Received: 10 September 2021 | Revised: 27 October 2021 | Accepted: 3 November 2021

DOI: 10.1111/jcpt.13574

REVIEW ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Clinical review of subcutaneous semaglutide for obesity

Anna Phillips PharmD Candidate[1] |
Jennifer N. Clements PharmD, FCCP, FADCES, BCPS, CDCES, BCACP, BC-ADM[2]

[1]Presbyterian College School of Pharmacy, Clinton, South Carolina, USA

[2]Department of Nursing Administration, Spartanburg Regional Healthcare System, Spartanburg, South Carolina, USA

Correspondence
Jennifer N. Clements, PharmD, FCCP, FADCES, BCPS, CDCES, BCACP, BC-ADM, Clinical Pharmacist - Diabetes Transition, Department of Nursing Administration, Spartanburg Regional Healthcare System, 101 East Wood Street, Spartanburg, SC 29303, USA.
Email: jclements1027@outlook.com; jclements@srhs.com

Funding information
The author(s) received no financial support for the research, authorship and/or publication of this article.

Abstract

What is known and objective: The purpose of this review paper is to review the efficacy and safety of subcutaneous semaglutide, marketed as Wegovy, a glucagon-like peptide-1 receptor agonist for obesity management.

Methods: A MEDLINE search (1970 to June 2021) was conducted to identify Phase 3 trials of subcutaneous semaglutide for obesity management. Published Phase 3 trials from The Semaglutide Treatment Effect in People with obesity (STEP) program were reviewed and summarized.

Results and discussion: Based on four Phase 3 trials, subcutaneous semaglutide as 2.4 mg once weekly was compared in efficacy and safety among 5000 randomized participants who were overweight or had obesity. A change in body weight from baseline to end of study was the primary outcome in the STEP program. Participants who received semaglutide had a dose-dependent reduction in body weight from baseline, compared to placebo. Higher percentages of participants had 5%–10% weight reduction from baseline when receiving subcutaneous semaglutide. The patient population was mainly middle-aged female participants with Class II obesity. Additional studies are needed, especially active-comparator trials, to determine the efficacy and safety of semaglutide in a diverse patient population.

What is new and conclusion: Subcutaneous semaglutide is another available option as adjunct therapy to lifestyle modifications for people who are overweight or have obesity based on body weight and body mass index. It resulted in more weight reduction than placebo with gastrointestinal adverse events being the most common safety concerns. Clinical utilization of subcutaneous semaglutide will be determined, as insurance coverage will be a limitation for this new medication.

KEYWORDS
GLP-1 receptor agonist, glucagon-like peptide-1, obesity, overweight, semaglutide

1 | WHAT IS KNOWN AND OBJECTIVE

According to the Obesity Medicine Association, obesity is chronic and treatable disease state from multiple factors with a complex pathophysiology leading to potential health consequences.[1] Many factors affect the prevalence of obesity with the most common factors including age, gender, race and economic status.[2] Health consequences of obesity can include type 2 diabetes (T2D), dyslipidaemia, hypertension, cardiovascular disease, osteoarthritis and obstructive sleep apnea.[1]

In 2015, it was estimated that 603.7 million adults had their weight classified as obesity, with an overall prevalence of 12% worldwide in adults.[2] This study also discovered that approximately 4 million deaths and increasing rates of disability were associated

with the negative health effects of a higher body mass index (BMI).[2] In 2019, the Centers for Disease Control estimated the national prevalence of 31.4% for obesity in the United States.[3] During 2020, it was noted that people with obesity were at an increased risk of mortality when infected with COVID-19.[4] The health and cost burden of obesity on patients, families and health systems does not appear to be going away. It is projected that 1 in 2 adults will have obesity and 1 in 4 adults will have severe obesity in the United States by 2030.[5] Therefore, new, innovative medications to treat both obesity and its weight-related comorbidities would be ideal for clinical practice.

The current clinical guidelines are all similar by recommending a goal to improve the health of the patient by preventing and/or treating weight-related complications through weight loss by non-pharmacologic, pharmacologic, or surgical measures when necessary. The short-term treatment goal is reduction of weight by 5%–10% over 3–6 months, with a long-term goal of maintenance of weight loss.[6–8] The aggressiveness of a patient's weight loss is often driven by their BMI and other comorbidities. The guidelines define overweight as a BMI between 25 and 29.9 kg/m^2 and obesity as a BMI of equal to or above 30 kg/m^2.[8] First-line therapy should be non-pharmacologic therapy such as behavioural therapy in conjunction with increased physical activity and significant caloric reduction for 6 months. If non-pharmacologic therapy is not adequate after 6 months, then pharmacotherapy with an anti-obesity agent can be initiated as adjunct therapy. The guidelines recommend the implementation of non-pharmacologic and pharmacologic therapy in people with BMI ≥30 kg/m^2 or in those with a BMI ≥27 kg/m^2 with one or more cardiovascular risk factors, such as hyperlipidaemia, hypertension or diabetes.[6–8] The guidelines are limited when it comes to choosing an anti-obesity agent for weight management. However, the choice would be determined based on risks and benefits.[9] With lorcaserin removed from the market in 2020, there are now only five medications, approved by the Food and Drug Administration (FDA), for long-term weight management: orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide and most recently semaglutide. The purpose of this review was to provide an analysis of subcutaneous semaglutide as a pharmacotherapeutic option for obesity.

2 | METHODS

In people with diabetes, glucagon-like peptide-1 receptor agonists (GLP-1 RA) promote weight reduction. The weight loss benefits of this class of medications have led to the investigation of certain GLP-1 RA, at higher doses, for the treatment of obesity. For people with obesity, weight loss and glycaemic improvement from GLP-1 RA are not the only potential benefits. In clinical trials, long-acting GLP-1 RA appear to also be cardioprotective through the reduction of blood pressure and cholesterol.[9] Due to the potential health care consequences from obesity, people at an increased risk for cardiovascular events may benefit from a GLP-1 RA for cardioprotection. The first GLP-1 RA approved by the FDA for the treatment of obesity was liraglutide, marketed by Novo Nordisk as Saxenda. Based on efficacy and safety outcomes from Phase 3 trials, subcutaneous semaglutide was approved by the FDA on 4 June 2021, for the indication of long-term weight management. A MEDLINE search (1970 to June 2021) was conducted to identify Phase 3 trials of subcutaneous semaglutide for obesity management. Published Phase 3 trials from The Semaglutide Treatment Effect in People with obesity (STEP) program were reviewed and summarized.

3 | RESULTS AND DISCUSSION

3.1 | GLP-1 RA

Semaglutide has shown improved weight reduction compared to liraglutide in patients with or without type 2 diabetes. Superiority of semaglutide to liraglutide in weight reduction was initially shown in a dose-finding trial for treatment of patients with T2D.[10] In this trial, participants were treated with either semaglutide once weekly without dose escalation (0.1–0.8 mg), semaglutide once weekly with dose escalation (0.4 mg escalated every 1–2 weeks until reaching 0.8 or 1.6 mg), liraglutide once daily (1.2 or 1.8 mg) or placebo. At the end of the 12 weeks, participants in both the liraglutide and semaglutide experienced ≥5% dose-dependent weight reduction, however, only participants in the semaglutide group experienced ≥10% dose-dependent weight reduction.[10] Results like this, began the investigation of semaglutide's therapeutic potential for the treatment of obesity.

In a trial investigating the efficacy of semaglutide compared with liraglutide and placebo, participants were treated with once daily semaglutide at varying doses (initiated at 0.05 mg per day, and escalated to 0.1, 0.2, 0.3 or 0.5 mg per day by 0.05 mg every 4 weeks), liraglutide (initiated at 0.6 mg per day, and escalated to 3.0 mg by 0.06 mg per week), or placebo.[11] At the end of 52 weeks, semaglutide was shown to be superior to liraglutide 3.0 mg per day with a dose of 0.2 mg or more per day. In this study, the liraglutide group experienced a mean weight reduction of 7.8% at a dose of 3.0 mg per day which was significantly less than the semaglutide group which experienced weight reduction of 11%–14% at a dose of 0.2 mg per day or more.[11] In both trials, both the liraglutide and semaglutide groups had discontinuation due to adverse effects. The most common adverse effects from these early trials were gastrointestinal-related, mainly nausea, vomiting and diarrhoea.[10,11] In the second trial, the semaglutide group experienced higher dose-related gastrointestinal adverse events than the liraglutide group.[11] This could be potentially explained by the fact the semaglutide group experienced more dose titration over a longer period of time than the liraglutide group. The adverse events of GLP-1 RA are thought to be dose dependent, present during the titration phase and transient in nature.[12] From these trials, it can be concluded that both liraglutide and semaglutide play a role in the treatment of obesity. In the future, the choice of which agent to use will likely be based on the individual weight reduction goals of each patient.

An endogenous hormone, GLP-1 is produced in response to the intake of food by the L cells within the intestinal mucosa.[9] GLP-1 receptors are present throughout the body. However, the receptors within the pancreas, gastrointestinal tract, heart and brain are what potentially play a role in diabetes, weight management and the cardioprotective effects of GLP-1 RA.[12] The exact mechanism behind how GLP-1 RA promote weight reduction is not entirely understood. Many potential mechanisms of action have been suggested. In the pancreas, GLP-1 upregulates the secretion of insulin from pancreatic beta cells, while increasing insulin sensitivity throughout the body. GLP-1 also acts on the alpha cells of the pancreas to simultaneously decrease the release of glucagon.[9,12] GLP-1 also appears to have other effects on metabolism such as promoting fat oxidation over carbohydrates and decreasing hepatic gluconeogenesis.[9] In the gastrointestinal tract, GLP-1 works to slow down gastrointestinal motility, increase satiety, as well as potential protective effects of decreased acid production from the parietal cells and increased intestinal mucus secretion.[12] In the heart, GLP-1 receptors are found mainly on the sinoatrial nodes and myocytes, which may be the cause of the sustained increase in heart rate with GLP-1 RA treatment.[12] In the brain, GLP-1 communicates with the hypothalamus, regulating the appetite by increasing satiety signalling.[9,12] Semaglutide is thought to affect the brain with a unique mechanism apart from other GLP-1 receptor agonists. Treatment with semaglutide has been associated with the food/reward system, increasing an individual's ability to control food intake and altering food preferences (ie, a lower liking for high-fat foods).[12] Taking all of these potential mechanisms of action into consideration, there does not appear to be just one main mechanism behind how GLP-1 RA promote weight reduction. It is most likely that each mechanism plays a role in a combined effect which ultimately leads to improved weight control.

Both liraglutide and semaglutide are modified to reversibly bind to serum albumin in the body, increasing the half-life of these agents through protecting the peptide from dipeptidyl peptidase-IV degradation and renal filtration.[12] Semaglutide's structure is 94% homologous to the endogenous hormone GLP-1. Three modifications to semaglutide's structure improve it is half-life to 165 hours which is approximately 1 week.[13] These modifications include, the substitution of alanine to alpha-aminoisobutyric acid at position eight, lysine to arginine at position thirty-four, and finally, acylation of the lysine in position twenty-six that includes a spacer consisting of two 8-amino-3,6-dioxaoctanoic acid moieties, a C-18 fatty di-acid side chain and a glutamic acid moiety.[12,13] Metabolism of semaglutide occurs slowly through proteolysis of the peptide backbone, as well as beta oxidation of the di-fatty acid side chain.[13] The degradation products are then excreted through the urine and faeces, with a very limited amount of unchanged semaglutide excreted in the urine approximately three per cent.[13] Due to no single organ being implicated in semaglutide's metabolism, dose adjustment may not be necessary for patients with hepatic or renal impairment.[14,15]

3.2 | Clinical trials

The FDA has a guiding document of clinical trials for obesity management.[16] To determine effectiveness, the FDA suggested an endpoint of weight loss from baseline; clinical significance would be met if an active medication results in a 5% or more placebo-subtracted difference for the primary outcome. The guiding document also suggests additional endpoints, including percentage of participants achieving 5% or 10% of weight loss from baseline. This endpoint aligned with recommended weight loss from clinical practice guidelines. For this endpoint, clinical significance would be met if either the active medication had 35% or more of the participants have a weight loss of 5% or at least double the number of participants with the active medication had a weight loss of 5%, compared to placebo. Most likely these three outcomes would also be statistically significant upon analysis.[16]

In the Semaglutide Treatment Effect in People with obesity (STEP) program with semaglutide, all participants were adults with obesity or were overweight regardless of diabetes status.[17–20] Counselling on lifestyle modifications were provided periodically by a dietitian or healthcare professional and throughout the trial. In addition, participants also received tools for physical activity, such as kettlebells and jump ropes. Lifestyle modification did vary though among the five clinical trials. In STEP 1, 2, 4 and 5, participants were advised on a daily 500 calorie reduction and 150 min of physical activity, whereas participants in STEP 3 were encouraged to follow intensive behavioural therapy with a low-calorie diet. Overall, there were more than 5000 participants in the STEP program to evaluate semaglutide versus placebo. In all clinical trials, semaglutide was titrated to a maximum dose of 2.4 mg subcutaneously per week. Refer to Table 1 for baseline characteristics of participants within STEP 1–4 trials.[17–20]

3.3 | Efficacy

STEP 1 was a randomized, double-blind, multi-centred, placebo-controlled trial. In this trial, adults with a BMI of ≥30 or a BMI of ≥27 kg/m^2 with one or more treated or untreated weight-related co-existing conditions, such as hypertension, cardiovascular disease or obstructive sleep apnoea, who reported at least one unsuccessful dietary effort to lose weight were included in this trial.[17] Individuals who had diagnosed diabetes, a haemoglobin A1C of ≥6.5%, a history of chronic pancreatitis, acute pancreatitis within 180 days before enrolment, previous surgical obesity treatment, or the use of anti-obesity medication within 90 days were all excluded from enrolment in this trial. Randomized in a 2:1 ratio, 1961 participants either received semaglutide at a dose of 2.4 mg administered subcutaneously once a week for 68 weeks or a matching placebo combined with lifestyle interventions. Lifestyle interventions include counselling sessions every 4 weeks to help participants adhere to a reduced calorie diet and increased physical activity of 150 min per week. The coprimary endpoints

TABLE 1 Baseline characteristics of participants in STEP program[17–20]

	Step 1 *N* = 1961	Step 2 *N* = 1210	Step 3 *N* = 611	Step 4 *N* = 902
Female, *n* (%)	1453 (74.1)	616 (50.9)	495 (81.0)	717 (79.5)
Age, y	46.5 ± 12.7	55.3 ± 10.6	46.2 ± 12.7	46.4 ± 11.9
Race, *n* (%)				
White	1472 (77.2)	751 (62.1)	465 (76.1)	751 (83.3)
African American	111 (5.8)	100 (8.3)	116 (19.0)	123 (13.6)
Asian	261 (13.7)	317 (26.2)	11 (1.8)	19 (2.1)
Hispanic	236 (12.0)	155 (12.8)	121 (19.8)	70 (7.8)
Other	62 (3.2)	42 (3.5)	19 (3.2)	9 (1.0)
BMI, kg/m^2	37.9 ± 6.7	35.7 ± 6.3	38.0 ± 6.7	38.3 ± 7.0
Waist Circumference, cm	114.7 ± 14.7	114.6 ± 14.1	113.0 ± 15.5	115.1 ± 15.6
Blood pressure, mmHg)				
Systolic	126.5 ± 14.3	130.0 ± 13.5	124.4 ± 14.8	126.4 ± 14.3
Diastolic	80.3 ± 9.6	79.8 ± 9.0	80.5 ± 9.7	80.9 ± 9.9
Cholesterol, mg/dl				
Total	4.9 ± 20.0	4.4 ± 23.3	4.8 ± 19.7	5.0 ± 19.5
HDL	1.3 ± 25.5	1.1 ± 24.5	1.3 ± 23.6	1.29 ± 24.6
LDL	2.9 ± 28.7	2.3 ± 35.6	2.8 ± 28.5	3.0 ± 27.3
VLDL	0.6 ± 51.1	0.8 ± 51.6	0.6 ± 48.1	0.6 ± 53.6
Triglycerides	1.4 ± 70.0	1.8 ± 64.2	1.2 ± 49.8	1.4 ± 54.9
Overall eGFR, ml/min/1.73 m^2	96.6 ± 17.2	93.7 ± 19.5	96.8 ± 19.5	97.6 ± 17.8

were the percentage change in body weight and a weight reduction of at least 5%. At week 68, in the semaglutide group, the mean change in body weight was −14.9% compared to −2.4% in the placebo group ($p < 0.001$). In the semaglutide group, 86.4% of participants achieved weight reductions of ≥5%, and 69.1% of participants achieved weight reductions of ≥10%, compared to 31.5% and 12.0% of participants within the placebo group ($p < 0.001$, NNT = 2).[17] Limitations to consider are the relative short duration of the trial, the limited representation of minorities, and the higher percentage of women in participation of this study than men. In STEP 1, 2.4 mg of semaglutide once weekly was associated with clinically relevant reductions in body weight.

STEP 2 was a randomized, double-blind, multi-centred, placebo-controlled, superiority trial.[18] Adults who were eligible for this trial must have reported at least one unsuccessful dietary effort to lose weight, a BMI of at least 27 kg/m^2, a haemoglobin A1C of 7%–10% and had been diagnosed with T2D within 180 days before screening and were managed with diet and exercise alone or with up to three different oral glucose-lowering agents for at least 90 days before screening.[18] Adults who reported body weight changes of more than 5 kg within 90 days before screening or who had previous or planned obesity treatment with surgery, or a weight loss device were excluded from this study. Randomized in a 1:1:1 ratio, 1210 participants, received once weekly either 2.4 mg of semaglutide, 1.0 mg of semaglutide or placebo subcutaneously for 68 weeks combined with lifestyle interventions. Lifestyle interventions were the same as those listed above in the STEP 1 trial. Patients were counselled every 4 weeks, by a qualified health professional and were encouraged to keep a food and activity diary. The coprimary endpoints were the percentage change in body weight and a weight reduction of at least 5%. At week 68, in the 2.4 mg semaglutide group, the mean change in body weight was −9.64% compared to −6.99% in the 1.0 mg semaglutide group, and −3.42% in the placebo group ($p < 0.001$). The percentages of participants who achieved weight reduction of ≥5% were 68.8%, in the 2.4 mg semaglutide group, 57.1% in the 1.0 mg semaglutide group, and 28.5% in the placebo group ($p < 0.001$). The percentages of participants who achieved weight reduction of ≥5% were 68.8%, in the 2.4 mg semaglutide group, 57.1% in the 1.0 mg semaglutide group, and 28.5% in the placebo group ($p < 0.001$, NNT = 4). The percentages of participants who achieved weight reduction of ≥10% were 45.6%, in the 2.4 mg semaglutide group, 28.7% in the 1.0 mg semaglutide group and 8.2% in the placebo group ($p < 0.001$).[18] A limitation from the STEP 2 trial could be the exclusion of patients who are on insulin, as this patient population could benefit from the weight loss associated with the add on of semaglutide with insulin; this information is difficult to extrapolate to individuals on insulin therapy. In STEP 2, 2.4 mg of semaglutide once weekly achieved superior and clinically relevant reductions in body weight compared with placebo in participants who were overweight or obese, with T2D.

TABLE 2 Confirmatory secondary endpoints[17-20]

	STEP 1		STEP 2			STEP 3		STEP 4	
	Semaglutide ($n = 1306$)	Placebo ($n = 655$)	Semaglutide 2.4 mg ($n = 403$)	Semaglutide 1.0 mg ($n = 402$)	Placebo ($n = 402$)	Semaglutide ($n = 407$)	Placebo ($n = 204$)	Semaglutide ($n = 535$)	Placebo ($n = 268$)
Weight reduction of ≥10% (%)	69.1	12.0	45.6	28.7	8.2	75.3	27.0	N/A	N/A
Weight reduction of ≥15% (%)	50.5	4.9	25.8	13.7	3.2	55.8	13.2	N/A	N/A
Changes from baseline to week 68									
WC (cm)	−13.54	−4.13	−9.4	−6.7	−4.5	−14.6	−6.3	−6.4	3.3
SBP (mmHg)	−6.16	−1.06	−3.9	−2.9	−0.5	−5.6	−1.6	0.5	4.4
SF-36	2.21	0.41	2.5	2.4	1.0	2.4	1.6	1.0	−1.5
IWQOL-Lite	14.67	5.25	10.1	8.7	5.3	N/A	N/A	N/A	N/A

Abbreviations: IWQOL-Lite, Impact of Weight on Quality of Life – Lite; SBP, systolic blood pressure; SF-36, Short Form 36; WC, waist circumference.

STEP 3 was a randomized, double-blind, placebo-controlled, multi-centred trial.[19] In this trial, adults with a BMI of ≥30 kg/m^2 or a BMI of ≥27 kg/m^2 with one or more treated or untreated weight-related co-existing conditions, who reported at least one unsuccessful dietary effort to lose weight were included in this trial. Adults who had diagnosed diabetes, a haemoglobin A1C of ≥6.5%, who reported body weight changes of more than 5 kg within 90 days before screening or who had previous or planned obesity treatment with surgery, or a weight loss device were excluded from this study. In the trial, 611 participants were randomized 2:1 to receive either once weekly 2.4 mg of semaglutide subcutaneously or placebo, combined with a low-calorie diet for the first 8 weeks and behavioural therapy during the 68 weeks. For the first 8 weeks, participants received low-calorie (1000–1200 kcal/d) meal replacements provided by Nutrisystem. After 8 weeks, participants transitioned to a hypo-caloric diet (1200–1800 kcal/d) of conventional food for the remaining 68 weeks. Participants were also prescribed 100 min of physical activity per week which was increased weekly by 25 min until participants reached 200 min/wk. Participants also received 30 individual therapy visits with a registered dietician who counselled on diet, physical activity and behavioural strategies. The coprimary endpoints were the percentage change in body weight and a weight reduction of at least 5%. At week 68, the mean weight reduction in the semaglutide group was −16.0% compared to the placebo group which was −5.7% ($p < 0.001$). The percentage of those who achieved ≥5% weight reduction in the semaglutide group was 86.6% and 47.6% in the placebo group ($p < 0.001$, NNT = 3). The percentage of those who achieved ≥10% weight reduction in the semaglutide group was 75.3% and 27.0% in the placebo group ($p < 0.001$).[18] Limitations of this trial include the short duration of the trial and the inability to identify the separate contributions to weight loss of the lifestyle modifications. Overall, semaglutide in combination with both a low-calorie diet and behavioural therapy resulted in significantly greater weight loss than placebo based on results from the STEP 3 trial.

The STEP 4 was a randomized, double-blind, placebo-controlled, multi-centred withdrawal study.[20] Included in this trial was adults with a BMI of ≥30 kg/m^2 or a BMI of ≥27 kg/m^2 with one or more treated or untreated weight-related co-existing conditions, who reported at least one unsuccessful dietary effort to lose weight. Excluded were those who reported body weight changes of more than 5 kg within 90 days before screening or a haemoglobin A1C of ≥6.5%. For 20 weeks, all 803 individuals participated in a run-in period. During this period, participants received semaglutide starting at 0.25 mg and titrated up to 2.4 mg by week 16 and continued to week 20. At week 20, participants were randomized 2:1 to either continue the semaglutide 2.4 mg or to receive placebo for the remaining 48 weeks. All participants received behavioural therapy, a reduced calorie diet and increased physical activity during the 68 weeks. The primary endpoint of this study was the per cent change in body weight from week 20 to week 68. At week 68, the mean per cent body weight change in the semaglutide 2.4 mg group was −7.9% compared to 6.9% in the placebo group ($p < 0.001$).[20] Limitations to consider in the STEP4

trial are the potential selection bias due to the run-in period and withdrawal design, and the lack of assessment of adherence to lifestyle modifications. In STEP 4, continued treatment with semaglutide showed sustained clinically relevant weight loss as compared to switching to placebo.

3.4 | Other outcomes

In the STEP trials, confirmatory secondary endpoints were achievement of a reduction in body weight of ≥10% and ≥15% by week 68 and the change from baseline to week 68 in waist circumference, systolic blood pressure and physical function score on the *Short Form Health Survey* (SF-36) version 2 and on the *Quality of Life-Lite Clinical Trials Version* questionnaire (IWQOL-LiteCT).[17–20] Table 2 summarizes the confirmatory secondary endpoints from the STEP program.

Supplementary secondary endpoints in all trials were changes from baseline to week 68 in BMI, body weight, A1C, fasting plasma glucose, diastolic blood pressure and a fasting lipid panel.[17–20] Other supplementary secondary endpoints not included in every trial was a body weight reduction ≥20% in STEP 1 and 3, body composition changes in STEP 1 and changes in baseline C-reactive protein in STEP trials 1, 2 and 3.[17–19]

In STEP 1, other exploratory endpoints favoured the use of semaglutide. In the prediabetes subpopulation, 84.1% of participants had normoglycemia at week 68 compared to 47.8% in the placebo group.[17] The comparison of A1C levels from baseline to week 68 showed a reduction of 0.52 percentage points in the semaglutide group compared to a reduction of 0.17 percentage points in the placebo group.[17] In STEP 2, the exploratory endpoint focused around the potential reduction of other glucose-lowering medications with semaglutide use.[18] In STEP 2, the 2.4 mg semaglutide group experienced a 28.6% reduction in concomitant use of glucose-lowering medication as compared to 25.1% in the 1.0 mg semaglutide group and 7.1% in the placebo group.[18] Table 3 highlights secondary endpoints from the STEP 1–4 trials.

3.5 | Safety

In STEP 1–4, the most frequently reported adverse effects were gastrointestinal such as nausea, vomiting, diarrhoea and constipation.[17–20] These adverse effects were reported more often in the semaglutide group than the placebo group. Mild-to-moderate in severity, the gastrointestinal adverse effects usually resolved without discontinuation of semaglutide.[17–20] In the STEP 3 trial, the median time of nausea was 5 days in both groups, 2 days of vomiting in both groups, 3 days of diarrhoea in both groups, and 27 days of constipation in the semaglutide group compared to 16 days in the placebo group.[19] The deaths which were reported, were not thought to be associated with the study treatment.[17,18] Refer to Table 4 for summary of adverse events in STEP 1–4 trials.

3.6 | Investigational trials

Additional trials will complete the STEP program for semaglutide in obesity management. Maintenance or long-term benefit of semaglutide over a 2-year period will be determined in the STEP 5 trial (NCT03693430).[21] The efficacy and safety of semaglutide, compared to placebo among East Asian participants who are overweight or have obesity; this trial as STEP 6 has been completed and published results will be forthcoming on the change in body weight from baseline to Week 68 and proportion of participants with at least 5% reduction in body weight (NCT03811574).[22] In STEP 7, Chinese participants are being recruited to determine the efficacy and safety of semaglutide versus placebo among the same outcomes for the STEP 6 trial.[23] The STEP 7 trial will evaluate intervention over a 44-week period (NCT04251156).[23] Semaglutide will be investigated in an active-comparator trial in the STEP 8 trial.[24] The dose of 2.4 mg semaglutide will be compared in efficacy and safety to liraglutide 3.0 mg, which is the recommended dose of liraglutide for obesity management. STEP 8 trial will have a primary outcome of change in body weight from baseline to Week 68 (NCT04074161). [24] A cardiovascular trial will conclude in 2023 to determine the effect of semaglutide in participants with cardiovascular disease. The Semaglutide Effects on cardiovascular Outcomes in People with Overweight or Obesity (SELECT) will determine semaglutide's effect on the time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke over 31 to 59 months (NCT03574597).[25]

4 | WHAT IS NEW AND CONCLUSION

Semaglutide, marked as Wegovy™ (Novo Nordisk), is available in a prefilled, single-dose pen with an integrated needle.[26] Following administration, the prefilled pen can be disposed of in the trash. Five strengths are available in the pen (0.25, 0.5, 1.0, 1.7 and 2.4 mg) and each box would be packaged with 4 pens for a 1-month supply. The 2.4 mg dose of semaglutide is approved for obesity management, and the monthly titration is recommended to improve tolerance and minimize gastrointestinal adverse events. The benefit with a prolonged titration with semaglutide is unknown but may be acceptable in clinical practice for those who experience intolerable gastrointestinal adverse events. The manufacturer provides specific instructions for missed doses of semaglutide and time frame to the next dose (eg, less than or more than 2 days). Semaglutide may be resumed at the individual's normal administration schedule or restarted at 0.25 mg once weekly to minimize gastrointestinal adverse events if more than two consecutive doses have been missed. Semaglutide can be administered under the skin of the abdomen, upper arm or thigh on a weekly basis. As a GLP-1 RA, there may be some effect on the absorption of oral medications due to gastric emptying from the general mechanism of the therapeutic class. For those with T2D and obesity, caution should be considered if semaglutide is added

TABLE 3 Supplementary secondary endpoints[17–20]

	STEP 1		STEP 2			STEP 3		STEP 4	
	Semaglutide (*n* = 1306)	Placebo (*n* = 655)	Semaglutide 2.4 mg (*n* = 403)	Semaglutide 1.0 mg (*n* = 402)	Placebo (*n* = 402)	Semaglutide (*n* = 407)	Placebo (*n* = 204)	Semaglutide (*n* = 535)	Placebo (*n* = 268)
Changes from baseline to week 68									
BMI	−5.54	−0.92	−3.5	−2.5	−1.3	−6.0	−2.2	−2.6	2.2
Body weight (kg)	−15.3	−2.6	−9.7	−6.9	−3.5	−16.8	−6.2	−7.1	6.1
Change in A1C (percentage points)	−0.45	−0.15	−1.6	−1.5	−0.4	−0.51	−0.27	−0.1	0.1
Fasting plasma glucose (mg/dl)	−8.35	−0.48	−2.1	−1.8	−0.1	−6.73	−0.65	−0.8	6.7
DBP (mmHg)	−2.83	−0.42	−1.6	−0.6	−0.9	−3.0	−0.8	0.3	0.9
Cholesterol parameters (mg/dl)									
Total cholesterol	0.97	1.00	0.99	0.98	0.99	−3.8	2.1	5	11
HDL	1.05	1.01	1.07	1.05	1.04	6.5	5.0	18	18
LDL	0.97	1.01	1.00	0.99	1.00	−4.7	2.6	1	8
VLDL	0.78	0.93	0.79	0.83	0.90	−22.5	−6.6	−6	15
Free fatty acids	0.83	0.93	0.84	0.86	0.99	−11.9	4.0	−18	−14
Triglycerides	0.78	0.93	0.78	0.83	0.91	−22.5	−6.5	−6	15
CRP (mg/L)	0.47	0.85	0.51	0.58	0.83	−59.6	−22.9	N/A	N/A
Weight reduction of ≥20% (%)	32.0	1.7	N/A	N/A	N/A	35.7	3.7	N/A	N/A

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure.

TABLE 4 Adverse events and tolerability profile.

	STEP 1		STEP 2			STEP 3		STEP 4	
	Semaglutide ($n = 1306$)	Placebo ($n = 55$)	Semaglutide 2.4 mg ($n = 403$)	Semaglutide 1.0 mg ($n = 402$)	Placebo ($n = 402$)	Semaglutide ($n = 407$)	Placebo ($n = 204$)	Semaglutide ($n = 535$)	Placebo ($n = 268$)
Any adverse event	1171 (89.7)	566 (86.4)	353 (87.6)	329 (81.8)	309 (76.9)	390 (95.8)	196 (96.1)	435 (81.3)	201 (75.0)
Serious adverse events	128 (9.8)	42 (6.4)	40 (9.9)	31 (7.7)	37 (9.2)	37 (9.1)	6 (2.9)	41 (7.7)	15 (5.6)
Adverse events leading to discontinuation	92 (7.0)	20 (3.1)	25 (6.2)	20 (5.0)	14 (3.5)	24 (5.9)	6 (2.9)	13 (2.4)	6 (2.2)
GI events	59 (4.5)	5 (0.8)	17 (4.2)	14 (3.5)	4 (1.0)	14 (3.4)	0	N/A	N/A
Fatal events	1 (0.1)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.4)
Acute pancreatitis	3 (0.2)	0	1 (0.2)	0	1 (0.2)	0	0	0	0
Malignant neoplasms	14 (1.1)	7 (1.1)	5 (1.2)	7 (1.7)	8 (2.0)	3 (0.7)	1 (0.5)	6 (1.1)	1 (0.4)

Abbreviation: GI, gastrointestinal.

All information reported as *n* (%).

to a regimen of insulin or sulfonylurea therapy due to the risk of hypoglycaemia. If hypoglycaemia occurs, the insulin or sulfonylurea therapy should be reduced or discontinued.[26]

For the general management of obesity, lifestyle modifications are the cornerstone of a successful weight loss program. If an individual does not achieve 5% weight loss over 6 months with lifestyle modifications, then an anti-obesity agent may be indicated. Anti-obesity therapy can be considered for individuals who are overweight (eg, BMI >27 kg/m^2) with a comorbid condition, such as hypertension, hyperlipidaemia or T2D. Those with obesity (eg, >30 kg/m^2) are also considered candidates for anti-obesity therapy. Specific therapy should be determined based on drug-specific (eg, efficacy, safety, administration, cost) and patient-specific factors (eg, BMI, comorbid conditions, current medications and insurance). Overall, a major limitation with anti-obesity therapy is insurance coverage as these agents are often labelled for cosmetic purposes, rather than management of a chronic disease state. Policy changes should be considered to allow individuals access to anti-obesity agents, such as semaglutide. Employee formularies may offer the semaglutide at a lower cost or through specific criteria for use (eg, enrolment in weight loss clinics), whereas copay and discount cards are other options, as cost will vary per insurance.

Overall, the clinical implications of semaglutide are promising based on efficacy from randomized, placebo-controlled trials especially the larger response or weight reduction from the clinical trials. The large response of semaglutide on weight loss from baseline is greater than other anti-obesity therapies and could be comparable to certain types of bariatric procedures. While it is the first anti-obesity therapy since 2014, semaglutide has restrictions for some patient populations, such as pregnant women or those with personal or family history of medullary thyroid carcinoma. Similar to other GLP-1 RA, caution should be utilized when considering semaglutide for those with gastroparesis. If an individual has a history of acute pancreatitis, semaglutide should not be used and should be discontinued if a patient develops acute pancreatitis after initiation.

A successful weight loss program includes lifestyle modifications of reduced caloric intake and increased physical activity, and behavioural modifications. It is important for lifestyle modifications and behavioural interventions to be part of all weight loss programs. If non-pharmacological interventions are not successful for the individual in losing a desired weight percentage over a specific time period, then pharmacological therapy would be appropriate and should be chosen based on several factors, including cost. Overall, pharmacological therapy is indicated when individuals have a BMI equal to or above 30 kg/m^2 or 27 kg/m^2 in the presence of a comorbid condition. Semaglutide, as a once-weekly injection for obesity, would be indicated based on similar criteria and has resulted in weight loss similar to bariatric surgery. Gastrointestinal events are common for the safety profile of semaglutide, which is similar to other GLP-1 RA. If initiated for weight loss, an individual should be monitored on a monthly basis for efficacy and safety. Overall, semaglutide is a promising addition to the class of anti-obesity agents with its greatest challenge being insurance coverage.

CONFLICTS OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

ORCID

Jennifer N. Clements https://orcid.org/0000-0003-2431-6651

REFERENCES

1. Bays HE, McCarthy W, Burridge K, et al. Obesity Algorithm eBook, presented by the Obesity Medicine Association. www.obesityalgorithm.org. 2021. https://obesitymedicine.org/obesity-algorithm
2. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362
3. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. Data, Trend and Maps [online]. Accessed May 23, 2021. https://www.cdc.gov/nccdphp/dnpao/data-trends-maps/index.html
4. Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S. Obesity and mortality of COVID-19. Meta-analysis [retracted in: Obes Res Clin Pract. 2021 Jan-Feb;15(1):100]. *Obes Res Clin Pract*. 2020;14(4):295-300. doi:10.1016/j.orcp.2020.07.002
5. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med*. 2019;381(25):2440-2450. doi:10.1056/NEJMsa1909301
6. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(Suppl 3):1-203. doi:10.4158/EP161365.GL
7. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100:342-362.
8. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOC guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology, American Heart Association task force on practice guidelines and The Obesoty Society. *J Am Coll Cardiol*. 2014;63:2985-3023.
9. Isaacs D, Prasad-Reddy L, Srivastava SB. Role of glucagon-like peptide 1 receptor agonists in management of obesity. *Am J Health Syst Pharm*. 2016;73(19):1493-1507. doi:10.2146/ajhp150990
10. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients With type 2 diabetes. *Diabetes Care*. 2016;39(2):231-241. doi:10.2337/dc15-0165
11. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637-649.
12. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. *Front Endocrinol (Lausanne)*. 2019;10:155. doi:10.3389/fendo.2019.00155
13. Jensen L, Helleberg H, Roffel AD, et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. *Eur J Pharm Sci*. 2017;104:31-41. doi:10.1016/j.ejps.2017.03.020
14. Marbury TC, Flint A, Jacobsen JB, Derving Karsbøl J, Lasseter K. Pharmacokinetics and tolerability of a single dose of semaglutide, a human glucagon-like peptide-1 analog, in subjects with and without

renal impairment. *Clin Pharmacokinet*. 2017;56(11):1381-1390. doi:10.1007/s40262-017-0528-2
15. Baekdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, safety, and tolerability of oral Semaglutide in subjects with hepatic impairment. *J Clin Pharmacol*. 2018;58(10):1314-1323. doi:10.1002/jcph.1131
16. Food and Drug Administration. Guidance for industry: Developing products for weight management (draft guidance). Accessed August 1, 2021. http://www.gda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf
17. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989. doi:10.1056/NEJMoa2032183
18. Davies M, Færch L, Jeppesen OK, et al. 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. *Lancet*. 2021;397(10278):971-984. doi:10.1016/S0140-6736(21)00213-0
19. Wadden TA, Bailey TS, Billings LK, et al. 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
20. 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 o: The STEP 4 Randomized Clinical Trial. *JAMA*. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224
21. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03693430, Two-year research study investigating how well semaglutide works in people suffering from overweight or obesity (STEP 5). Accessed September 8, 2021. http://clinicaltrials.gov/ct2/show/NCT03693430
22. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03811574, STEP 6: Research study investigating how well semaglutide works in people living with overweight or obesity. Accessed September 8, 2021. http://clinicaltrials.gov/ct2/show/NCT03811574
23. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04251156, Research study of how ell semaglutide works in people living with overweight or obesity (STEP 7). Accessed September 8, 2021. http://clinicaltrials.gov/ct2/show/NCT04251156
24. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04074161, Research study to investigate how well semaglutide works compared to liraglutide in people living with overweight or obesity (STEP 8). Accessed September 8, 2021. http://clinicaltrials.gov/ct2/show/NCT04074161
25. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03574597, Semaglutide effects on heart disease and stroke in patients with overweight or obesity (SELECT). Accessed September 8, 2021. http://clinicaltrials.gov/ct2/show/NCT03574597
26. Wegovy (semaglutide) [package insert]. Novo Nordisk, Inc; 2021.

How to cite this article: Phillips A, Clements JN. Clinical review of subcutaneous semaglutide for obesity. *J Clin Pharm Ther*. 2022;47:184–193. doi:10.1111/jcpt.13574