

Next Generation Antiobesity Medications: Setmelanotide, Semaglutide, Tirzepatide and Bimagrumb: What do They Mean for Clinical Practice?

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There is a new generation of antiobesity drugs in development or just arriving on the scene. First, setmelanotide has been approved for three of the ultrarare genetic conditions that cause obesity—pro-opiomelanocortin deficiency, proprotein convertase subtilisin and kexin type 1 (an important enzyme in the melanocortin pathway) and leptin receptor deficiency. Setmelanotide marks the first in a personalized medicine approach to obesity. Second, semaglutide 2.4 mg once weekly has been submitted to regulators in the United States and the European Union for approval for patients with obesity (body mass index [BMI] ≥ 30 kg/m²) or overweight (BMI ≥ 27 kg/m²) and at least one weight related comorbidity. This drug has been studied in five phase 3 clinical trials, four discussed herein: semaglutide produces roughly twice as much weight loss as we have seen in older anti-obesity medications. Semaglutide is already in use for treatment of diabetes and, as a glucagon-like peptide 1 (GLP-1) receptor analog, is part of a class of drugs used widely in diabetes. Tirzepatide, a glucose-insulin peptide and GLP-1 dual agonist is in phase 3 study for obesity management, and bimagrumb is a new agent in phase 2 with a unique mechanism of action; they are generating much interest. The purpose of this narrative review is lay the groundwork for a discussion of the clinical impact of these new medications on the clinical practice of obesity. Further, these developments shall be used to launch a speculation of what is likely to be their impact on the future of obesity pharmacotherapy.

Key words: Anti-obesity agents, Anti-obesity drugs, Weight loss agents, Setmelanotide, Semaglutide, Tirzepatide, Bimagrumb

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INTRODUCTION

Our expectations for antiobesity medications have been tempered by the modest weight loss that is associated with the currently available medications. These drugs received regulatory approval with the expectation that they would produce approximately 5% greater weight loss on average than placebo, when both drug and placebo are given with a lifestyle intervention. The goal of medically supervised weight loss has been modest, or at most, moderate, weight

loss—principally because that is all that could be regularly achieved. We are now seeing the emergence of second generation medications. Setmelanotide has just been approved for a personalized medicine approach. Semaglutide is coming before regulators in the United States and the European Union in 2020. Then there are other drugs in the pipeline (tirzepatide and bimagrumb) that are interesting and unique. The purpose of this review is to examine these four compounds and to speculate on how these tools will transform the practice of obesity medicine.

SETMELANOTIDE

Setmelanotide is a cyclized octapeptide (Fig. 1) that binds and activates multiple melanocortin receptors—MC4R, MC3R, and MC1R selectively over MC5R and MC2R.¹ Setmelanotide is one of multiple MC4R agonists that have been studied as potential antiobesity medications.¹ Some of these activate the sympathetic nervous system with blood pressure elevation and increased heart rate making them unacceptable in clinical care, while setmelanotide has not been shown to have this characteristic.¹ In a diet-induced obese nonhuman primate model, setmelanotide produced persistent weight loss (–13.5%) over 8 weeks.² Importantly, it did not increase heart rate or blood pressure. In a phase 1b study in humans, individuals with obesity and heterozygous for complete or partial loss of function mutations in MC4R were treated with setmelanotide by infusion or placebo over 28 days.³ Interestingly, both groups lost weight similarly, in comparison to placebo. There were no increases in heart rate or blood pressure in this study, but the most frequent side effect was skin darkening, or “tanning” associated with setmelanotide.³ This early study demonstrated that there would probably be no advantage for setmelanotide in heterozygous individuals and the clinical development of the drug then focused on identifying homozy-

gous individuals with genetic defects that might respond to setmelanotide.

Setmelanotide was developed with a personalized medicine approach, targeting the drug for individuals with defects in the melanocortin pathway. Setmelanotide showed excellent outcomes in two patients with pro-opiomelanocortin (POMC) deficiency, reversing hyperphagia and producing dramatic weight loss in both patients.⁴ When given to three patients with leptin receptor (LEPR) deficiency, setmelanotide produced clinically significant reduction in both body weight and hyperphagia.⁵ The drug has also been studied⁶ in seven patients with Bardet Biedl syndrome, showing hunger reduction and mean weight loss at 1 year of –16.3% (90% confidence interval [CI], –19.9% to –12.8%; n=7). Bardet Biedl continues to be studied as potential indication for setmelanotide.

The regulatory approval of setmelanotide rests on studies in 21 participants,⁷ where the genetic defects were biallelic variations in either the prohormone, POMC (n=9), proprotein convertase subtilisin/kexin type 1 (PCSK1; n=1), an important enzyme in activating the melanocortin 4 receptor pathway, or the LEPR (n=11), which is essential for POMC function. The study was designed with a variable period of dose-finding where the drug was administered daily, and dose adjusted to manage hyperphagia. Then

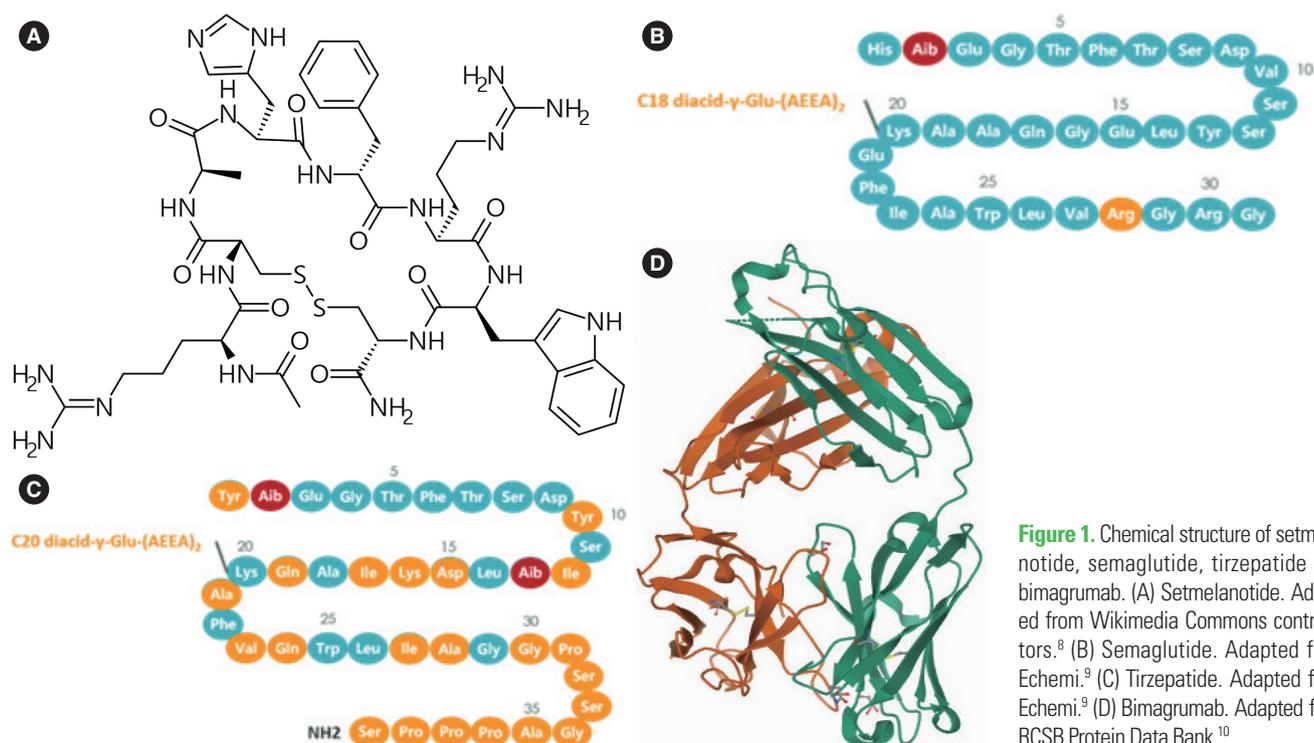


Figure 1. Chemical structure of setmelanotide, semaglutide, tirzepatide and bimagrumb. (A) Setmelanotide. Adapted from Wikimedia Commons contributors.⁸ (B) Semaglutide. Adapted from Echemi.⁹ (C) Tirzepatide. Adapted from Echemi.⁹ (D) Bimagrumb. Adapted from RCSB Protein Data Bank.¹⁰

a 10-week open label period occurred, and participants were required to lose 5 kg or 5% if the body weight was less than 100 kg to continue the study. Successful patients entered an 8-week placebo-controlled phase inclusive of a 4-week placebo period and then continued for 32 weeks of open-label therapy.

The study showed that for the 10 patients with POMC or PCSK1 deficiency, eight of 10 met the primary outcome of 10% or more weight loss at 1 year; among all enrollees, mean weight loss was -25.6%.⁷ These results are shown in Fig. 2. For the 11 patients with LEPR deficiency, the response was more variable. Of those 11, four failed to achieve the required 5% weight loss by week 12 and only five (45%) achieved the primary outcome of 10% or more weight loss at 1 year.⁷ Still, all five achieved 15% or more weight loss and two achieved 20% or more weight loss.⁷ These results are also shown in Fig. 2. For both LEPR and POMC deficiency patients, tolerability and safety seemed acceptable. The most common adverse events were injection site reactions, skin darkening and nausea, vomiting and diarrhea.⁷ Other side effects included spontaneous penile erections and spontaneous female arousal, depression and suicidal thoughts and darkening of moles. Compared to those with LEPR deficiency, the results with setmelanotide were best for patients with POMC deficiency. We cannot be sure of the response in the one patient with PCSK1 deficiency, since that patient had to drop out of study because the patient developed depression after hyperphagia recurred during a required blinded placebo phase.⁷ While the results were not as encouraging for all patients with LEPR deficiency as those

with POMC deficiency in terms of amount of weight loss, this should be interpreted in the face of no alternative treatments for this severe disease. Fig. 2 displays weight loss in patients with POMC and LEPR deficiency with setmelanotide.

Setmelanotide was approved by the U.S. Food and Drug Administration¹¹ with an indication for “chronic weight management (weight loss and weight maintenance for at least 1 year) in patients 6 years and older with obesity due to three rare genetic conditions: POMC deficiency, PCSK1 deficiency, and LEPR deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes considered pathogenic (causing disease), likely pathogenic, or of uncertain significance.” The drug is marketed as Imcivree. It is priced at \$330 per mg, making annual costs very high for this drug which requires daily subcutaneous injection and where doses begin at 1 mg.¹²

What does setmelanotide mean for the practice of obesity medicine? Regulatory approval has come only for patients with proven genetic defects in the leptin-melanocortin pathway. Having a drug that is effective would then drive clinicians to increase genetic testing for patients with a history of severe early-onset obesity. Thus, the impact of setmelanotide in the obesity clinic is likely to mean a renewed appreciation for the biologic underpinnings of obesity and an increase in genetic screening to identify a subset of patients. Still, the three genetic conditions for which setmelanotide has been approved are ultrarare. They are associated with severe childhood obesity and hyperphagia and may be associated with various other

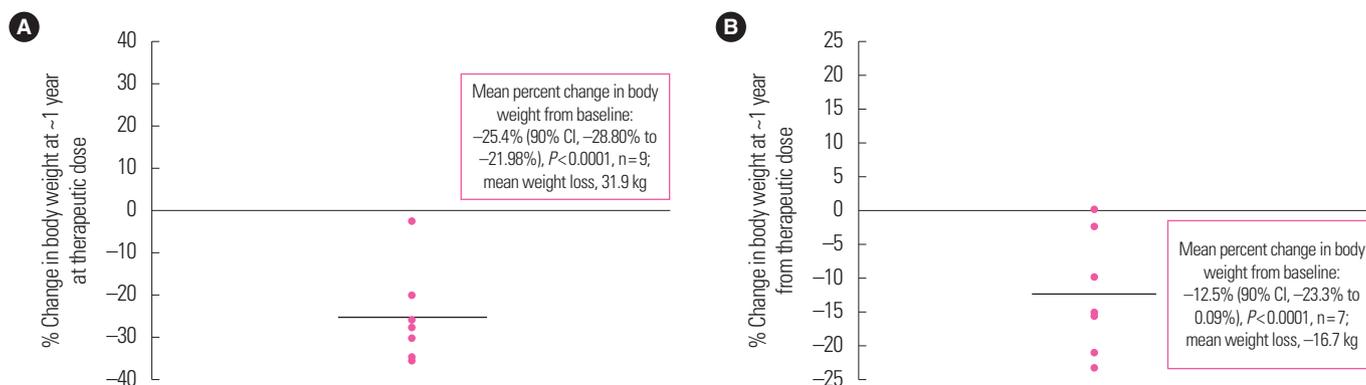


Figure 2. (A) Setmelanotide and pro-opiomelanocortin (POMC) deficiency. Weight loss percentages from baseline for nine participants at week 52 are shown. There were 10 patients enrolled (nine with POMC deficiency and one with proprotein convertase subtilisin/kexin type 1 [PCSK1] deficiency). The patient with PCSK1 deficiency dropped out following the drug withdrawal placebo phase of the clinical trial, when hyperphagia recurred and the patient experienced suicidal ideation. Nine patients completed the trial and of those, eight achieved the primary endpoint ($\geq 10\%$ weight loss). (B) Setmelanotide in leptin receptor (LEPR) deficiency. Weight loss percentages from baseline for seven participants at week 52 are shown. There were 11 patients enrolled. One patient died in an auto accident. Five patients achieved the primary endpoint ($\geq 10\%$ weight loss). Not shown are data from two patients who did not lose at least 5% during the initial open-label period. Data from Clément et al.¹³

endocrinopathies, e.g., adrenocorticotrophic hormone deficiency, hypothyroidism, hypogonadism, hypopigmentation, hypoglycemia, and others. The number of individuals in the United States proposed to have genetic mutations in the melanocortin pathway if we tested widely is estimated to be 12,800,¹⁴ a miniscule fraction of the population with obesity. While they may occur only rarely, these conditions present enormous challenges for health care providers, parents, and patients. Thus, the primary users of setmelanotide are likely to be clinics where children with severe obesity are referred for evaluation. Practitioners must await guidance on adults - when and whom to test. Certainly, a history of early onset severe obesity would be the clinical presentation might stimulate genetic testing.

There will be efforts to identify other patients with other genetic obesity syndromes that might respond to setmelanotide. Setmelanotide is being tested in Bardet-Biedl syndrome and Alström syndrome in a phase 3 trial (NCT03746522), as well as SRC1, SH2B1, and MC4R deficiency, and Smith-Magenis syndrome in a basket Phase 2 trial (NCT03013543). Still, this is unlikely to expand the user base for setmelanotide significantly. Given the global prevalence of obesity, the obvious question is, “Could setmelanotide have a broader indication for weight management?”

The data in non-human primates² and in humans with obesity used as controls³ demonstrate that there is some weight loss efficacy with setmelanotide in those without genetic melanocortin pathway defects. But the chief side effect, tanning, must be considered. That side effect might make the drug undesirable from a patient perspective. Will patients accept tanning if weight loss is robust? This question and other safety considerations could only be answered through the expensive and time-consuming drug development process requiring large patient numbers to establish safety and efficacy. That is not likely to happen and for now, setmelanotide is likely to remain solely in the realm of treatment for those with proven genetic defects in the melanocortin pathway. The search for other indications will continue, however, with attempts to identify genotypes that would be highly responsive to this drug.

SEMAGLUTIDE

Semaglutide is an analog of native glucagon like peptide 1 (GLP-1) and has 94% homology with the peptide sequence. In semaglu-

tide, arginine replaces lysine at position 28, aminoisobutyric acid replaces glycine at position 2 (to resist degradation) and a C-18 fatty acid and lengthy spacer is attached to Lysine (to promote albumen binding) (Fig. 1).¹⁵ While native GLP-1 has a half-life of 1-2 minutes, the half life of semaglutide is 165 hours, allowing it to be dosed subcutaneously once weekly.¹⁵

GLP-1 receptor analogs have pleiotropic effects.¹⁶ There are multiple agents in this class approved for type 2 diabetes, but liraglutide is the only GLP-1 analog approved for weight management. Semaglutide is approved for management of diabetes at doses of 0.5 mg and 1.0 mg weekly and oral semaglutide in doses up to 14 mg is also approved for diabetes. Furthermore semaglutide 0.5 mg and 1.0 mg have been shown to reduce cardiovascular events in persons with type 2 diabetes.¹⁷ In phase 2, semaglutide 0.4 mg daily produced mean weight loss at 52 weeks of -13.8% compared with -7.8% for liraglutide 3.0 mg and -2.3% for placebo.¹⁸ The 0.4 mg daily dose was modeled, and the dose of 2.4 mg weekly was chosen for phase 3.

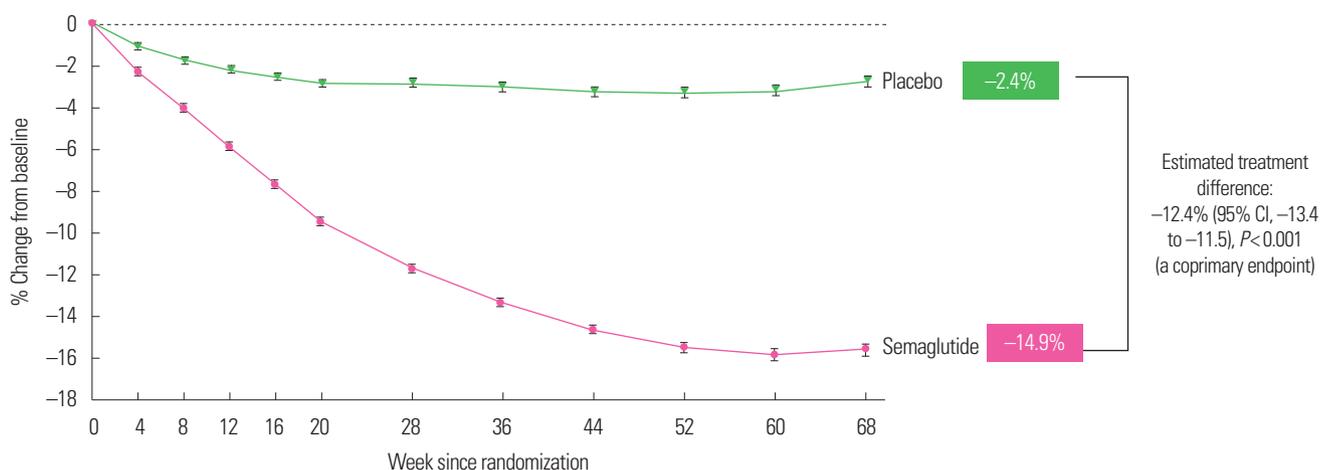
Semaglutide has now been submitted to regulators in Europe and was approved by the U.S. Food and Drug Administration in June 2021. It is generating much excitement and attention about the amount of weight loss it produced in the phase 3 studies. Five phase 3 studies, all called STEP (Semaglutide Treatment Effect in People with obesity) are now completed;¹⁹ four have been published,²⁰⁻²³ and we will discuss the weight loss efficacy and design of those trials, first, and then safety and tolerability. In these studies, a “treatment policy estimand” was used for the primary analysis. This is like an intention-to-treat analysis where all assigned participants are considered, and missing data are accounted for with statistical measures of multiple imputation. Another “trial product estimand” was calculated which considered observations on treatment. This review will report the more conservative “treatment policy estimand” for the discussion of results across trials.

The characteristics of the three STEP trials are shown in Table 1. STEP 116 enrolled 1,961 adults with body mass index (BMI) ≥ 30 kg/m² or BMI ≥ 27 kg/m² with a comorbidity. More than 70% patients had a comorbidity and while none had diabetes, almost 44% had prediabetes. Both placebo and semaglutide 2.4 mg groups received a lifestyle intervention with a 500 kcal/day deficit diet and recommendations to increase physical activity to 150 minutes per week. The trajectory of mean weight loss is shown in Fig.

Table 1. Characteristics of 3 recently published phase 3 studies of semaglutide 2.4 mg weekly for obesity

	STEP 1 (Wilding et al., 2021) ²⁰	STEP 2 (Davies et al., 2021) ²¹	STEP 3 (Wadden et al., 2021) ²²	STEP 4 (Rubino et al., 2021) ²³
Population	1,961 Adults with BMI ≥ 30 kg/m ² or BMI ≥ 27 kg/m ² with ≥ 1 weight-related comorbidity, without diabetes enrolled at 129 sites in 16 countries	1,210 Adults with BMI ≥ 27 kg/m ² with type 2 diabetes enrolled at 149 clinics in 12 countries	611 Adults with BMI ≥ 30 kg/m ² or BMI ≥ 27 kg/m ² with ≥ 1 weight-related comorbidity, without diabetes enrolled at 41 sites in the United States	902 Adults with BMI > 30 kg/m ² or BMI > 27 kg/m ² with > 1 weight-related comorbidity entered 20-week run-in; 806 reached 2.4 mg dose semaglutide and entered randomization; 73 sites in 10 countries
Randomization scheme	Randomized 2:1 to 2.4 mg semaglutide vs. placebo	Randomized 1:1:1 to 2.4 mg semaglutide vs. 1.0 mg semaglutide* vs. placebo	Randomized 2:1 to 2.4 mg semaglutide vs. placebo	At week 20, those who achieved 2.4 mg dose semaglutide were randomized 2:1 to continued 2.4 mg semaglutide vs. placebo
Drug treatment scheme	Pre-filled pens; initial semaglutide dose 0.25 mg subcutaneously once weekly for the first 4 weeks; semaglutide dose increased every 4 weeks to reach 2.4 mg; treatment duration 68 weeks	Pre-filled pens for two injections once weekly; initial semaglutide dose 0.25 mg subcutaneously once weekly for the first 4 weeks; semaglutide dose increased every 4 weeks to reach 2.4 mg; treatment duration 68 weeks	Pre-filled pens; initial semaglutide dose 0.25 mg subcutaneously once weekly for the first 4 weeks; semaglutide dose increased every 4 weeks to reach 2.4 mg; treatment duration 68 weeks	First 20 weeks, open-label treatment with once-weekly subcutaneous semaglutide 0.25 mg, increased every 4 weeks to the maintenance dose of 2.4 mg by week 16, and continued to week 20. Then, randomized to pre-filled pens with placebo or semaglutide 2.4 mg weekly for double-blind therapy
Background treatment	Both groups received lifestyle intervention: 500 kcal/day deficit diet, and increased physical activity to 150 min/wk	All groups received lifestyle intervention: 500 kcal/day deficit diet, and increased physical activity to 150 min/wk	Both groups received low-calorie diet for 8 weeks; followed by intensive behavioral therapy (i.e., 30 counseling visits)	Both groups received lifestyle intervention: 500 kcal/day deficit diet, and increased physical activity to 150 min/wk
Primary end point(s)	Percentage change in body weight and weight reduction of at least 5% at week 68	Percentage change in body weight and weight reduction of at least 5% at week 68	Percentage change in body weight and weight reduction of at least 5% at week 68	Percentage change in body weight from week 20 to week 68
Trial completion rate (%)	93.4	96	92.8	98.0 of randomized
Treatment adherence rate (%)	81.1	87	82.7	92.3 of randomized
Baseline characteristics	Female, 74.1%; white, 75.1%; mean age, 46 years; mean weight, 105.3 kg; mean BMI, 37.9 kg/m ² ; prediabetes, 43.7%; one or more coexisting conditions, 70.5%	Female, 50.9%; white, 62.1%; mean age, 55 years; mean weight, 99.8 kg; mean BMI, 35.7 kg/m ² ; mean HbA1c, 8.1%; biguanide drug use, 91.8%	Female, 81.0%; white, 76.3%; mean age, 46 years; mean weight, 105.9 kg; mean BMI, 38.0 kg/m ² ; one or more comorbidity at screening, 74.1%	Female, 79%; white, 83.7%; mean age, 46 years; mean weight, 107.2 kg; mean BMI, 38.4 kg/m ² ; 1–3 comorbidities, 64.8%
Mean change in body weight at week 68 (%)	-14.9	-9.6*	-16.0	-7.9 from week 20
Semaglutide 2.4 mg	-2.4	-3.4	-5.7	-17.4 from week 0
Placebo				+6.9 from week 20
				-5.9 from week 0
Proportion achieving > 5% weight loss at week 68 (%)				
Semaglutide 2.4 mg	86.4	68.8	86.6	88.7 from week 0
Placebo	31.5	28.5	47.6	46.6 from week 0
Proportion reporting serious adverse events (%)				
Semaglutide 2.4 mg	9.8	9.9	9.1	7.7
Placebo	6.4	9.2	2.9	5.6
Proportion discontinuing because of adverse events				
Semaglutide	7.0	6.2	5.9	2.4
Placebo	3.1	3.5	2.9	2.2

*Body weight change at week 68 was -6.99% for semaglutide 1.0 mg weekly. STEP, Semaglutide Treatment Effect in People with obesity; BMI, body mass index; HbA1c, glycosylated hemoglobin.



No. at risk	
Placebo	655 649 641 619 615 603 592 571 554 549 540 577
Semaglutide	1,306 1,290 1,281 1,262 1,252 1,248 1,232 1,228 1,207 1,203 1,190 1,212

Figure 3. Observed mean weight loss with semaglutide 2.4 mg weekly compared to placebo over 68 weeks of treatment. Error bars are standard error. Line graph shows participants in the full analysis set from randomization to last contact with trial site. CI, confidence interval. Adapted from Wilding et al. *N Engl J Med* 2021;384:989-1002 with permission.²⁰

3, where plateau of weight loss appears to occur at approximately week 60 for semaglutide-treated participants and much earlier for placebo-treated participants. Fig. 4 shows the average weight loss for semaglutide and placebo for the four STEP trials discussed here. The ability for trial participants to achieve $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, or $\geq 20\%$ weight loss is shown in Fig. 5A. In STEP 1, when the semaglutide-treated group is compared to the placebo-treated group, there were greater improvements in cardiometabolic risk factors and a greater increase in participant-reported physical functioning.

STEP 2²¹ enrolled 1,210 persons with type 2 diabetes and randomized them 1:1:1 to semaglutide 2.4 mg weekly, semaglutide 1.0 mg weekly or placebo. The weight loss trajectory for semaglutide 2.4 mg and 1.0 mg was like that in STEP 1, except the mean weight losses for semaglutide 2.4 mg in STEP 2 were lesser than those in STEP 1 at the same dose, albeit greater than semaglutide 1.0 mg or placebo (Fig. 4). One of the coprimary endpoints was percent weight loss at 68 weeks for semaglutide 2.4 mg versus placebo. Mean change in body weight was -9.6% at week 68 for semaglutide 2.4 mg and -3.4% for placebo, with an estimated treatment difference of 6.21% (90% CI, $7.28-5.15$; $P < 0.0001$). For the semaglutide 1.0 mg treatment group mean weight loss at week 68 was -7.0% at week 68. Fig. 4, which displays categorical weight losses with sema-

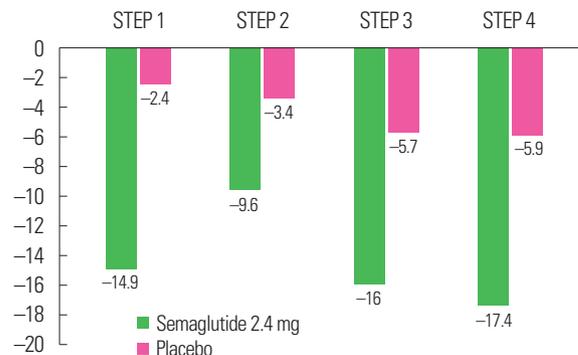


Figure 4. Mean weight loss from baseline to week 68 for semaglutide or placebo in Semaglutide Treatment Effect in People with obesity (STEP) trials 1–4. Results are shown for treatment policy estimand. This is like an intention-to-treat analysis where all assigned participants are considered, and missing data are accounted for with statistical measures of multiple imputation for the primary estimand. STEP 1: modified from Wilding et al. *N Engl J Med* 2021;384:989-1002.²⁰ STEP 2: modified from Davies et al. *Lancet* 2021;397:971-84.²¹ STEP 3: modified from: Wadden et al. *JAMA* 2021;325:1403-13.²² STEP 4: modified from: Rubino D et al. *JAMA* 2021; 325:1414-25.²³

glutide 2.4 mg in each study, illustrates that weight losses with semaglutide 2.4 mg were less in STEP 2 compared to STEP 1. How might we explain the differences in weight loss with semaglutide 2.4 mg in STEP 1 and STEP 2? The background lifestyle intervention follows the same protocol in both studies, but the populations differ; STEP 2 consists of persons with type 2 diabetes. Although this is not a head-to-head comparison, the differences in the two

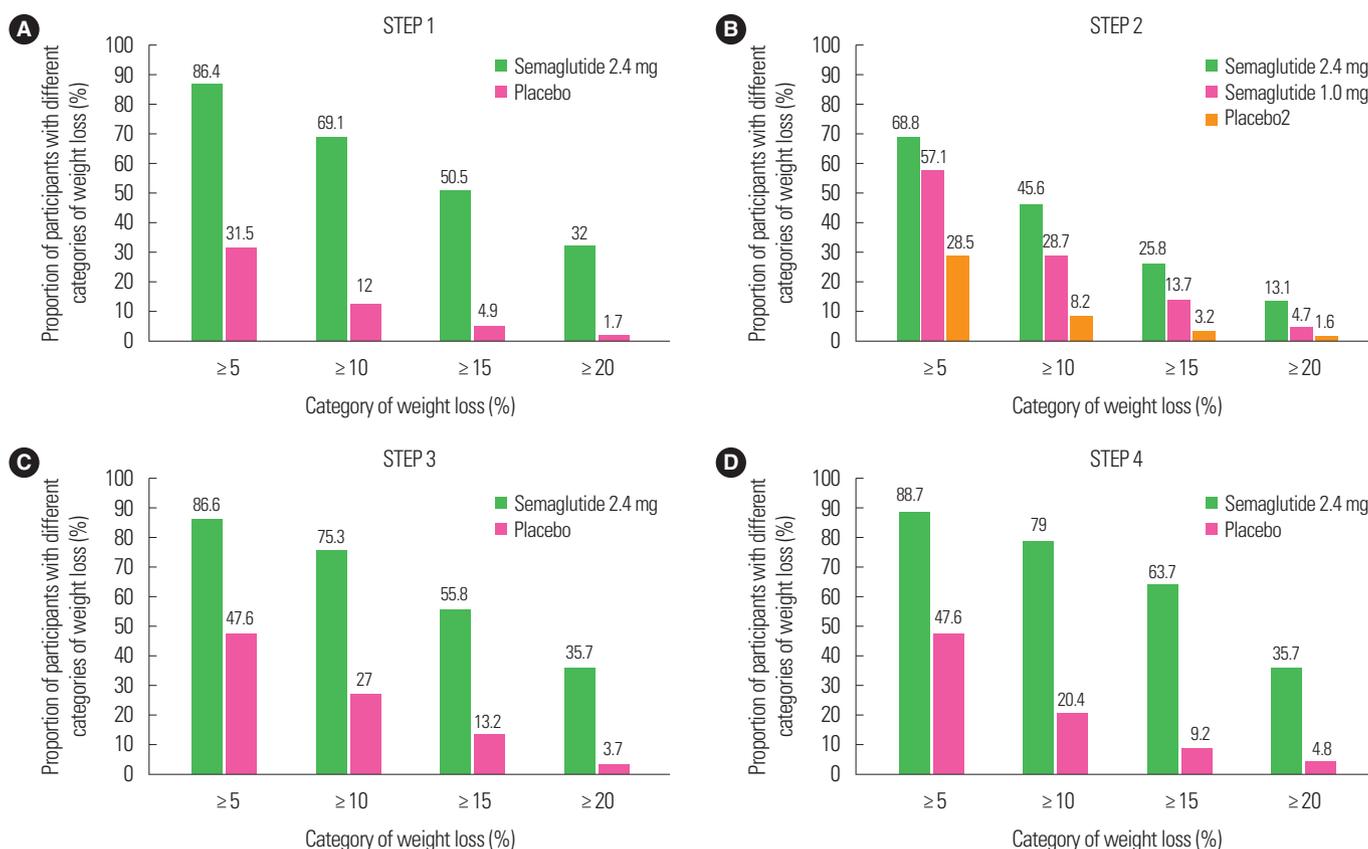


Figure 5. Categorical weight loss for semaglutide and placebo in Semaglutide Treatment Effect in People with obesity (STEP) trials 1–4. Note that in STEP 2, the achievement of higher categories of weight loss was less in the semaglutide 2.4 mg treated participants, compared to STEP 1 and STEP 3. Note the greater achievement in weight loss categories in the placebo group in STEP 3. In STEP 3 in the presence of a more intensive behavioral intervention resulted in greater efficacy in the placebo group but in the semaglutide treatment group the categorical weight losses were less than in STEP 1 and STEP 3. (A) STEP 1: adapted from Wilding et al. *N Engl J Med* 2021;384:989-1002 with permission.²⁰ (B) STEP 2: modified from Davies et al. *Lancet* 2021;397:971-84.²¹ (C) STEP 3: modified from Wadden et al. *JAMA* 2021;325:1403-13.²² (D) STEP 4: modified from Rubino D et al. *JAMA* 2021;325:1414-25.²³

populations are notable. One explanation that might explain the lesser weight loss in the STEP 2 population would be that there was not a personalized approach to hypoglycemia prevention. There was biguanide use in 91.8% of enrolled persons in STEP 2. The protocol called for a 50% dose reduction of biguanide medication at study start. It is important to reduce or stop insulin secretagogues when patients enter negative energy balance through dietary restriction, not only to avoid symptomatic hypoglycemia but because even mild hypoglycemia stimulates food intake, thwarting dietary restriction efforts. Was a 50% dose reduction sufficient? In Look AHEAD (Action for Health in Diabetes) study, a lifestyle intervention that produced 9.6% weight loss at 52 weeks, there was a personalized protocol for stopping or reducing diabetes medications, whereby persons with acceptable diabetes control at baseline had medications stopped at the start of the dietary intervention.²⁴

Granted, symptomatic hypoglycemia was reported in only 5.7%, 5.5% and 3.0% in the semaglutide 2.4 mg, 1.0 mg, and placebo groups, respectively.

In STEP 3,²² enrolled participants received and intensive behavioral intervention which consisted of an initial 8-week low-calorie diet (1,000–1,200 kcal/day) provided as meal replacements. Then, this highly structured diet was transitioned to a diet with 1,200–1,800 kcal/day of conventional food for the remainder of the 68 weeks. Physical activity began with 100 minutes of physical activity per week and increased by 25 minutes every 4 weeks to ultimately 200 minutes per week. The mean weight loss in this study with placebo reflects the greater intensity of the lifestyle intervention; placebo treated participants lost on average –5.7% at week 68. Although not head-to-head comparisons, this is greater than the mean weight loss of –2.4% in a similar population in STEP 1 (Fig. 4) who re-

ceived a similar intervention. The more intensive lifestyle approach is also reflected in the categorical analysis of weight loss in Fig. 5. The placebo treatment along with more intensive lifestyle intervention (ILI) was more likely to produce $\geq 5\%$, $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$ in STEP 3 than in STEP 1. However, the mean weight loss in the semaglutide 2.4 mg treatment group was -16.0% ; this is greater than STEP 1 (-14.9%), but not by much. The estimated treatment differences in mean weight loss at 68 weeks between placebo and semaglutide 2.4 mg were -12.4% in STEP 1 and -10.3% in STEP 3. This is interesting and may reflect the powerful impact of appetite as a mediator of response.

STEP 4²³ was designed to show the long-term impact (48 weeks) of continuing semaglutide after reaching the 2.4 mg dose at 20 weeks. All participants received semaglutide open label during a dose escalation period over 16 weeks and then the dose was continued for 4 weeks. Of the 902 individuals who enrolled, 806 (92%) reached the 2.4 mg dose and were randomized to placebo or continued semaglutide 2.4 mg. Those who continued semaglutide after randomization continued to lose weight reaching a plateau at week 60 to week 68 and ultimately achieving -17.4% weight loss from entry. In comparison, those on placebo gradually regained weight (Fig. 4). The weight loss with semaglutide 2.4 mg was associated with improvements in cardiometabolic risk factors in this study.

The safety and tolerability across STEP 1, 2, 3, and 4 demonstrated the predicted findings with this drug and class. In all studies, gastrointestinal disorders (typically nausea, diarrhea, vomiting, and constipation) were the most frequently reported events and occurred in more participants receiving semaglutide than those receiving placebo. Most gastrointestinal events were mild-to-moderate in severity, were transient, and resolved without permanent discontinuation of the regimen. Gallbladder-related disorders (mostly cholelithiasis) were reported more often in STEP 1 and STEP 3. In STEP 1,²⁰ gallbladder disorders occurred in 2.6% and 1.2% of participants in the semaglutide and placebo groups, respectively. In STEP 3,²² gallbladder-related disorders (mainly cholelithiasis) were reported in 4.9% of semaglutide treated participants and 1.5% of those on placebo. Acute pancreatitis also occurred in small numbers in semaglutide-treated patients (3 in STEP 1,²⁰ 1 in STEP 2,²¹ 0 in STEP 3,²² and 1 in STEP 4²³). Overall, there were no unexpected safety findings in the reports of the four trials.

There is one safety issue that deserves discussion and that is the quality of the weight loss with semaglutide 2.4 mg. The aim of weight management should be normalization of body composition, not just reducing weight. In STEP 1,²⁰ dual emission X-ray absorptiometry (DEXA) data were reported on a subset of participants ($n = 140$). In that substudy,²⁰ there was mean loss of -8.36 kg of total body fat mass and -5.26 kg of total body lean mass in the semaglutide-treated participants. In the placebo group the mean loss was -1.37 kg fat mass and -1.83 kg lean mass. The usual proportion lean loss in total weight loss is 25%.²⁵ It is important to reduce excess abnormal fat mass, without adversely affecting muscle and bone. Look AHEAD, a study comparing ILI to diabetes support and education (DSE) in persons with type 2 diabetes is informative. As expected with weight loss, ILI led to greater reductions in fat mass than DSE, but also greater loss of lean body mass during active weight loss and when ILI participants regained weight, they regained mainly fat mass.²⁶ In addition, there were greater decreases in bone density for both total hip (-1.4% vs. -0.4% , $P < 0.001$) and femoral neck (-1.5% vs. -0.8% ; $P < 0.009$) in ILI vs DSE at 1 year.²⁶ The relationship to hip fracture in Look AHEAD is uncertain. The risk for hip fracture was elevated in ILI compared to DSE (hazard ratio, 1.78; 95% CI, 0.98–3.25; $P = 0.06$), but this finding was not statistically significant.²⁶ It cannot be determined with accuracy from DEXA what the loss of muscle mass or bone mass might be. But this issue deserves further study with more advanced techniques to measure body composition changes. Meanwhile, we will need to reinforce the importance of weight bearing exercise and strength training in patients who are losing weight with semaglutide and use caution in patients with sarcopenic obesity.

There is excitement around semaglutide 2.4 mg being used for an antiobesity indication. To understand this excitement, one must consider it in the context of efficacy of other obesity medications. The current medications indicated for chronic weight management in the United States or Europe (orlistat, phentermine-topiramate, naltrexone-bupropion and liraglutide 3.0 mg) generally produce on average 4%–7% greater weight loss than placebo.²⁷ Semaglutide appears to produce twice that. Furthermore, semaglutide is already in use at a dose of 1.0 mg weekly for diabetes and other drugs of the GLP-1 analog class are widely used. Thus, there is already a degree of comfort with the safety profile of the drug. Since nausea and

vomiting are the main tolerability issues, a dose escalation period is required for all drugs in this class. The chief safety issues with drugs of this class are the rare occurrence of pancreatitis and a prohibition of use in patients with a personal or family history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Semaglutide 1.0 mg weekly has been shown to reduce cardiovascular events in persons with diabetes and other GLP-1 receptor agonists have also demonstrated cardioprotection.²⁸ The confidence in semaglutide for obesity will likely increase if the ongoing SELECT study²⁸ demonstrates that semaglutide 2.4 mg weekly is associated with reduction of cardiovascular events in persons with overweight and obesity and who have pre-existing cardiovascular disease.

The average weight loss of 15% means a real prospect for clinical improvement for patients with obesity-related diseases. Health care providers will have a tool to produce meaningful weight loss for most patients. For years, obesity medicine specialists have promoted the benefits of modest weight loss (5% to 10%), in part because that is all that can be achieved in most patients using older therapeutic approaches, excepting bariatric surgery. Modest weight loss (5% to 10%) is associated with improvement in glycemia, cardiovascular risk factors like blood pressure and lipids and improvements in how patients feel and function.²⁹ However, greater amounts of weight loss (> 10%) produce continued improvement in these outcomes. Further, 10% or more weight loss is needed for improvement in symptoms of obstructive sleep apnea and for improvements in Non-Alcoholic Steatotic Hepatitis (NASH) Activity Scores in patients with NASH.²⁹ For diabetes remission, 15% weight loss is needed; and for reduction in cardiovascular events, 15% or more weight loss is probably needed. An interesting phenomenon in weight reduction is that different amounts of weight loss produce different effects on different tissues.²⁹ Visceral and ectopic fat stores are mobilized preferentially,³⁰ and this may account for the metabolic improvements with more modest weight loss, while greater weight loss is required for other conditions.

FUTURE DIRECTIONS IN OBESITY PHARMACOTHERAPY

Semaglutide has brought us a long way in showing how to affect energy balance by affecting appetite.³¹ And setmelanotide is a great

example of personalizing obesity therapy, albeit with a challenge of identifying a broader population that might benefit from the drug, beyond the ultra-rare genetic and syndromic obesities. Tirzepatide, now in phase 3, and bimagrumab, in phase 2, are illustrative of what is likely to make an impact on clinical practice.

TIRZEPATIDE

Tirzepatide, a single-molecule with a dual-action, given as once weekly injection, targets both the GLP-1 receptor and the glucose-insulin peptide (GIP) receptor (see Fig. 1 for the chemical structure). In a phase 2 trial it produced mean weight loss in the range of up to 12% at 26 weeks at a dose of 15 mg/day and had potent effects on glycemia.³² Tirzepatide is being evaluated for obesity in a Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1), a phase 3 randomized double-blind, placebo-controlled trial with 2,400 participants who have obesity and comorbidity, but not diabetes.³³ The drug is also being evaluated for an indication for type 2 diabetes in a series of studies, SURPASS.³⁴ The results of one of the phase 3 studies has been released publicly,³⁵ but not yet published in a peer-reviewed format. In that study, the highest dose (15 mg) of tirzepatide produced 13.1% weight loss over 40 weeks in persons with type 2 diabetes.³⁵ The 5 mg dose of tirzepatide was associated with 8.5% weight loss in that study.³⁵ The safety and efficacy of tirzepatide in persons with obesity will be watched closely. The combined targeting of GLP-1 and GIP is interesting, and it will be important to understand the mechanistic pathway by which tirzepatide produces weight loss—appetite, lipolysis and energy expenditure effects should all be investigated.

BIMAGRUMAB

Bimagrumab is a human monoclonal antibody that binds to the activin type II receptor to block natural ligands that negatively regulate skeletal muscle growth.^{36,37} Bimagrumab was tested in a double-blind, placebo-controlled, 48-week, phase 2 randomized clinical trial³⁸ in adults with type 2 diabetes and BMI 28–40 kg/m². Bimagrumab was dosed at 10 mg/kg up to 1,200 mg in 5% dextrose solution and compared to placebo every 4 weeks for 48 weeks; both

groups received diet and exercise counseling. One of the strengths of the study was the body composition methodology with both DEXA and magnetic resonance imaging being used. At week 48, the changes for bimagrumab vs placebo were as follows: fat mass, -20.5% (-7.5 kg; 80% CI, -8.3 to -6.6 kg) vs. -0.5% (-0.18 kg; 80% CI, -0.99 to 0.63 kg) ($P < 0.001$); lean mass, 3.6% (1.70 kg; 80% CI, 1.1 to 2.3 kg) vs. -0.8% (-0.4 kg; 80% CI, -1.0 to 0.1 kg) ($P < 0.001$).³⁸ Thus rather loss of both lean and fat with weight loss with the typical ratio of 25:75,²⁹ bimagrumab was associated with loss of fat mass and gain in lean mass.³⁸ Safety will need to be evaluated further; there were cases of elevations of pancreas and liver enzymes with bimagrumab compared to placebo in this small study.³⁸

There are other drugs in the pipeline that show various degrees of promise and the reader is referred to recent reviews for addition information on individual drugs.^{39,40} Rather than singling out individual agents, a few comments on the path forward are in order. We need more drugs that work through appetite, like semaglutide does in targeting the GLP-1 receptors in the areas of the brain that affect appetite. Not all patients respond to semaglutide with enough weight loss; not all patients can tolerate semaglutide; additional medications are needed. We need more medications that take a personalized approach, like setmelanotide. With better phenotyping and better genotyping, we should be better able to develop targeted therapies for individuals based on the personal profile of the patient with obesity. We need to consider other mechanisms of promoting negative energy balance other than reducing food intake through appetite effects. One positive aspect of setmelanotide is that it increases energy expenditure, an important quality in the face of the metabolic adaptation found with the weight reduced state. It appears to do this without cardiovascular effects of increased blood pressure and pulse. Tirzepatide offers the intriguing possibility that its effectiveness in weight loss may be more than just food intake. Increasing lipolysis is a viable hypothetical mechanism for one of this drug's mechanism of action. Bimagumab gives the first evidence that we might succeed in targeting improved quality of weight loss for our patients. We might be able to preserve or even increase lean mass, especially muscle and bone, in our patients as they lose weight.

CONCLUSIONS

The goal of weight loss is health improvement. Obesity medicine specialists want to reduce the excess abnormal adipose tissue that is driving ill health. At the same time, we want to achieve healthy weight reduction with preservation of muscle and bone. Can we achieve these goals pharmacologically? Of course, it would be better to live in a world where healthy eating and active living were the default behaviors and where those behaviors were reinforced in a world without undue emotional and financial stress. All of us need to work toward creating that world, but we also need to explore better pharmacologic options for weight management for those who need to lose weight as a pathway to better health. The next generation of antiobesity medications is emerging, bringing the possibility of sufficient weight loss sufficient to produce meaningful health improvement in many patients with obesity. But we need to continue the efforts to identify other medications and to shift our focus to more than just weight loss. We need to start thinking about improved quality of weight loss.

The clinical practice of obesity medicine has been a struggle for patients and providers. At last, we are getting some powerful tools to help our patients. The focus can shift from treating the comorbidity with antihypertensives, with lipid lowering drugs, with glycemia management drugs. We can finally focus on the root cause of these comorbidities—obesity—because we can finally do something about it.

CONFLICTS OF INTEREST

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