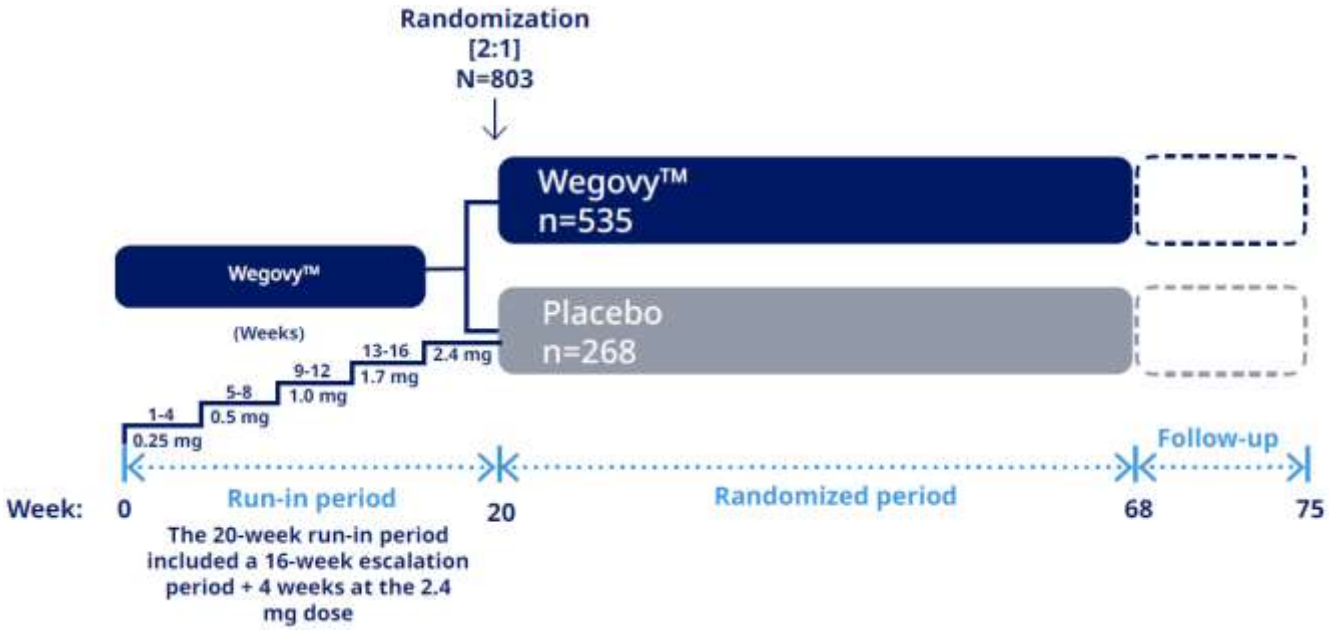

Figure 1. Trial design[1]

Patients were off-treatment during the follow-up period from Week 68 to Week 75.

Table 1. Key Trial Endpoints During the Randomized Period (Week 20-Week 68) in STEP 4[1]

	Wegovy® (n=535)	Placebo (n=268)
Mean body weight at randomization (Week 20) — (lb)	212.7	210.3
PRIMARY ENDPOINT		
Mean change in body weight — (%)	–7.9	6.9
ETD (95% CI); *P*-value	–14.8 (–16.0 to –13.5); *P*<.001	
CONFIRMATORY SECONDARY ENDPOINTS		
Mean waist circumference at randomization (Week 20) — (in)	41.5	41.2
Mean change in waist circumference — (in)	–2.5	1.3
ETD (95% CI); *P*-value	–3.8 (–4.3 to –3.3); *P*<.001	
Mean systolic blood pressure at randomization (Week 20) — (mmHg)	121	121
Mean change in systolic blood pressure — (mmHg)	0.5	4.4
ETD (95% CI); *P*-value	–3.9 (–5.8 to –2.0); *P*<.001	
Mean SF-36v2 physical functioning score at randomization (Week 20)[a,b]	53.8	54.1
Mean change in SF-36v2 physical functioning score	1.0	–1.5
ETD (95% CI); *P*-value	2.5 (1.6 to 3.3); *P*<.001	

a. Scores on the SF-36v2 are norm-based, transformed to a scale on which the 2009 general population of the United States has a mean score of 50 and a standard deviation of 10; higher scores indicate better quality of life.
b. There were 534 patients in the Wegovy® treatment arm that were analyzed for this endpoint.
Abbreviations: ETD: estimated treatment difference; CI: confidence interval; in: inches; SF-36v2: 36-Item Short-Form Health Survey, acute version

Table 2. STEP 4 Safety Overview During the Run-In Period (Week 0-Week 20)[2,a]

Safety Outcomes, n (%)	Wegovy® (n=902)
Patients with ≥1 adverse event	760 (84.3)
Patients with ≥1 serious adverse event	21 (2.3)
Adverse events leading to treatment discontinuation	48 (5.3)
Adverse events reported in ≥5% of patients	
Nausea	422 (46.8)
Diarrhea	212 (23.5)
Constipation	200 (22.2)
Vomiting	140 (15.5)
Dyspepsia	103 (11.4)
Decreased appetite	102 (11.3)
Headache	96 (10.6)
Nasopharyngitis	92 (10.2)
Eructation	71 (7.9)
Abdominal pain	68 (7.5)
Fatigue	67 (7.4)
Gastroesophageal reflux disease	58 (6.4)
Abdominal distension	50 (5.5)
Flatulence	50 (5.5)
Abdominal pain upper	49 (5.4)

a. Based on the safety analysis population, which includes all patients exposed to ≥1 dose of treatment during this period.[1]

Table 3. STEP 4 Safety Overview During the Randomized Period (Week 20-Week 68)[1,a]

Safety Outcomes, n (%)	Wegovy® (n=535)	Placebo (n=268)
Patients with ≥1 adverse event	435 (81.3)	201 (75.0)
Patients with ≥1 serious adverse event	41 (7.7)	15 (5.6)
Adverse events leading to treatment discontinuation	13 (2.4)	6 (2.2)
Adverse events reported in ≥5% of patients		
Diarrhea	77 (14.4)	19 (7.1)
Nausea	75 (14.0)	13 (4.9)
Constipation	62 (11.6)	17 (6.3)
Nasopharyngitis	58 (10.8)	39 (14.6)
Vomiting	55 (10.3)	8 (3.0)
Headache	41 (7.7)	10 (3.7)
Influenza	39 (7.3)	19 (7.1)
Abdominal pain	35 (6.5)	8 (3.0)
Back pain	28 (5.2)	18 (6.7)
Arthralgia	25 (4.7)	14 (5.2)

a. Based on the safety analysis population, which includes all patients exposed to ≥1 dose of treatment during this period.

References

1. Rubino D, Abrahamsson N, Davies M, et al. 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.* 2021;325(14):1414-1425. Link to Access the Full Text
2. Rubino D, Abrahamsson N, Davies M, et al. Supplement 1 to: 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.* 2021;325(14):1414-1425. Link to Access the Full Text