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Evolving Approaches for Pharmacological Therapy of Obesity

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Abstract

Obesity is a global health concern. Progress in understanding the physiology of obesity and weight reduction has provided new drug targets. Development and testing of new antiobesity medications (AOMs) has the potential to quickly expand options for treatment. In this review, we briefly summarize the physiology of obesity and weight reduction, as well as medications currently approved for weight management. We highlight the increasing use of incretin and nutrient-stimulated hormone-based therapies. We conclude with an overview of AOMs progressing through the pipeline and discuss their implications for the rapidly evolving field of obesity management.

INTRODUCTION

Obesity is defined by abnormal or excessive accumulation of body fat that presents a risk to health (1) and is commonly categorized as a body mass index (BMI) $\geq$30 kg/m^2. Obesity is a global health concern. When defined using the identified BMI threshold, it affects more than one billion people worldwide (2), with projections showing that approximately two billion people will have the disease by 2035 (3). Obesity is associated with over 200 comorbidities that impact every organ system (4). Annual medical care costs for adults with obesity are double those of individuals with normal weight (5).

The cornerstone of obesity treatment is lifestyle intervention, which includes diet, physical activity, and behavior therapy. Lifestyle intervention is indicated for adults with a BMI $\geq$25 kg/m^2 with at least one obesity-related comorbidity and those with a BMI $\geq$30 kg/m^2 (6). For individuals with a BMI $\geq$27 kg/m^2 with at least one obesity-related comorbidity or those with a BMI $\geq$30 kg/m^2, antiobesity medications (AOMs) can be considered when provided as an adjunct to a reduced-calorie diet and increased physical activity. The advent of highly efficacious AOMs is transforming the landscape of obesity treatment. In this review, we provide an overview of the etiology of obesity and physiology of the weight-reduced state, which has served as a road map for drug discovery. We highlight the therapeutic strategies developed to improve obesity treatment, including the growing use of nutrient-stimulated hormone-based (NUSH) medications. Lastly, we summarize AOMs in the pipeline and implications of the changing landscape of medications for obesity treatment.

ETIOLOGY OF OBESITY

Obesity results from a complex interaction of factors that include a biological predisposition toward the disease in the setting of an obesogenic environment, shaped by lifestyle, psychological, socioeconomic, and cultural influences (7, 8). Navigating the obesogenic environment is challenging, as inexpensive, high-calorie foods are readily available and extensively promoted, while a sedentary lifestyle has become the prevailing norm (9). In a given environment, there is considerable diversity in BMI and adiposity, with biological factors playing a crucial role in accounting for these discrepancies.

Over 30 gut hormones, neuropeptides, and neurotransmitters are associated with appetite and satiation (10), with the list continually expanding with new discoveries. These hormones are part of a complex process that contributes to the homeostatic and hedonic regulation of energy balance and weight. Circulating hormones influence eating behaviors on an acute (meal-to-meal) and chronic basis. Some of the most widely investigated hormones include those that act as appetite stimulators, such as ghrelin, and satiation signals, such as glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), amylin, glucagon, and peptide YY (PYY) (11, 12). Identification of these hormones has formed a foundation of drug targets for second-generation AOMs and several agents in the development pipeline.

PHYSIOLOGY OF THE WEIGHT-REDUCED STATE

Weight loss occurs when energy expenditure exceeds energy intake, resulting in a caloric deficit. This deficit can be accomplished by decreasing food consumption, increasing physical activity, and preferably, by combining both. With weight reduction, 75% of the loss is typically derived from fat and 25% from fat-free mass (i.e., Quarter Fat-Free Mass Rule), though the proportions may be moderated by factors such as age, caloric restriction level, diet composition, sex, baseline adiposity, and physical activity (13). When the body requires more energy than the available caloric intake, it

uses stored sources to release energy and meet physiologic needs. During the first days of weight loss, glycogen stores are used. Once these are depleted, weight loss predominately occurs from the shrinking of white adipose tissue via reduction in the size of adipocytes and to a lesser extent from reserves of lean and muscle mass (14).

Weight reduction achieved through behavioral treatment precipitates a complex interplay of physiological and metabolic processes to defend an elevated fat mass set point. Weight loss induced through behavioral treatments produces short- (<6 months) and longer-term (≥1 year) increases in circulating levels of adipose, pancreatic, and gastrointestinally derived hormones involved in homeostatic and hedonic feeding (15). These changes in hormones include increases in fasting and postprandial levels of ghrelin and declines in most satiety hormones (15, 16). Counterregulatory physiological changes encourage compensatory eating that contributes to weight regain and limits the amount of weight lost through behavioral interventions. In addition, reductions in energy expenditure and metabolic adaption that occur with weight loss can contribute to weight regain (17). To maintain weight loss in an obesogenic environment, people must exert high persistent effort and constant vigilance to fight these compensatory mechanisms. Understanding hormonal changes that occur with weight loss has generated numerous targets for AOMs. Second-generation AOMs produce weight losses that are larger and more sustained than behavioral obesity treatment (18). These AOMs appear to temper the powerful counter-regulatory mechanisms that occur in a weight-reduced state.

HISTORY OF ANTIOBESITY MEDICATIONS

Numerous attempts have been made to create effective AOMs that produce sustainable weight loss with minimal adverse effects. Unfortunately, many medications have failed to progress in clinical development or were withdrawn due to adverse effects that were not fully recognized until after approval. At least 25 AOMs have been withdrawn postmarketing, with the majority being centrally acting monoamine neurotransmitters (19). For example, fenfluramine, a serotonergic receptor activator, was withdrawn due to cardiac valvopathy and pulmonary hypertension (19). Rimonabant, a selective endocannabinoid (CB1) receptor antagonist, was withdrawn due to concerns over psychiatric side effects, including increased risk of depression and suicidal ideation and behavior. Sibutramine, a serotonin and noradrenaline reuptake inhibitor, was withdrawn due to cardiovascular toxicity. In 2020, lorcaserin, a selective serotonin 2C receptor agonist, was voluntarily withdrawn due to concerns about cancer risks (20), though it was not clear whether this was causal or related to early cancer detection due to weight loss. Given the serious adverse effects that have been reported with withdrawn AOMs, including cardiovascular events, suicidality, risk of abuse and dependence, and cancer, the US Food and Drug Administration (FDA) and European Medicines Agency have highlighted the importance of cardiovascular and central nervous system (CNS) safety (21, 22).

MEDICATIONS CURRENTLY APPROVED FOR OBESITY MANAGEMENT

Medications approved by the FDA for weight management can be divided into two classes (23): those approved for short-term use, usually interpreted as less than 12 weeks, or for chronic weight management, interpreted as indefinite use, in a manner similar to drugs provided for hypertension, type 2 diabetes (T2D), lipid disorders, and other chronic diseases. The FDA requires extensive testing, of at least one year, to demonstrate a medication's safety and efficacy for chronic weight management.

MEDICATIONS APPROVED FOR SHORT-TERM USE

Four noradrenergic sympathomimetic agents—phentermine, benzphetamine, diethylpropion, and phendimetrazine—are FDA approved for short-term weight management. These medications reduce appetite and food intake by stimulating the release of norepinephrine or inhibiting its reuptake into nerve terminals (24). Phentermine, approved in 1959, is one of the least expensive AOMs (<$20 per month for generic) in the United States and the most widely used, accounting for 75% of AOM prescriptions (25, 26). Phentermine is a scheduled medication due to the potential for abuse, though studies have not supported this concern (27). A meta-analysis revealed that, when prescribed as 15 to 30 mg per day, the drug produced a mean total weight loss of 6.3 kg, which was 3.6 kg greater than observed with placebo (28). Side effects of phentermine include tachycardia, elevated blood pressure, dryness of the mouth, headache, and insomnia. Phentermine is frequently prescribed off-label in clinical practice for longer durations, though few studies have systematically investigated the drug's long-term efficacy and safety as a monotherapy.

MEDICATIONS APPROVED FOR CHRONIC WEIGHT MANAGEMENT

Seven AOMs are currently approved in this category. **Table 1** briefly describes, in chronological order of their approval (with the exception of setmelanotide), each drug's dosing, mechanisms of action, efficacy at approximately one year, and side effects. Greater attention is devoted to semaglutide 2.4 mg and tirzepatide 10–15 mg than to the earlier, less effective AOMs.

Medications Approved Before GLP-1 Agents

Orlistat (29–31), phentermine-topiramate [extended release (ER)] (32, 33), and naltrexone-bupropion (slow release) (34, 35) were all approved from 1999 to 2014, and their mechanisms of action, safety, efficacy, and side effects have been well described (36, 37). A meta-analysis revealed that orlistat and naltrexone-bupropion, compared with placebo, increased mean weight loss by only 2.6 kg and 5.0 kg, respectively (38), amounts that generally do not meet patients' weight loss expectations (39). In contrast, phentermine-topiramate ER (15/92 mg) increased weight loss by 8.8 kg, compared with placebo, making it the most effective older AOM (38). The medication's use, however, has been limited by side effects described in **Table 1**, as well as by an increased risk of oral clefts in infants born to women who took the drug during pregnancy (32).

Liraglutide 3.0 mg

Liraglutide is a glucagon-like peptide 1 receptor agonist (GLP-1RA) that was first approved at 1.2 and 1.8 mg per day for T2D (40, 41). The drug is an incretin-based medication, taken daily by subcutaneous injection, that has 97% homology with native GLP-1, which is released by L cells of the small intestine and colon in response to nutrient (meal) intake. Native GLP-1 stimulates insulin secretion and inhibits glucagon release in a glucose-dependent manner to control postprandial blood sugar. It also reduces energy intake by slowing gastric emptying and increasing satiety signaling in the hindbrain and hypothalamus (40). The 3.0-mg-per-day dose of liraglutide, approved for overweight/obesity in persons without T2D (42), increases mean weight loss by 5.3 kg compared with placebo (38, 42, 43). The drug is associated with multiple gastrointestinal side effects (**Table 1**) and an increased risk of gallbladder-related complications. It should not be used by individuals with a personal or family history of medullary thyroid cancer (42).

Semaglutide 2.4 mg

Like liraglutide, semaglutide 2.4 mg is a GLP-1RA, but with a half-life of 180 h, allowing once-weekly subcutaneous injection (44, 45), as originally approved at lower doses for T2D (40). The

Table 1 Current pharmacological agents approved in the United States for chronic weight management

Name (brand name), year approved	Dosing	Mechanisms of action	Trial/study	Weight loss	Select common side effects
Orlistat (Xenical), 1999	One 120-mg capsule at each meal containing fat	Gastrointestinal lipase inhibitor	Sjöström et al. (31)	10.2%	Oily spotting, flatus with discharge, fecal urgency, fatty or oily stool, oily evacuation, increased defecation, fecal incontinence
Phentermine-topiramate (Qsymia), 2012	Start at 3.75-mg/23-mg capsule daily for 14 days Increase to 7.5 mg/46 mg daily Take in the morning	Phentermine: sympathomimetic amine Topiramate: unknown	EQUIP (33)	10.9% with 15 mg/92 mg 5.1% with 3.75 mg/23 mg	Dizziness, dysgeusia, paresthesia, insomnia, constipation, dry mouth
Naltrexone/bupropion (Contrave), 2014	Start at 1 tablet (8 mg naltrexone/90 mg bupropion) daily in the morning for 1 week Increase to 1 tablet in the morning and 1 tablet in the evening for week 2 Increase to 2 tablets in the morning and 1 tablet in the evening for week 3 For week 4 and onward, take 2 tablets in the morning and 2 tablets in the evening	Naltrexone: opioid receptor antagonist Bupropion: norepinephrine and dopamine reuptake inhibitor	COR-I (34)	6.1% with 32 mg naltrexone plus 360 mg bupropion 5.0% with 16 mg naltrexone plus 360 mg bupropion	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea
Liraglutide (Saxenda), 2014	Start at 0.6 mg daily for 1 week Increase the dose by 0.6 mg every week until max dose of 3 mg is reached	GLP-1 receptor agonist	SCALE (43)	8.0%	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase
Semaglutide (Wegovy), 2021	Start at 0.25 mg once weekly for 4 weeks Every 4 weeks, increase the dose until max dose of 2.4 mg is reached 2.4 mg and 1.7 mg weekly are recommended maintenance doses	GLP-1 receptor agonist	STEP-1 (44)	14.9%	Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with T2D, flatulence, gastroenteritis, gastroesophageal reflux disease, nasopharyngitis
Tirzepatide (Zepound), 2023	Start at 2.5 mg once weekly Increase to 5 mg weekly after 4 weeks If needed, increase by 2.5 mg with a max dose of 15 mg weekly	GIP/GLP-1 receptor coagonist	SURMOUNT-1 (56)	15.0% with 5 mg 19.5% with 10 mg 20.9% with 15 mg	Nausea, diarrhea, decreased appetite, constipation, vomiting, dyspepsia, abdominal pain
Setmelanotide (Imcivree), 2020	For individuals ≥12 years old, start at 2 mg daily for 2 weeks then titrate to 3 mg daily For individuals ages 6–12 years old, start at 1 mg daily for 2 weeks, then titrate to 2 mg daily with a recommended target of 3 mg daily	MC4R agonist	Clément et al. (61)	25.6% in participants with POMC deficiency 12.5% in participants with LEPR deficiency	Skin hyperpigmentation, injection site reaction, nausea, headache, diarrhea, abdominal pain, vomiting, depression, spontaneous penile erection

Abbreviations: GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin; T2D, type 2 diabetes.

medication is introduced over 16 weeks to limit gastrointestinal side effects (45) (**Table 1**). The safety and efficacy of semaglutide 2.4 mg were established in four 68-week, placebo-controlled Phase III trials referred to as semaglutide treatment effect in people (STEP) with obesity. STEP trials 1, 3, and 4 enrolled participants with overweight/obesity but not T2D; STEP 2 included persons with overweight/obesity and T2D (46). STEP 1 found that semaglutide, combined with monthly, brief lifestyle counseling, reduced baseline body weight by 14.9% versus 2.4% with placebo (12.5 percentage point difference) (44). Reductions in baseline weight of ≥10% and ≥15% were achieved by 69% and 51% of semaglutide participants, respectively, values roughly 1.5 to 3 times greater than with earlier AOMs. One-third of semaglutide participants lost 20% or more. STEP 2 found that patients with T2D lost 9.6% of baseline weight, approximately one-third less than observed in STEP 1 (47). A similar attenuation in efficacy has been reported in patients with T2D treated by other AOMs (48).

STEP 3 reported that combining semaglutide with 30 concurrent sessions of intensive behavioral therapy and an initial 1,000–1,200-kcal-per-day meal-replacement diet reduced mean body weight by 16.0%, only slightly more than the loss in STEP 1 with less frequent counseling (49). Additional studies have suggested that semaglutide's reduction of hunger and food cravings, coupled with enhancement of satiation (50), decreases the need for traditional behavioral strategies for achieving energy restriction (e.g., daily calorie counting) (51).

STEP 4 revealed the importance of participants remaining on semaglutide to facilitate continued weight loss and to prevent weight regain (52). After achieving a mean 10.6% reduction in baseline body weight on a 20-week semaglutide run-in, participants assigned to remain on the drug for another 48 weeks lost an additional 7.9% of randomization weight versus a gain of 6.9% in those switched to placebo. STEP 5 demonstrated excellent maintenance of weight loss in patients who continued on semaglutide for two years (53), whereas a one-year follow-up of participants in STEP 1 revealed marked weight regain following medication discontinuation (54). Collectively, these data clearly indicate that obesity can be managed with chronic pharmacotherapy.

Health improvements in the STEP trials included clinically meaningful reductions in systolic and diastolic blood pressure, HbA1c, triglycerides, C-reactive protein, and impairments in physical function. The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial further showed, in patients with a history of a prior cardiovascular event, that semaglutide compared with placebo reduced the risk of major adverse cardiovascular events by 20%, the first such demonstration in a randomized controlled trial (RCT) of an obesity therapy (55). Adverse events and safety concerns with semaglutide are similar to those described with liraglutide (45) (**Table 1**).

Tirzepatide 10–15 mg

Tirzepatide combines in a single molecule both GIP and GLP-1 receptor agonism, which is delivered via a once-weekly subcutaneous injection (56, 57). The safety and efficacy of tirzepatide for chronic weight management, which was first approved for T2D, were established by four pivotal Phase III RCTs, SURMOUNT-1–4, which paralleled the design of STEP 1–4 (56, 58–60). All SURMOUNT trials were 72 weeks to allow gradual introduction of the highest dose of tirzepatide over 20 weeks to mitigate gastrointestinal adverse events (**Table 1**).

SURMOUNT-1 observed mean reductions in baseline body weight of 19.5% and 20.9% with tirzepatide doses of 10 and 15 mg per day, respectively, compared with a 3.1% reduction for placebo. With the 15-mg-per-day dose, reductions in baseline weight of ≥10%, ≥15%, ≥20%, and ≥25% were achieved by 84%, 71%, 57%, and 36% of participants, respectively. The mechanisms by which the combination of GIP/GLP-1 receptor agonism increases weight loss over GLP-1 alone are not well understood.

SURMOUNT-2 found, similar to STEP 2, that participants with T2D and overweight/obesity lost about one-third less weight than participants in SURMOUNT-1 (without T2D) (58). In contrast to STEP 3, however, SURMOUNT-3 observed that sequentially combining intensive lifestyle intervention and tirzepatide appeared to increase maximum weight loss with the medication (59). A 12-week lifestyle intervention was first used, without drug, to induce a mean loss of 6.9% in successful program completers. Participants subsequently assigned to tirzepatide (maximally tolerated dose of 10–15 mg per day) lost an additional 18.4% of randomization weight at week 72, compared with a gain of 2.5% for those assigned to placebo. When examined from the start of the lead-in program, participants assigned to tirzepatide achieved a cumulative 24.3% reduction in baseline body weight, compared with 4.5% for those who received placebo. These findings support combining intensive lifestyle intervention and medication sequentially rather than concurrently as in STEP 3, at least in terms of weight loss outcomes.

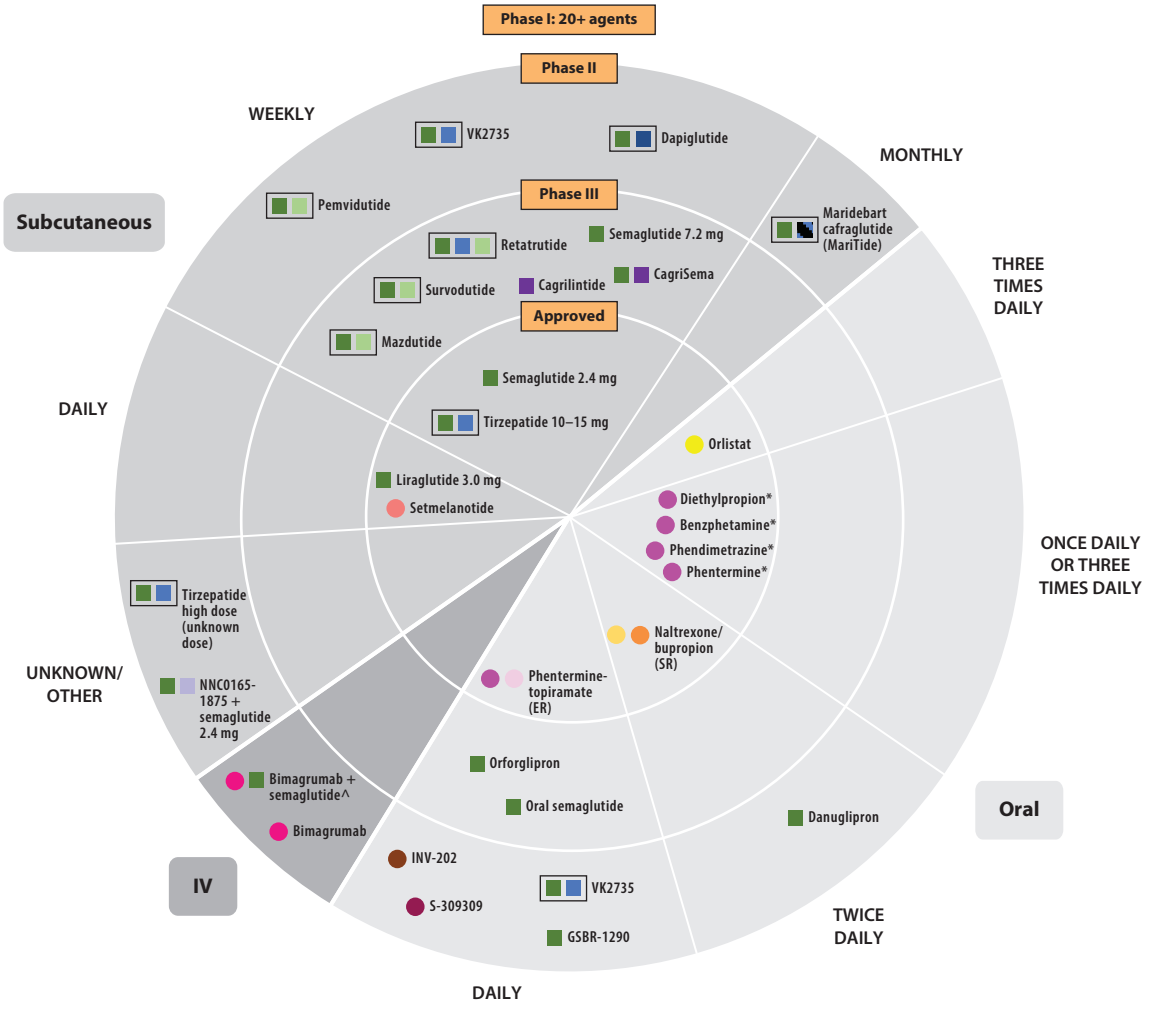
SURMOUNT-4 confirmed the importance of long-term medication adherence for maintaining weight loss and preventing weight regain (60). Following a mean 20.9% reduction in baseline weight after a 36-week lead-in on tirzepatide, participants assigned to remain on medication for 52 more weeks lost an additional 5.5% of randomization weight; those switched to placebo gained 14.0%. Tirzepatide's safety and adverse event profiles (**Table 1**) are similar to semaglutide's, as are improvements in cardiometabolic risk factors and physical function. A cardiovascular outcomes trial of tirzepatide is currently underway (SURMOUNT-MMO; NCT05556512).

Setmelanotide

Setmelanotide is a melanocortin 4 receptor (MC4R) agonist that was FDA approved in 2020 for individuals 6 years of age and older for the treatment of obesity due to proopiomelanocortin (POMC), proprotein convertase/subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency (61, 62). A supplemental indication was added for Bardet-Biedl syndrome in 2022. Setmelanotide may help to re-establish MC4R pathway activity to reduce food intake and increase energy expenditure. In Phase III trials of participants aged 6 years and above with obesity and genetically confirmed or suspected POMC deficiency or LEPR deficiency, percent change from baseline to 1 year was 25.6% and 12.5%, respectively (61). In participants with Bardet-Biedl or Alström syndrome, initial weight loss was 5.2% (63). Adverse effects have included disturbance in sexual arousal, depression and suicidal ideation, and skin pigmentation and darkening of pre-existing nevi (61, 63) (**Table 1**).

NOVEL PHARMACOTHERAPIES IN DEVELOPMENT FOR OBESITY TREATMENT

The continued search for efficacious treatments that are well tolerated has resulted in a plethora of new AOMs in the drug development pipeline, which could rapidly increase the options available for obesity in the near future. The approvals of the incretin-based medications, liraglutide, semaglutide, and tirzepatide, have laid the groundwork for new agents. Based on the recognition of the multiple mechanisms of action of these agents and other targets within appetite-related enteroendocrine and endocrine pancreatic hormonal pathways, incretin-based medications have now been referred to within the wider umbrella term of NUSH medications (64). Novel NUSH medications and other emerging classes of agents have been developed as monotherapies or coformulated or combined with GLP-1RA as dual or triple agonists/antagonists. AOMs in development can be categorized by several differentiating characteristics highlighted in **Figure 1**, including NUSH versus non-NUSH, mechanism of action, number of targets (mono, dual, triple), mode of delivery (subcutaneous, oral, intravenous), frequency of administration (e.g., one to three times a day, daily, weekly), and whether medications are combinations of different



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Select medications in the AOM development pipeline. Medications are categorized by several differentiating characteristics, including NUSH versus non-NUSH, mechanism of action, number of targets (mono, dual, triple), mode of delivery (subcutaneous, oral, intravenous), frequency of administration (e.g., one to three times a day, daily, weekly), and whether medications are combinations of different molecules or unimolecular peptides targeting one or more pathways. Abbreviations: AOM, antiobesity medication; ER, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP, glucagon-like peptide; IV, intravenous; NUSH, nutrient-stimulated hormone-based; PYY, peptide YY; SR, slow release.

molecules or unimolecular agents that target one or more pathways. Below we highlight select results from Phase I–III trials with an emphasis on select molecules in Phase III trials. Many agents do not make it through the pipeline because of issues with efficacy and safety, as well commercial decisions due to the potential costs and rewards of developing these medications.

High-Dose GLP-1RA and High-Dose GLP-1/GIP Dual Receptor Agonist

GLP-1RAs have demonstrated a dose-response relationship with weight loss, but with a dose-dependent increase in gastrointestinal side effects and acute elevations in heart rate (65). The maximum dose of semaglutide did not demonstrate a clear plateau for weight loss, suggesting that higher doses may produce additional therapeutic benefits (66). Subcutaneous semaglutide is currently being tested in the Phase III A Research Study to See How Semaglutide Helps People with Excess Weight, Lose Weight (STEP UP) trial at 7.2 mg once weekly (NCT05646706). High-dose subcutaneous tirzepatide is being tested in people with T2D and obesity in a Phase II trial (NCT06037252).

Monotherapy: NUSH-Based AOMs

Multiple NUSH-based monotherapies are in development.

Oral GLP-1RA. Patients may be unwilling or unable to use subcutaneous injections; thus, oral formulations of GLP-1RA have been developed. Oral peptide drug delivery has been limited by low permeability of the gastrointestinal tract and rapid enzymatic and pH-induced degradation in the stomach (67). However, several strategies have been developed and tested to address these challenges. At least four oral GLP-1RAs are in the pipeline.

Semaglutide was identified as a peptide candidate for oral delivery due to its low molecular weight, long half-life, and high potency (68). Oral semaglutide was coformulated with sodium *N*-[8-(2-hydroxybenzol) amino caprylate], which promotes absorption across the gastric mucosa. Stable steady-state concentrations were achieved with once-daily dosing due to the long half-life of semaglutide. In the Phase III Research Study to Investigate How Well Semaglutide Tablets Taken Once Daily Work in People Who Are Overweight or Living with Obesity (OASIS-1) trial, from baseline to week 68, oral semaglutide 50 mg reduced weight by 15.1% versus 2.4% with placebo (69) (**Figure 2**). Mild to moderate gastrointestinal events were reported in 80% of participants assigned to oral semaglutide compared to 46% of those randomized to placebo.

Orforglipron is an oral small-molecule, nonpeptide GLP-1RA dosed once daily (70). In a 36-week Phase II trial of adults with obesity, orforglipron produced a mean loss of 9.4% to 14.7% versus 2.3% for placebo (**Figure 2**). The most common adverse events were gastrointestinal related, were of mild to moderate severity, and led to discontinuation in 10–17% of participants. This medication is being tested in the Phase III A Study of Orforglipron (LY3502970) in Adult Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN) clinical trial development program (NCT05869903).

Danuglipron is an oral small GLP-1RA. In a Phase IIb trial, danuglipron was tested as a twice-daily medication (71). Weight losses ranged from 8% to 13% at 32 weeks. However, the drug

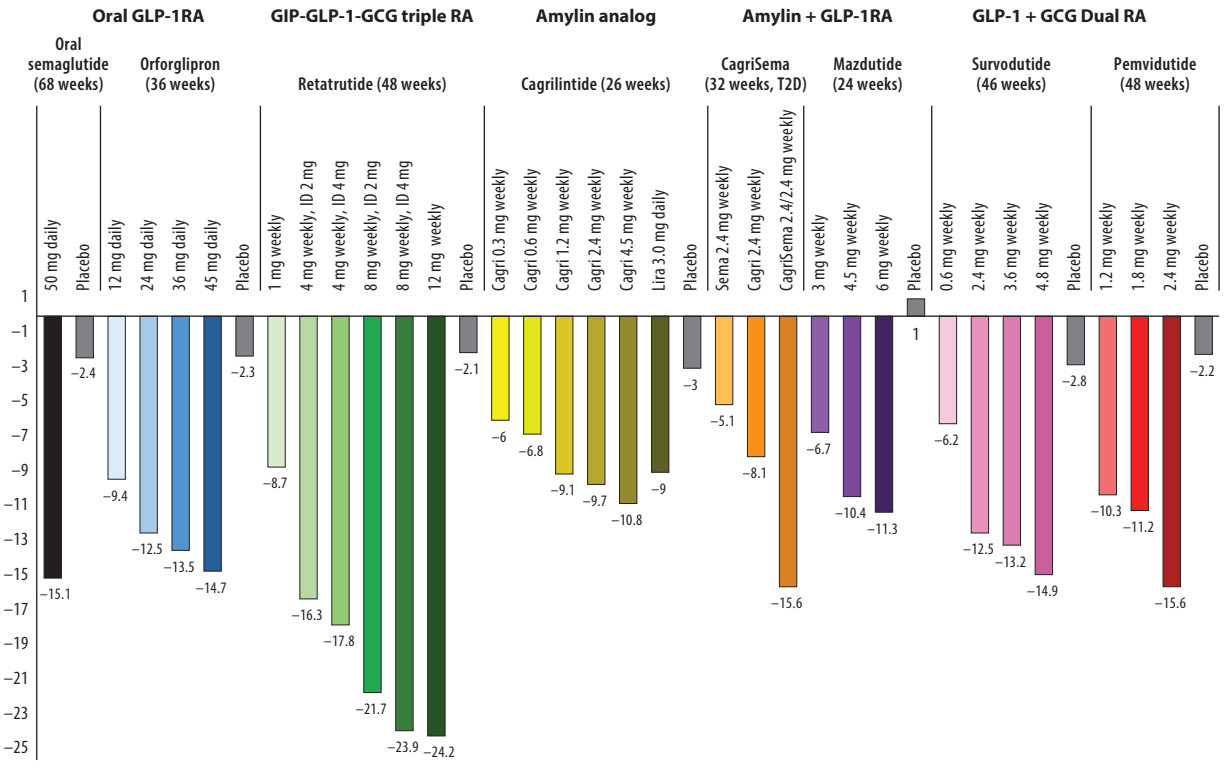


Figure 2

Percent initial weight loss from select Phase II and III trials with results at or after 24 weeks from AOMs in the development pipeline (69, 70, 79, 89, 94–96, 109). Oral semaglutide was the only Phase III trial. All other results were from Phase II trials. The CagriSema trial was among participants with T2D. Abbreviations: AOM, antiobesity medication; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GLP-1RA, glucagon-like peptide 1 receptor agonist; ID, initial dose; RA, receptor agonist; T2D, type 2 diabetes.

was not advanced to Phase III in the twice-daily form due to discontinuation rates greater than 50% across all doses, compared to 40% with placebo. A once-daily version is in development with alterations to the drug release mechanism. GSBR-1290 and CT-996 are once-daily GLP-1RAs that are also being tested.

Amylin receptor agonist. Amylin is a pancreatic β cell hormone costored and coreleased with insulin in response to nutrient stimuli (72). It is part of the calcitonin family and slows gastric emptying, suppresses glucagon secretion, and acts as a satiety signal postprandially. Native human amylin can form amyloid fibers that self-aggregate (73). Pramlintide contains proline substitutions of part of the molecule (Pro^{25}, Pro^{28}, Pro^{29}), which created a stable, soluble, nonaggregating, and nonadhesive agent that demonstrated similar benefits to native amylin (74). Pramlintide was FDA approved in 2005 as a subcutaneous injection for type 1 and 2 diabetes as an adjunct to preprandial insulin therapy. It was investigated alone and in combination with recombinant leptin for obesity (75). In participants with obesity without T2D, pramlintide 240 and 360 μg twice or three times daily via subcutaneous injection 15 min before meals produced a 6.0% to 7.9% initial weight loss versus a 1.1% loss for placebo at one year (76). The necessity for three daily injections and the limited weight loss above placebo led to the discontinuation of further development (77).

Amylin analogs are being tested as a monotherapy, as well as an add-on to GLP-1RA-based therapy (CagriSema, which is detailed below). Cagrilintide, a long-acting acylated amylin analog, contains the proline solutions found in pramlintide and additional substitutions to increase potency, solubility, and duration of action by binding to albumin (78). In a 26-week Phase II trial of people with overweight or obesity, cagrilintide (0.3–4.5 mg per week) decreased weight by a mean of 6.0% to 10.8% relative to 3.0% with placebo (79) (**Figure 2**). Additional amylin analogs under investigation in Phase I trials include "amylin agonist long acting" from Eli Lilly, petrelintide (ZP8396), and AZD6234.

Monotherapy: Non-NUSH

Several non-NUSH-based AOMs are in Phase I or II of development.

Cannabinoid-1 receptor inverse agonist. Cannabinoid-1 receptor (CB1R) inverse agonists, also known as CB1R blockers, have significant effects on metabolism and weight. First-generation CB1R inverse agonists (e.g., rimonabant) were associated with worsening anxiety, depression, and suicidal ideation, especially in patients with a history of depression, which was attributed to the medication's penetration and accumulation in the CNS (80). This association led to their withdrawal. It was originally thought that CNS penetration was necessary to reduce appetite and weight. However, studies have shown that peripherally restricted CB1Rs produced positive effects (81). INV-202 is a CB1R blocker that is a small-molecule, oral, once-daily medication that has limited CNS penetration and was tested in a Phase Ib trial in adults with metabolic syndrome (82). INV-202 is being tested in a Phase II trial of patients with obesity and metabolic syndrome (NCT05891834).

Mitochondrial uncouplers. Mitochondrial uncouplers such as 2,4-dinitrophenol (DNP) have long been known to promote both weight loss and heat generation (83). The weight loss is mediated by an effect of chemical uncouplers to increase the rate at which mitochondria oxidize substrates. However, in the presence of uncouplers, mitochondria use energy derived from substrate oxidation to generate heat rather than ATP. The increased heat generation is associated with an increased risk of hyperthermia, a serious adverse effect that led the FDA to remove DNP from the market in 1938. Shulman and colleagues (84) demonstrated that the risk of hyperthermia could be substantially mitigated by a twofold strategy of targeting the uncoupler to the liver and minimizing peak drug levels (C_{max}). Following this strategy, HU6 was designed as a prodrug that is metabolized in the liver to produce DNP. A Phase IIa clinical trial demonstrated that HU6 decreased mean liver fat content by 35.6% and body weight by 2.75 kg (85). Because HU6 is activated in the liver, it offers hope of mitigating DNP's serious safety issues (e.g., hyperthermia) by minimizing extrahepatic pharmacology. As expected, this prodrug strategy sacrificed weight-loss efficacy—that is, 2.75 kg in response to 61 days of HU6 therapy as compared to 1.5 kg per week for DNP (85). Notwithstanding the modest weight loss, HU6 offers the potential to induce clinically significant improvements in obesity-associated metabolic abnormalities, including decreased hepatic steatosis and decreased HbA1c.

Other agents. Several other types of molecules are being investigated, with some showing potential and others being dropped from the pipeline. Glucagon helps to regulate lipid metabolism, energy expenditure, and satiety, supporting its role in obesity treatment. HM15136 is a long-acting glucagon analog that, compared to native glucagon, has an extended half-life, improved solubility, and subcutaneous bioavailability and has been tested in a Phase I trial for overweight and obesity (86). Additional molecules that target glucagon are being developed as dual coagonists with GLP-1RA as outlined below. Growth differentiation factor 15 (GDF-15) is a cysteine knot protein that is

elevated as a result of cellular stress (87). Due to its effects on appetite and weight, it has generated interest as a target for obesity treatment. While some molecules are progressing (e.g., CIN-109 and CIN-209 as dual GLP-1RAs), some trials have noted only modest effects on body weight and are no longer in the pipeline (e.g., LY3463251, LA-GFD 15). Monoacylglycerol acyltransferase 2 (MGAT2) is an enzyme responsible for triglyceride resynthesis in the small intestine. S-309309 is a MGAT2 inhibitor that is being tested as an oral capsule in a Phase II trial (NCT05925114).

Dual Therapy: NUSH/NUSH and NUSH + NUSH

There are redundancies in appetite regulation and energy balance systems. Thus, the added and possibly synergistic effects of combination medications are being investigated. Dual therapies involve unimolecular agents that target more than one pathway, similar to tirzepatide (i.e., NUSH/NUSH), or combinations of separate molecules, such as phentermine-topiramate. Treatment of multiple pathways may yield better results than strategies to modify one pathway alone and may be more tolerable.

GLP-1RA + amylin receptor agonist. In a Phase Ib trial in which subcutaneous cagrilintide 4.5 mg was combined with subcutaneous semaglutide 2.4 mg per week (i.e., CagriSema), mean weight loss was 15.4% at 20 weeks (88). In a Phase II trial of participants with overweight/obesity and T2D, CagriSema induced a mean 15.6% reduction in baseline weight at 32 weeks (89) (**Figure 2**). The safety profile was similar to GLP-1RAs and amylin analogs with mild or moderate gastrointestinal effects that mostly had an onset during dose escalation. Cagrilintide with and without semaglutide is being tested in the Phase III A Research Study to See How Well CagriSema Helps People with Excess Body Weight Lose Weight (REDEFINE) trial (NCT05567796).

GLP-1/glucagon dual receptor agonist. GLP-1RA is being paired with other hormones belonging to the proglucagon family, including glucagon. Glucagon is secreted by α cells of the pancreatic islets and stimulates glycogenolysis and gluconeogenesis, yet also decreases food intake, and increases satiety and potentially energy expenditure. Since glucagon increases blood glucose, antagonism rather than agonism was pursued for T2D treatment (90). However, use of glucagon antagonists was limited due to findings of increased plasma alanine aminotransferase, low-density lipoprotein cholesterol, blood pressure, body weight, and hepatic steatosis, likely due to blockade of glucagon's lipolytic properties in the liver (90). Glucagon agonism was investigated despite its glucose-mobilizing effects due to the potential catabolic and thermogenic nature of the peptide. Studies demonstrated that simultaneous activation of GLP-1 and glucagon possessed dose-dependent synergism to enhance food intake while maintaining glycemic control (91). The native peptide oxyntomodulin is a weak agonist of GLP-1/glucagon receptors. Optimization of oxyntomodulin and unimolecular GLP-1 and glucagon receptor agonists (RAs) has been pursued for obesity treatment (92, 93). Two GLP-1/glucagon dual RAs are in Phase III trials: survodutide and mazdutide (94, 95). Pemvidutide has Phase II trial results (96). It is possible that there will be increased efficacy of these agents (**Figure 2**) compared to GLP-1RA monotherapy due, in part, to elevated energy expenditure triggered by the activation of glucagon receptors in the liver and adipose tissue (97). This activation promotes processes such as gluconeogenesis, glycogenolysis, and lipolysis. Another glucagon/GLP-1 receptor coagonist (NN1177) resulted in dose-dependent clinically relevant weight loss in Phase I trials. However, safety concerns such as increased heart rate, markers of inflammation, aspartate and alanine aminotransferase, and impaired glucose tolerance halted its development (98).

Other dual therapies. Several other combinations of NUSH dual agents are in the pipeline. Several agents that, like tirzepatide, are GLP-1/GIP dual RAs are being developed, including

CT-388 and subcutaneous weekly and oral daily versions of VK2735. In opposition to the GIP agonism of tirzepatide, AMG133 (Maridebart cafraglutide, or MariTide) is a GIP antagonist. MariTide is an antibody-peptide conjugate bispecific molecule engineered by conjugating a fully human monoclonal antihuman GIP RA antibody of two GLP-1 analog agonist peptides using amino acid linkers that is being investigated at monthly dosing (99). GIP promotes adipogenesis; circulating GIP is elevated with obesity, and genetic ablation of GIP receptors led to a decrease in body weight in diet-induced obese mice (100). MariTide is being tested in a Phase II trial (NCT05669599).

PYY is a gut hormone, part of the NPY family, which includes peptides that exhibit a significant degree of amino acid sequence homology (101). PYY is cosecreted with GLP-1 and oxyntomodulin in response to nutrient ingestion and acts as a satiety hormone (101, 102). PYY analogs have been developed that modify the peptide sequence of secondary structures to increase the half-life and enhance physiological activity. Long-acting PYY (PYY1875) was tested in a Phase II trial combined with semaglutide (NCT04969939). GLP-2 is a trophic hormone cosecreted with GLP-1, which helps to maintain intestinal epithelial morphology and function (103). Dapiglutide is a long-acting, dual GLP-1R/GLP-2RA that is administered subcutaneously once weekly. Dapiglutide is being tested in Phase II trials for overweight/obesity [Dapiglutide for the Treatment of Obesity (DREAM) trial; NCT05788601]. Dual amylin and calcitonin receptor agonists (DACRAs) have high potency with both amylin and calcitonin receptors to increase food intake (104). "DACRA QW II" is being investigated in Phase I trials, although there is concern that calcitonin might increase cancer incidence, thus calling into question the long-term safety of calcitonin agonists.

Dual Therapy: NUSH + Non-NUSH

Dual therapies can also consist of NUSH and non-NUSH medications that simultaneously target multiple pathways. One such example is GLP-1RA plus an activin receptor.

Previously, drugs that target pathways in metabolic tissues—such as adipocytes, liver, and skeletal muscle—showed potential in preclinical studies but did not reach clinical development. Bimagrumab is a monoclonal antibody designed as an inhibitor of activin type II receptors (ACVR2s) (105). In a 48-week Phase II RCT conducted in patients with T2D (106), bimagrumab and placebo reduced baseline fat mass by 20.5% and 0.5%, respectively. Bimagrumab was associated with a 3.6% increase in baseline lean mass, as compared with a reduction of 0.8% with placebo. The authors hypothesized that the drug-induced increase in lean mass reflected an increase in skeletal muscle mass—possibly mediated by blockade of the action of endogenous myostatin. An increase in muscle mass could mediate beneficial metabolic effects, as well as increase capacity for physical activity. Adverse events were observed in drug-treated patients, including elevation of serum lipase levels in 14% of participants and pancreatitis in 2.7%. In addition, inactivating mutations in ACVR2s have been observed in several type of cancers (107), raising the possibility that chronic treatment with bimagrumab might be associated with increased progression of cancer. Furthermore, by inhibiting the effects of activin on follicle-stimulating hormone production, blockade of ACVR2 is predicted to exert adverse effects on reproductive function (108). Bimagrumab is being tested alone and in combination with the GLP-1RA semaglutide in a Phase II trial to investigate whether this combination can help to preserve or even increase muscle mass in the presence of reductions in body weight and fat mass (NCT05616013).

Triple Therapy Combinations

Triple therapies combine actions of three gut hormones, with the rationale that this will enhance weight loss. Head-to-head trials will be needed to examine the relative benefits of mono, dual, and triple therapies.

Retatrutide is a unimolecular, triple GIP, GLP-1, and glucagon RA (109). Each impacts food intake and satiety through different mechanisms. In a Phase II trial, at 48 weeks the mean reduction in baseline body weight in the retatrutide groups was 24.2% (at the highest dose, **Figure 2**), compared with 2.1% for placebo (109). Adverse events were higher with larger doses and were lower with a more gradual dose titration. The discontinuation rates were 6% to 16% among those who received retatrutide and 0% in those on placebo. Like other medications in this class, the most frequently reported adverse events were gastrointestinal, occurred during dose escalation, and were mild to moderate in severity. The medication is currently being tested in a set of Phase III studies [e.g., A Study of Retatrutide (LY3437943) in Participants Who Have Obesity or Overweight (TRIUMPH)].

FUTURE PERSPECTIVES

The field of obesity is undergoing a paradigm shift. With the advent of second-generation AOMs and a robust pipeline of new medications, enthusiasm is high about the potential to improve the lives of persons with obesity. Several strategies are being developed, including increasing doses of approved medications and novel mono and combination therapies. Use of combination therapies may help to expand the therapeutic range and minimize the risk of side effects.

Several factors characterize medications on the horizon, including their mechanisms of action, number of targets, mode of delivery, frequency of administration, and whether the medications are combinations of different molecules or unimolecular peptides. Most medications on the horizon are NUSH, unimolecular agents that are delivered subcutaneously. However, several other potentially promising types of drugs are in the pipeline. As more data emerge, short- and long-term efficacy (both for weight reduction and amelioration of specific obesity-related complications), tolerability and safety, and cost and cost-effectiveness will be important differentiating factors among medications. Studies are needed to examine predictors of heterogeneity of responses and adverse effects. Knowledge of the efficacy of improvements in obesity-related complications will also benefit from research examining weight loss–dependent and weight loss–independent effects. Algorithms and guidance will be needed to help practitioners navigate clinical decision making, including how to select a medication for a particular patient, when and how often to monitor for response, when to stop a medication, strategies for switching drugs, and how to optimize medication adherence and thus long-term improvements in body weight and health.

While the focus has been on weight loss efficacy of AOMs, the field is shifting attention to the quality of weight loss. The ideal obesity treatment would minimize the proportion of weight loss from fat-free mass relative to total weight loss. Studies have consistently shown improvements in physical functioning with second-generation AOMs. However, there is a dearth of research on the effects of AOMs on the quantity and quality of lean mass lost and of patient factors (e.g., age, gender, activity level) that may affect these outcomes.

Intensive lifestyle modification, characterized during the first six months by 14 or more sessions of individual or group treatment with a trained interventionist, has long been considered the cornerstone of weight management (9). As noted previously, semaglutide's and tirzepatide's effectiveness in reducing appetite and energy intake have decreased the need for lifestyle modification in achieving these goals (51). Further study is now required to determine the content and frequency of lifestyle counseling required to achieve optimal changes in body composition, health, and quality of life in persons treated with the new AOMs. Three recommendations appear warranted at this time (51). First, patients are encouraged to engage in regular physical activity, including $\geq$150 min per week of aerobic activity (e.g., brisk walking) and 2 days per week of strength training (110, 111). Such activity improves cardiovascular health independent of its effects on body weight and could

spare the loss of lean body mass during rapid weight loss with AOMs. Second, lean mass may also be preserved by patients' consuming daily at least 0.8 kg of protein per kilogram of body weight, with a minimum goal of 60 g per day (112). Additional dietary targets include consuming more fruits and vegetables, maintaining adequate hydration, and avoiding highly processed foods, including those high in fat and sugar. The latter efforts may help mitigate the previously described gastrointestinal side effects of AOMs (51). Third, as advised by the FDA, health-care professionals should monitor patients for the emergence of depression or suicidal ideation or behavior. Persons with severe obesity are known to be at high risk for both depression and anxiety (113, 114), independent of receiving an AOM, and should be referred for psychiatric care when needed (51).

Despite the remarkable achievements and promise of AOMs, there are numerous barriers. Only approximately 2% of individuals who are eligible for AOMs receive them (115). Several factors contribute to this underutilization, the first of which is cost. GoodRx lists the following prices for one month of treatment with the following GLP-1RAs: $1,388 for Saxenda (liraglutide), $1,388 for Wegovy (semaglutide), and $1,092 for Zepbound (tirzepatide). The cost of the medications is exacerbated by the fact that many insurers, including Medicare, do not cover the use of AOMs. The drugs are expensive to manufacture, and construction of new manufacturing plants costs over a billion dollars per plant. Thus, it seems unlikely that manufacturing capabilities will increase sufficiently to fully meet the demand for these drugs in the near future. Thus, high demand and prices, combined with limited reimbursement, will continue to adversely affect patient access and health equity.

Small-molecule GLP-1RAs hold the promise of addressing issues related to price and availability. For example, orforglipron has been reported to provide comparable weight loss efficacy as injectable GLP-1RAs (70). Such small molecules are likely to be simpler and less expensive to manufacture as compared to biologics such as liraglutide, semaglutide, and tirzepatide. In Lilly's fourth quarter (2023) investor call, the company announced that it is investing to ramp up manufacturing capacity for small-molecule GLP-1RAs while they are still in clinical development and prior to regulatory approval. If and when small-molecule GLP-1RAs receive regulatory approval, their availability could substantially decrease the cost and increase patients' access to these highly effective agents. Such developments are critical to improving access to weight management in socioeconomically disadvantaged populations in which rates of obesity—and its pernicious health complications—are extremely high.

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