PharmaNote®

Vol. 37, Issue 4 January 2022 Established 1985

Wegovy® (semaglutide): A Once-Weekly Weight Loss Injectable

Timothy Mason, PharmD Candidate

Obesity is a rapidly growing global health issue that carries various risk factors and comorbidities for both men and women. The World Health Organization (WHO) defines obesity as a body mass index (BMI) of > 30 kg/m^2 and defines a person with a BMI of > 25 kg/m^2 as overweight.[1] In 2016, the WHO estimated 1.9 billion adults 18 years old and older (39% of the global population) were overweight and 650 million of these as obese (13% of the global population). It is estimated that worldwide obesity nearly tripled between 1975 and 2016, highlighting an alarming trend with global consequences.[1]

Being obese or overweight carries a myriad of health consequences, such as developing cardiovascular disease (hypertension, dyslipidemia, stroke, etc.).[1-4] A 2013 meta-analysis of eight studies including 61,386 patients found that overweight and obese patients were at an increased risk (RR: 2.70, 95% CI, 2.08–3.30; and 2.65, 95% CI, 2.18–3.12, respectively) of cardiovascular events when compared to healthy normal weight patients (RR: 1.24, 95% CI, 1.02–1.55).[4] Overweight and obese patients are also at an increased risk of insulin resistance and type II diabetes (T2DM).[2,3,5] A 2009 meta-analysis found across nine studies that overweight and obese men (RR: 2.40; 95% CI, 2.12–2.72; and 6.74, 95% CI, 5.55-8.19, respectively) and women (RR: 3.92; 95% CI, 3.10-4.97; and 6.74, 95% CI, 5.55-8.19, respectively) were at an increased risk of developing T2DM.[5] This meta-analysis also found that elevated BMI was linked with increased rates various cancers including breast, endometrial, ovarian, colorectal, esophageal, kidney, pancreatic, and prostate cancers.[5] Additionally, elevated BMI has been shown to increase rates of non-alcoholic fatty liver disease, musculoskeletal disorders such as osteoarthritis, asthma, gallbladder disease, and chronic back pain.[1,3,5,6] This non-exhaustive list of BMI-linked complications calls attention to the importance of having a robust evidence-based plan for weight management to provide the best care for patients.

The 2019 outbreak of SARS-CoV-2 (COVID-19) has only further accentuated the need for weight management in the global population. Since the COVID-19 pandemic began, elevated BMI has been linked to an increased risk of COVID-19 related mortality.[7,8] A 2020 whole-population study in England was conducted and examined in-hospital death from March 1, 2020 to May 11, 2020. The study identified an increased risk of mortality found in overweight and obese patients when compared to normal weight patients with a BMI of less than 20 kg/m^2 (HR: 2.33, 95% CI, 2.11-3.56, p<0.0001 and HR: 1.60, 95% CI, 1.47-1.75, p<0.0001, respectively). This study found that patients with T2DM were at an increased risk of mortality for in-hospital COVID-19 related death (OR: 3.51, 95% CI, 3.16-3.90) compared to those without T2DM.[7] These findings indicate that weight management is indeed an important aspect of patient care, particularly in a peri-COVID-19-pandemic world.

The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2016 guidelines provide a framework and recommendations for weight management in overweight and obese patients.[9] These guidelines grade the severity of obesity as follows: BMI <25 kg/m^2 is normal weight (no obesity); BMI 25-29.9 kg/m^2 is overweight stage 0 (with no complications); BMI >30 kg/m^2 is obesity stage 0 (with no complications); BMI >25 kg/m^2 with 1 or more mild to moderate complications is obesity stage 1; and BMI >25 kg/m^2 with at least 1 severe complication is obesity stage 2.[9]

Overarching treatment recommendations include a multimodal approach to lifestyle therapy, weight-loss medications, and bariatric surgery.[9] Current treatment recommendations include a healthy lifestyle with a healthy diet and frequent exercise for primary prevention in normal weight individuals. AACE describes a healthy diet as a caloric intake equal to output, high in protein (15% of diet, minimum 30 g/day), low in fat (<30%), and high in fiber containing carbohydrates (50-55% carbohydrates with >35g fiber/day). Weight-loss medication is recommended in patients with obesity stages 0 and 1 if lifestyle therapy has failed or in addition to lifestyle therapy if their BMI is > 27. Patients with obesity stage 2 should initiate weight-loss medications concurrently with if their BMI is > 27 or if their BMI is > 35, bariatric surgery should be considered.[9]

Guideline-recommended weight management pharmacotherapy consists of both short term (< 12 weeks) and long term (> 12 weeks) therapies.[10] For short term treatment, phentermine monotherapy is recommended and has been shown to result in a mean 1-year weight loss of 5.5% and 6.1% from baseline (7.5mg and

IN THIS ISSUE

15mg doses, respectively).[10] Long-term weight management pharmacotherapy includes both prescription and over-the-counter (OTC) therapies outlined in **Table 1**. Orlistat has been shown to aid in a mean 1-year weight loss of 5.6% (OTC) to 9.6% (prescription), but carries with it side effects of steatorrhea, flatulent, and fecal discharge along with contraindications with cyclosporin, pregnancy, and malabsorption.[2,9,10]

Oral prescription only therapies include naltrexone/bupropion and phentermine/topiramate that result in a 1-year weight loss of 5.0% and 7.8-9.8% (7.5mg/46mg and 15mg/92mg), respectively.[9,10] Naltrexone/bupropion is a twice daily tablet with common side effects of nausea and constipation, and is contraindicated in patients with seizures, eating disorders, drug or alcohol withdrawal, or aged < 24 with depression.[2,10] In contrast, phentermine monotherapy and phentermine /topiramate combination therapy are once daily tablets with common side effects significant for insomnia, xerostomia, and nausea, and is known for having various drug interactions. Phentermine/topiramate combination therapy has been shown to be 2.3-3.7% (7.5mg phentermine versus 7.5mg/46mg phentermine/topiramate and 15mg phentermine versus 15mg/92mg phentermine topiramate, respectively) more effective than phentermine monotherapy alone.[5,10]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as liraglutide, are primarily used for glycemic control in diabetic patients but have been shown to have a beneficial class effect of weight loss.[10] Liraglutide is a once-daily injectable prescription medication currently available under the trade names Victoza® and Saxenda.® Victoza® is approved by the Food and Drug Administration (FDA) for the treatment of T2DM, however, Saxenda® is approved specifically for the treatment of obesity and for chronic weight management.[10] Liraglutide has been shown to cause a 1-year weight loss of 4.7-6.0% (Victoza® 1.8mg and Saxenda® 3.0mg doses, respectively).[2,10] In addition to a daily injection, liraglutide also carries common side effects of nausea, vomiting, constipation, and an increased risk of pancreatitis.[11] These therapies, while shown to be effective, are prone to intolerable side effects, frequent dosing, or require daily injections that patients may not tolerate.

Another GLP-1 RA, semaglutide, is available in both daily oral tablets (Rybelsus®) and once-weekly injectable (Ozempic®, Wegovy®) formulations.[10] The most recent formulation, Wegovy®, is FDA-approved and indicated for use of weight-loss and has a higher maintenance dose (2.4mg) compared to Ozempic® (1mg) which is used for treatment in T2DM.[12] With once weekly dosing Wegovy® offers a significant advantage over daily liraglutide injections, thus potentially increasing patient tolerability and adherence. The purpose of this paper is to examine the efficacy of Wegovy® and the validity of this claim.

Pharmacology

Mechanism of Action

GLP-1 peptide is a physiological regulator of appetite and caloric intake that is released to help regulate glucose homeostasis in a glucose-dependent manner.[13] GLP-1 can be found in pancreatic beta cells and areas of that brain that are involved in appetite regulation, predominantly the arcuate nucleus, lateral parabrachial nucleus neurons, paraventricular hypothalamic nucleus, and nucleus tractus solitarus.[13,14] GLP-1 is released in response to carbohydrate intake. Semaglutide is a GLP-1 analogue with a 94% sequence homology to physiological human GLP-1. As such, semaglutide acts as a selective GLP-1 receptor agonist, activating the GLP-1 receptor. The activation of the GLP-1 receptor causes increased insulin secretion, suppression of glucagon secretion, delayed gastric emptying, and increased satiety. This increased satiety is credited for the weight-loss effects of semaglutide, as it is believed the effects are due to decreased caloric intake secondary to decreased appetite.[3,13,14]

Pharmacokinetics

Subcutaneous administration of semaglutide achieves peak concentration 1 to 3 days post dosing, with similar exposure via administration in the abdomen, thigh, or upper arm.[13] Steady state concentration for Wegovy® increased proportionally in patients with BMI > 27 kg/m^2 up to approximately 75 nmol/L at the 2.4 mg weekly dose. Subcutaneous semaglutide has an absolute bioavailability of 89% and a volume of distribution of 12.5 L.[12] Semaglutide is highly protein bound (>99%), leading to decreased renal clearance and protection from degradation.[13] Due to this, semaglutide has a half-life of approximately one week, with steady-state achieved in 4-5 weeks of administration.[12] Semaglutide metabolism is primarily through the proteolytic cleavage of the peptide backbone followed by sequential beta-oxidation of the fatty acid side chain. Approximately 3% of the semaglutide dose is excreted unchanged in the urine with associated metabolites primarily ex-

Table 1 | FDA-Approved Pharmacotherapy for Weight Management[2,9,10]

Drug Class	Mechanism of Action	1-Year Weight Loss (% from Baseline)	Side Effects	Contraindications	Special Populations
Liraglutide	GLP-1 RA[a]	4.7-6.0	Nausea Vomiting Constipation	Medullary thyroid cancer Multiple endocrine neoplasia type 2 History of pancreatitis	Type 2 Diabetes Mellitus
Naltrexone/ bupropion	Opiate antagonist/ Reuptake inhibitor of DA[b] and NE[c]	5.0	Nausea Constipation	History of seizure Eating disorders Drug or alcohol use Age <24 with depression	Addiction Disorders
Orlistat	Lipase inhibitor	5.6-9.6	Steatorrhea Flatulence Fecal discharge	Concurrent use with cyclosporin Malabsorption Pregnancy	Over-the-Counter
Phentermine/ topiramate	NE[c]-releasing agent/ GABA[d] receptor modulator	7.8-9.8	Insomnia Xerostomia Nausea	Pregnancy Multiple Drug Interactions	Patients without CVD[e] Risk Factors

[a]Glucagon-like peptide 1 receptor agonist; [b]Dopamine; [c]Norepinephrine; [d]Gamma-aminobutyric acid; [e]Cardiovascular disease

creted through urine and feces.[12,13] Table 2 provides a summary of pertinent semaglutide pharmacokinetic parameters.

Clinical Trials

The following section will review four phase III trials of injectable semaglutide from the Semaglutide Treatment Effect in People with obesity (STEPS) clinical trial series, as well as provide a brief overview of future trials in the series. The purpose of the STEPS trial series is to investigate the efficacy on weight loss, safety, and tolerability of subcutaneous semaglutide versus placebo in adults with obesity or who are overweight.[21] A summary of the STEPS clinical trial series can be found in Table 3.

STEP 1 Trial

The "Effect and Safety of Semaglutide 2.4 mg Once-weekly in Subjects With Overweight or Obesity" (STEP 1) trial is a phase III clinical trial that compared the efficacy of subcutaneous semaglutide 2.4 mg injections to placebo in overweight or obese patients.[3] The trial was conducted at 129 sites in 16 countries with 1,961 total participants. Patients were included in the STEP 1 trial if they were at least 18 years of age, reported a history of at least one unsuccessful dietary effort to lose body weight, and had a BMI of > 30 kg/m^2 or 27 kg/m^2 with a least one weight related comorbidity defined as hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Patients were excluded from the STEP 1 trial if they had a self-reported decrease in body weight of > 5 kg within 90 days before screening or an HbA1c value of > 6.5%.[3]

This trial evaluated two primary outcomes: percent change in body weight from baseline to week 68 in patients receiving semaglutide 2.4 mg versus placebo; and number of subjects who achieved > 5% body weight reduction with semaglutide versus placebo at week 68. Trial participants were randomized to either semaglutide 2.4 mg subcutaneous injections (n=1,306) or placebo injections (n=655) once weekly in a 2:1 ratio. Patients in both arms were instructed on lifestyle interventions including a 500 kcal per day reduction in diet and > 150 minutes of physical activity per week. Patients in the semaglutide 2.4 mg arm were initiated therapy at 0.25 mg once weekly for the first 4 weeks, with the dose titrating up to 2.4 mg by week 16. Participants in both arms of the trial received individualized counseling sessions to screen for adverse events and aid in adherence to diet and exercise. Participants were weighed at baseline, every 4 weeks, and at week 68 to assess for primary outcomes measures.[3]

For the primary outcome of percent change in body weight from baseline to week 68, semaglutide 2.4 mg once a week showed -14.85% at week 68, whereas placebo showed -2.41%. A difference of 12.44% (95% CI, -13.37 to -11.51, p<0.001) over placebo at week 68. For subjects who achieved > 5% body weight reduction compared to baseline, 86.4% of semaglutide 2.4 mg patients (OR: 11.2, 95% CI, 8.9-14.2, p<0.001) met this goal. In addition, 69.1% achieved a body-weight reduction compared to baseline of > 10% in the semaglutide 2.4 mg (OR: 14.7, 95% CI, 11.1-19.4, p<0.001) and 50.5% achieved a body weight reduction from baseline of > 15% (OR: 19.3, 95% CI, 12.9-28.8, p<0.001). Patients in the placebo group achieved a weight reduction from baseline with 31.5%, 12%, and 4.9% reaching the >5%, >10%, and >15% thresholds, respectively.[3]

In the semaglutide 2.4 mg arm, 7% of patients experienced an adverse event that led to discontinuation of the trial. In the placebo arm only 3.1% of patients discontinued the trial due to adverse events. Sudden cardiac death occurred in one patient in the semaglutide 2.4 mg group who had discontinued semaglutide and had a history of hypertension and obstructive sleep apnea. In the placebo group, one death occurred due to glioblastoma, aspiration pneumonia, and severe sepsis.[3]

both up and down?

Table 2 | Select Oral Semaglutide Pharmacokinetics[12,13]

Absorption	
T_{max}[a]	24-72 hours
Bioavailability	89%
C_{ss}[b]	75 nmol/L
Distribution	
V_{ss}[c]	12.5 L
Protein Binding	>99%
Metabolism	
Primary	Proteolytic cleavage
Secondary	Beta Oxidation
Elimination	
$T_{1/2}$[d]	7 days
Urine	3%

[a]Time to maximum concentration; [b]Concentration at steady state; [c]Steady state volume of distribution; [d]Half-life

STEP 2 Trial

The STEP 2 trial is a phase III clinical trial that compared the efficacy of subcutaneous semaglutide 2.4 mg injections to placebo in overweight or obese patients, with T2DM.[15] The trial was conducted at 149 sites in 12 countries with 1,210 total participants. Patients were included in the STEP 2 trial if they were at least 18 years of age, reported a history of at least one unsuccessful dietary effort to lose body weight, had a BMI of > 27 kg/m^2, and were diagnoses with T2DM (HgA1c 7-10%) 180 days or longer prior to screening.[4] Patients were excluded if they had a self-reported decrease in body weight > 5 kg within previous 90 days, diagnosed renal impairment determined by an estimated glomerular filtration rate (eGFR) value of < 30 mL/min/1.72m^2 (< 60mL/min/1.72m2 in subjects treated with sodium-glucose cotransporter 2 inhibitors), or if they had uncontrolled and potentially unstable diabetic retinopathy or maculopathy.[15]

This trial evaluated two primary outcomes: percent change in body weight from baseline to week 68; and number of subjects who achieved > 5% body weight reduction at week 68. Trial participants were randomized to semaglutide 2.4 mg subcutaneous injections (n= 404), semaglutide 1.0 mg subcutaneous injections (n= 403), or placebo injections (n=403) once weekly in a 1:1:1 ratio, followed by 7 weeks without treatment and a final evaluation at week 75. Patients were weighed and adverse events discussed at week 75, though this data was not reported or used for analysis. Patients in all arms were instructed on lifestyle interventions like in STEP 1. Patients in both semaglutide arms were initiated therapy at 0.25 mg once weekly for the first 4 weeks, with the dose titrating up to 1.0 mg by week 8 or 2.4 mg by week 16, respective to their assigned treatment. Participants were weighed at baseline, every 4 weeks, and at week 68 to assess for primary outcomes measures.[15]

Table 3 | Semaglutide Treatment Effect in People with Obesity (STEPS) Trial Series[3,15-17]

Trial	Treatment Arms	Dosing	Lifestyle Interventions	Primary Outcomes	Result (95% CI)	P-Value
STEP 1	SEM[a] 2.4mg (n=1,306)	Titration[b] Schedule	500 kcal/d deficit diet & ≥ 150 min/week physical activity	Percent change in body weight from baseline to week 68	-12.44 (-13.37 to -11.51)	< 0.001
	Placebo (n=655)			Percentage of subjects with ≥ 5% body weight reduction	54.5 (8.9 to 14.2)	< 0.001
STEP 2	SEM 2.4mg (n=404)	Titration[b]	500 kcal/d deficit diet & ≥ 150 min/week physical activity	Percent change in body weight from baseline to week 68	***SEM 2.4mg v. Placebo*** -6.21 (-7.28 to –5.15)	< 0.0001
	Placebo (n=403)				***SEM 2.4mg v. SEM 1.0mg*** -2.65 (-3.66 to –1.64)	< 0.0001
	SEM 1.0mg (n=403)	Modified[c] Titration		Percentage of subjects with ≥ 5% body weight reduction	***SEM 2.4mg v. Placebo*** 40.3 (1.21 to 2.18)	< 0.001
					SEM 2.4mg v. SEM 1.0mg 11.7 (3.58 to 6.64)	< 0.0001
STEP 3	SEM 2.4mg (n=407)	Titration[b]	Initial 100min physical activity, increasing up to max 200min/week Low calorie diet [d]for 8 weeks, then hypo-caloric diet[e] 30 individual intensive behavior therapy visits	Percent change in body weight from baseline to week 68	-10.3 (-12.0 to –8.6)	< 0.001
	Placebo (n=204)			Percentage of subjects with ≥ 5% body weight reduction	39.0 (4.0 to 9.3)	< 0.001
STEP 4	SEM 2.4mg (n=535)	Titration[b]	500 kcal/d deficit diet & ≥ 150 min/week physical activity	Percent change in body weight from week 20 to week 68	-14.8 (-16.0 to –13.5)	< 0.001
	Placebo (n=268)					

[a]Semaglutide; [b]**Weeks 1-4**:0.25mg,**Weeks 5-8**:0.5mg,**Weeks 8-12**:1.0 mg,**Weeks 12-16**:1.7 mg,**Weeks 16+:**2.4mg; [c]**Weeks 1-4:**0.25mg,**Weeks 5-8**:0.5mg,**Weeks 8+**:1.0 mg; [d]1,000-1,200 kcal/day; [e]1,200-1,800 kcal/day

For the primary outcome of percent change in body weight from baseline to week 68, semaglutide 2.4 mg subcutaneous injections showed -9.64% at week 68, semaglutide 1.0 mg subcutaneous injections showed -6.99% at week 68 and placebo injections showed -3.42% at week 68. The difference in outcomes between semaglutide 2.4 mg and placebo was -6.21% (95% CI, -7.28 to -5.15, p<0.0001) with a difference of -2.65% (95% CI, -3.66 to -1.64, p<0.0001) between semaglutide 2.4 mg and semaglutide 1.0 weekly. The difference in outcomes for percent change in body weight between semaglutide 1.0 mg and placebo was not assessed. For the primary outcome of subjects who achieved > 5% body weight reduction compared to baseline, 68.8% of semaglutide 2.4 mg patients (OR: 4.88, 95% CI, 3.58-6.64, p<0.0001) met this goal whereas 57.1% of semaglutide 1.0 mg patients (OR: 1.62, 95% CI, 1.21-2.18, p<0.001) and 28.5% of placebo patients achieved the same result. In addition to this, of the patients receiving semaglutide 2.4 mg 45.6% (OR: 7.41, 95% CI, 4.89-12.24, p<0.0001) achieved a body-weight reduction compared to baseline of > 10%, and 28.7% of semaglutide 1.0 mg patients (OR: 2.07, 95% CI, 1.53-2.80) and 8.2% of placebo patients achieved similar results. Further, 50.5% of semaglutide 2.4 mg (OR: 7.65, 95% CI, 4.11-14.22, p<0.0001) patients achieved a body weight reduction of > 15% compared to baseline, whereas 8.2% of semaglutide 1.0 mg patients (OR: 2.17, 95% CI, 1.50-3.15) and 3.2% of placebo patients achieved similar results.[15]

Adverse events that led to the discontinuation of the trial occurred in 5.0% and 6.2% of patients taking semaglutide. In the placebo arm only 3.5% of patients discontinued the trial due to adverse events with 1.0% being gastrointestinal disorders. One death was reported in each of the treatment groups, but specific details were not discussed.[15]

STEP 3 Trial

The STEP 3 trial is a phase III clinical trial that compared the efficacy of subcutaneous semaglutide 2.4 mg injections to placebo in overweight or obese patients as an adjunct to intensive behavioral therapy.[16] This trial was conducted at 41 sites within the United States with 611 total participants. Participants were included in the STEP 3 trial if they were at least 18 years of age, reported a history of at least one unsuccessful dietary effort to lose body weight, and had a BMI of > 30 kg/m^2 or 27 kg/m^2 with a least one weight related comorbidity such as hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Patients were excluded if they had a self-reported decrease in body weight of > 5 kg within 90 days before screening or an HbA1c value of > 6.5%.[16]

This trial evaluated two primary outcomes: percent change in body weight from baseline to week 68 in patients receiving semaglutide 2.4 mg versus placebo; and number of subjects who achieved > 5% body weight reduction with semaglutide versus placebo at week 68. Trial participants were randomized to semaglutide 2.4 mg subcutaneous injections (n=407) or placebo injections (n=204) once weekly in a 2:1 ratio, followed by 7 weeks without treatment and a final evaluation at week 75. Patients were weighed and adverse events discussed at week 75, though this data was not reported or used for analysis. Semaglutide was started and titrated in the same fashion as previous trials with weighed measured at baseline, every 4 weeks through 68 weeks. Patients in both arms were prescribed 100 minutes of physical activity per week spread across four to five days, increasing by 25 minutes every four weeks to a maximum of 200 minutes per week, as well as a low-calorie diet (1,000-1,200 kcal/day) for the first 8 weeks followed by a hypo-caloric diet (1200-1800 kcal/day) for the remainder of the trial period. Additionally, all participants were provided with 30 individual intensive behavior therapy visits to discuss diet, physical activity, and behavioral strategies with a registered dietician.[16]

For the primary outcome of percent change in body weight from baseline to week 68, semaglutide 2.4 mg subcutaneous injections showed -16.0% at week 68 and placebo injections showed -5.7% at week, difference of -10.3% (95% CI, -12.0 to -8.6, p<0.001). For subjects who achieved > 5% body weight reduction compared to baseline, 86.6% (OR: 6.1, 95% CI, 4.0-9.3, p<0.001) of semaglutide 2.4 mg patients met this goal in contrast to 47.6% of placebo patients. In addition to this, of the patients receiving semaglutide 2.4 mg 75.3% (OR: 7.4, 95% CI, 4.9-11.0, p<0.001) achieved a body-weight reduction compared to baseline of > 10% and 55.8% (Or: 7.9, 95% CI, 4.9-12.6, p<0.001) achieved a body weight reduction compared to baseline of > 15%, whereas placebo patients achieved 27.0% and 13.2%, respectively.[16]

In the semaglutide 2.4 mg arm 5.9% of patients experienced an adverse event that led to the discontinuation of the trial. In the placebo arm only 2.9% of patients discontinued the trial due to adverse. No deaths were reported during this study.[16]

STEP 4 Trial

The STEP 4 trial is a phase III clinical trial that compared continued once-weekly treatment with semaglutide 2.4 mg subcutaneous injections with switch to placebo injections for weight maintenance.[17] The trial was conducted at 73 sites in 10 countries with 902 total participants. Participants were included in the STEP 4 trial if they were at least 18 years of age, reported a history of at least one unsuccessful dietary effort to lose body weight, and had a BMI of > 30 kg/m^2 or 27 kg/m^2 with a least one weight related comorbidity defined as hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Patients were excluded from the STEP 4 trial if they had a self-reported decrease in body weight of > 5 kg within 90 days before screening or an HbA1c value of > 6.5%.[17]

This trial evaluated one primary outcome: percent change in body weight from week 20 to week 68 in patients receiving semaglutide 2.4 mg injections continued throughout the entire trial period versus patients switched to placebo after week 20. All participants were initiated semaglutide therapy at 0.25 mg once weekly for the first 4 weeks, with the dose titrating up to 2.4 mg by week 16, with 4 weeks of maintenance at 2.4 mg weekly. At week 20, trial participants were randomized to semaglutide 2.4 mg subcutaneous injections (n=535) or placebo injections (n=268) once weekly in a 2:1 ratio, followed by 7 weeks without treatment and a final evaluation at week 75. Patients were weighed and adverse events discussed at week 75, though this data was not reported or used for analysis. Participants were weighed at baseline, every 4 weeks, and at week 68 to assess for primary outcomes measures. Patients in both arms were instructed on lifestyle interventions including a 500 kcal per day reduction in diet and > 150 minutes of physical activity per week.[17]

For the primary outcome of percent change in body weight from week 20 to week 68, semaglutide 2.4 mg subcutaneous injections showed -7.9% (95% CI, -8.6 to -7.2, p<0.001) at week 68 and placebo injections showed 6.9% (95% CI, 5.8 to 7.9, p<0.001) with a difference of -14.8% (95% CI, -16.0 to -13.5, p<0.001) between groups. Additionally, patients continuing semaglutide 2.4 mg achieved a waist circumference reduction (cm) of -6.4 (95% CI, -7.1 to -5.7, p<0.001) compared to baseline with those in placebo experiencing an increase of 3.3 (95% CI, 2.3 to

Table 4 | Semaglutide Adverse Event Frequency in the STEPS Trial Series[3,15-17]

Trial	Treatment Arms	Adverse Events[b]	Serious Adverse Events	Dropout	Reported Deaths
STEP 1	SEM[a] 2.4mg (n=1,306)	89.7%	9.8%	7.0%	1
	Placebo (n=655)	86.4%	6.4%	3.1%	1
STEP 2	SEM 2.4mg (n=404)	87.6%	9.9%	6.2%	1
	Placebo (n=403)	81.8%	7.7%	5.0%	1
	SEM 1.0mg (n=403)	76.9%	9.2%	3.5%	1
STEP 3	SEM 2.4mg (n=407)	95.8%	9.1%	5.9%	0
	Placebo (n=204)	96.1%	6.0%	2.9%	0
STEP 4	SEM 2.4mg (n=535)	81.3%	7.7%	2.4%	1
	Placebo (n=268)	75.0%	5.6%	2.2%	1

[a]Semaglutide; [b]Prevents daily activities or results in acute or permanent harm to the patient

Table 5 | Incidence Rate of Common Adverse Effects with Semaglutide[3,15,16,22]

Adverse Effect[a]	Wegovy® 2.4mg (n=2,116)	Wegovy® 1.0mg (n=402)	Placebo (n=1,261)	Ozempic® 1.0mg (n=261)[22]
Nausea	44	32.1	16	20.3
Diarrhea	30	22.1	16	8.8
Vomiting	24	13.4	< 10	9.2
Constipation	24	12.7	11	3.1
Abdominal Pain	20	< 10	10	5.7

[a]Defined by >10% occurrence in STEP trials 1-3

4.3, p<0.001), with a calculated difference of -9.7 (95% CI, -10.9 to -8.5, p<001) between groups.[17]

In the semaglutide 2.4 mg arm 2.4% of patients experienced an adverse event that led to the discontinuation of the trial, versus 2.2% in the placebo switch arm.[15] One death was reported in each the continued semaglutide group and the placebo switch group.[15] The death in the continued semaglutide group was attributed to underlying chronic obstructive pulmonary disease, whereas the death in the placebo group was attributed to metastatic lung cancer with pericardial effusion.[17]

Future STEP Trials

Several additional STEP trials are currently recruiting, underway, or completed with no data currently published. The STEP 5 trial is a phase III clinical trial designed to evaluate the same outcomes as the previous STEP trials however for a duration of 104 weeks. STEP 5 was completed on March 23, 2021 but has not been published.[18] The STEP 6 trial is a phase III clinical trial designed to evaluate the same outcomes as the previous STEP trials focusing on East Asian patients from Japan and South Korea, with the addition of a third trial arm of semaglutide 1.7mg. STEP 6 was completed on November 20, 2020.[19] The STEP 7 trial is a phase III clinical trial designed to evaluate same outcomes as the previous STEP trials however for a duration of 44 weeks. The STEP 7 trial is currently in recruitment.[20] The STEP 8 trial is a phase III clinical trial designed to evaluate the percent change in body weight from baseline to week 68 in patients receiving semaglutide 2.4 mg versus liraglutide 3.0mg. STEP 8 was completed on May 11, 2021.[21] There are currently no publicly available release dates for any of these trials.

Across the four STEPS trials examined, adverse events occurred in 81.3-95.8% in semaglutide 2.4mg patients and 75.0-96.1% of placebo patients. Serious adverse events that prevent normal daily activity or results in acute or permanent harm to the patient occurred in 7.7-9.9% of semaglutide 2.4mg patients and 5.6-9.1% of placebo patients. Adverse events leading to dropout from the trials occurred in 2.4-7.0% of semaglutide 2.4mg patients and 2.2-3.5% of placebo patients. A total of 7 deaths were reported across all four trials. Statistical analyses comparing adverse events in semaglutide 2.4mg patients and placebo patients were not performed.[3,15,16,17] A detailed summary of each trial can be seen in **Table 4.**

Adverse Effects & Precautions

Adverse events the most common adverse events associated with Wegovy® use were primarily gastrointestinal disorders and are summarized in **Table 5**.[3,15,16] The common adverse events occurring in more than 10% of patients were nausea (44%), diarrhea (30%), vomiting (24%), constipation (24%), and abdominal pain (20%). In patients with T2DM, clinically significant hypoglycemia (< 54 mg/dL) was reported in 6.2% of Wegovy® patients.[3,13,15,16]

The FDA has issued a black box warning regarding the risk of thyroid C-cell tumors while taking semaglutide.[13] This is due to an observed causative relationship between semaglutide and thyroid C-cell tumors in rodents at clinically relevant exposures. The human relevance of rodent thyroid c-cell tumors has not been determined, but in an abundance of caution, the FDA issued this warning. The specific risk of Wegovy® causing thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) has not been evaluated. Use of Wegovy® in patients with a personal or family history of MTC, multiple endocrine neoplasia syndrome type 2, or a prior serious hypersensitivity reaction to semaglutide is contraindicated.[13]

Special Populations

Renal & Hepatic Impairment

A study examining the effects of semaglutide on patients with renal impairment (including end-stage renal disease) found no clinically relevant change in semaglutide pharmacokinetics.[12,13] Based on this, there are no recommended dose adjustments for patients with renal impairment while taking Wegovy®.[12,13]

A study examining the effects of semaglutide on patients with varying degrees of hepatic impairment found no clinically relevant change in semaglutide pharmacokinetics.[16,21] Based on this, there are no recommended dose adjustments for patients with hepatic impairment while taking Wegovy®.[12,13]

Pregnancy & Lactation

Available pharmacovigilance data and data from clinical trials with Wegovy® are insufficient to establish a drug-associated risk for major birth defects or embryofetal mortality.[13] Currently, use in pregnant patients is not recommended. Based on animal reproduction studies, fetal semaglutide exposure below the maximum recommended human dose has been identified as a potential risk factor for embryofetal mortality, structural abnormalities, and alterations to growth. These findings were consistent in pregnant rats, rabbits, and cynomolgus monkeys when semaglutide was administered during organogenesis. Additionally, weight loss has not been shown to offer benefit to a pregnant patient and may cause fetal harm. Novo Nordisk® has established a pregnan-

cy exposure registry and is continuing to monitor pregnancy outcomes.[13]

Available data does not show the presence of semaglutide or any of its metabolites in human breast milk.[13] There are no data on the effect of semaglutide on the breastfed infant or the effects on milk production. Animal studies in lactating rats have shown that semaglutide is present in milk at levels 3-12 fold lower than maternal plasma.[13]

Pediatric & Geriatric Patients

There is currently no data evaluating the safety and efficacy of Wegovy® in pediatric patients. In the STEP 1-4 series of clinical trials 233 (8.8%) of Wegovy® treated patients were between 65 and 75 years old, and 23 (0.9%) were 75 years of age or older.[3,15,16,17] The STEPS clinical trials did not find any overall differences in safety or efficacy between either of these age groups and the younger patient population, nor did they find sufficient evidence to rule out the possibility of increased sensitivity in elderly patients.[3,15,16,17]

Dosage and Administration

Wegovy® is a once weekly subcutaneous injection that is available in boxes of four pre-filled pen injectors with concentrations of 0.25mg/0.5mL, 0.5mg/0.5mL, 1mg/0.5mL, 1.7mg/0.75mL, and 2.4mg/0.75mL.[13] Wegovy® can be injected into the abdomen, thigh, or upper arm. Patients starting Wegovy® therapy are initiated at 0.25mg once weekly, then titrating dose upwards every four weeks to doses, 0.5mg, 1mg, 1.7mg up to a maintenance dose of 2.4mg after 16 weeks. If a patient is unable to tolerate a dose during escalation, it is recommended to delay escalation for an additional four weeks before attempting to escalate dose again. If a patient is unable to tolerate dose escalation to the 2.4mg dose after two attempts, manufacturer recommends discontinuing Wegovy® in its entirety as it has not been for efficacy at lower doses.[13] This recommendation may change in the future, as the STEP 6 trial is examining the efficacy of Wegovy® 1.7mg.[19]

The average retail price as of October 2021 for Wegovy® was $2,262.84 without insurance. Novo Nordisk® offers a Wegovy® patient copay assistance card that works with commercial insurance to bring a patient's copay down to a minimum of $25 per 28-day supply, with a maximum savings of $200 per 28 day supply.[23] As of November 11, 2021 Wegovy® is on long-term backorder due to unforeseen demand. Novo Nordisk® estimates it will be available again in early 2022.[23]

Conclusion

Semaglutide is a GLP-1 receptor agonist that has demonstrated efficacy in helping patients achieve glycemic control, weight loss, and has shown beneficial cardiometabolic effects. Wegovy® is a new formulation of semaglutide approved as an adjunct therapy to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, T2DM, or dyslipidemia).[13] The STEPS clinical trial series demonstrated the efficacy of Wegovy® as an effective adjunctive therapy for chronic weight management with two-year safety and efficacy data to come pending the publication of the STEP 5 trial. The ability of Wegovy® to be dosed once weekly provides a welcome alternative option from other injectable weight management medications and the frequent dosing of oral weight management medications.

References

1. World Health Organization. (n.d.). Obesity and overweight. World Health Organization. Retrieved October 27, 2021, from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Neeland, I. J., Poirier, P., & Després, J. P. (2018). Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation, 137(13), 1391-1406.
3. Wilding, J. P., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., ... & Kushner, R. F. (2021). Once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine.
4. Kramer, C. K., Zinman, B., & Retnakaran, R. (2013). Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. Annals of internal medicine, 159(11), 758-769.
5. Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L., & Anis, A. H. (2009). The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC public health, 9(1), 1-20.
6. Busetto, L., Dicker, D., Azran, C., Batterham, R. L., Farpour-Lambert, N., Fried, M., ... & Yumuk, V. (2018). Obesity management task force of the European Association for the study of obesity released "Practical Recommendations for the Post-Bariatric Surgery Medical Management". Obesity surgery, 28(7), 2117-2121.
7. Barron, E., Bakhai, C., Kar, P., Weaver, A., Bradley, D., Ismail, H., ... & Valabhji, J. (2020). Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. The lancet Diabetes & endocrinology, 8(10), 813-822.
8. Holman, N., Knighton, P., Kar, P., O'Keefe, J., Curley, M., Weaver, A., ... & Valabhji, J. (2020). Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. The lancet Diabetes & endocrinology, 8(10), 823-833.
9. Garvey, W. T., Mechanick, J. I., Brett, E. M., Garber, A. J., Hurley, D. L., Jastreboff, A. M., ... & Plodkowski, R. (2016). American association of clinical endocrinologists and American college of endocrinology comprehensive clinical practice guidelines formedical care of patients with obesity. Endocrine Practice, 22, 1-203.
10. American Diabetes Association. (2021). 8. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes—2021. Diabetes Care, 44(Supplement 1), S100-S110.
11. Liraglutide. ClinicalPharmacology. 2021 Elsevier. Accessed November 8, 2021.
12. Semaglutide. ClinicalPharmacology. 2021 Elsevier. Accessed October 27, 2021.
13. Wegovy [package insert]. Plainsboro, NJ. Novo Nordisk Inc. 2021 label (fda.gov)
14. Kabahizi, A., Wallace, B., Lieu, L., Chau, D., Dong, Y., Hwang, E. S., & Williams, K. W. (2021). Glucagon-like Peptide-1 (GLP-1) Signaling in the Brain: From Neural Circuits and Metabolism to Therapeutics. British Journal of Pharmacology.
15. Davies, M., Færch, L., Jeppesen, O. K., Pakseresht, A., Pedersen, S. D., Perreault, L., ... & STEP 2 Study Group. (2021). 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. The Lancet, 397(10278), 971-984.
16. Wadden, T. A., Bailey, T. S., Billings, L. K., Davies, M., Frias, J. P., Koroleva, A., ... & STEP 3 Investigators. (2021). 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, 325(14), 1403-1413.
17. Rubino, D., Abrahamsson, N., Davies, M., Hesse, D., Greenway, F. L., Jensen, C., ... & STEP 4 Investigators. (2021). 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, 325(14), 1414-1425.
18. Step 5: Two-year research study investigating how well semaglutide works in people suffering from overweight or obesity. ClinicalTrials.gov. (n.d.). Retrieved November 17, 2021, from https://clinicaltrials.gov/ct2/show/NCT03693430.
19. Step 6: Research study investigating how well SEMAGLUTIDE works in people living with overweight or obesity. ClinicalTrials.gov. (n.d.). Retrieved November 17, 2021, from https://clinicaltrials.gov/ct2/show/study/NCT03811574?term=NCT03811574&rank=1.
20. Step 7: Research study of how well semaglutide works in people living with overweight or obesity. ClinicalTrials.gov. (n.d.). Retrieved November 17, 2021, from https://clinicaltrials.gov/ct2/show/record/NCT04251156?term=NCT04251156&%3Brank=1.
21. Step 8: Research study to investigate how well semaglutide works compared to liraglutide in people living with overweight or obesity. ClinicalTrials.gov. (n.d.). Retrieved November 17, 2021, from https://clinicaltrials.gov/ct2/show/NCT04074161?term=NCT04074161&%3Brank=1.
22. DRUGS@FDA: FDA-approved drugs. (n.d.). Ozempic [package insert]. accessdata.fda.gov. Retrieved November 23, 2021 from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=209637.
23. Novo Nordisk. (n.d.). Wegovy Supply. Retrieved October 27, 2021, from https://www.novonordisk-us.com/products/product-supply-update.html?id=69961.

Drug Update:
New Indications and Dosage Forms
December 2021

Xaciato® (clindamycin) Vaginal Gel
New Formulation: Vaginal treatment for bacterial vaginosis approved for use in females 12 years of age and older

Entadfi® (finasteride/tadalafil) Oral Capsule
New Molecular Combination: Combination tablet indicated to initiate treatment of the signs and symptoms of benign prostatic hyperplasia in men with an enlarged prostate for use up to 26 weeks

Tarpeyo® (budesonide) Delayed-Release Oral Capsule
New Formulation: Corticosteriod indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally with a urine protein-to-creatinine ratio (UPCR) $\geq$1.5g/g

Apretude® (cabotegravir) Intramuscular Injection
New Formulation: HIV-1 integrase strand transfer inhibitor indicated for PrEP to reduce risk of sexually acquired HIV-1 infection dosed every 2 months after oral lead-in dosing

Xarelto® (rivaroxaban) Oral Suspension
New Formulation: Factor Xa inhibitor indicated for anticoagulation for treatment of DVT, PE, and reduction of stroke in nonvalvular atrial fibrillation dosed at 1mg/mL once reconstituted

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida

Editor-in-Chief
John G. Gums, PharmD, FCCP

Managing Editor
Jason Powell, PharmD, BCACP

Associate Editor
R. Whit Curry, MD

Assistant Editor
Christie R. Monahan, PharmD