



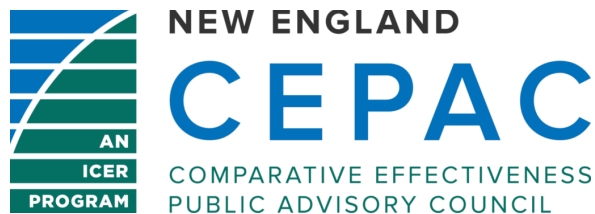
Medications for Obesity Management: Effectiveness and Value

Draft Evidence Report

July 13, 2022

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Prepared for



We identified errors in the economic model due to versioning issues. We have republished the draft Evidence Report without those errors. The updated base-case cost-effectiveness findings for bupropion/naltrexone are lower than previously reported.

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None of the above authors disclosed any conflicts of interest defined as more than \$10,000 in health care company stock or more than \$5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

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Steven J. Atlas served as the lead author for the Report. Molly Beinfeld led the systematic review and authorship of the comparative clinical effectiveness section of this Report in collaboration with Victoria Lancaster and Emily Nhan. Kibum Kim developed the cost-effectiveness model and authored the corresponding sections of the Report with assistance from Daniel R. Touchette, Pei-Wen Lien, and Kanya Shah. Development of the cost-effectiveness model was also assisted by Jessica Benitez-Burke and Lauren Lee. Ashton Moradi provided consultation on the cost-effectiveness analyses and developed the budget impact model. Francesca Beaudoin, David M. Rind, and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Laura Cianciolo, Monica Frederick, and Foluso Agboola for their contributions to this Report.

About ICER

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The findings contained within this Report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this Report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER Reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER’s researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft Evidence Report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:

https://icer.org/wp-content/uploads/2022/03/ICER_Obesity_Stakeholder-List_030322.pdf

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List of Acronyms and Abbreviations Used in this Report

A1C	Glycated hemoglobin
ACC	American College of Cardiology
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
dL	Deciliter
evLY	Equal value life year
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulintropic polypeptide
HRQoL	Health-related quality of life
IBT	Intensive behavioral therapy
IDS-SR	Inventory of Depressive Symptomatology Self-Report
IWQOL	Impact of Weight on Quality of Life
kg	Kilogram
LDL	Low density lipoprotein
m	Meters
MCS	Mental component summary
mg	Milligram
mmHg	Millimeter of mercury
mmol/L	Millimoles per liter
NMA	Network meta-analysis
PCS	Physical component summary
PHQ-9	Patient Health Questionnaire
QALY	Quality-adjusted life year
SBP	Systolic blood pressure
US	United States
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

Obesity is a common chronic disease that increases the risk of other conditions such as diabetes mellitus, cancer, and heart disease as well as death.^{1,2} Individuals with overweight and obesity also face considerable social stigma that can have both direct (e.g., mental health, wellbeing) and indirect consequences (e.g., engagement with health care providers).³ Body mass index (BMI, weight in kilograms/height in meters²) is commonly used to assess for obesity because it is easy to measure and correlates with body fat measurements.^{4,5} In 2015, the number of adults in the United States (US) with overweight or obesity was estimated to be 79 million and 70 million, respectively.^{6,7} The prevalence of obesity varies among racial and ethnic groups, being higher for Hispanic adults and highest among non-Hispanic Black women.^{8,9} The direct medical costs attributable to obesity are staggering, estimated to be \$260 billion in the US in 2016.¹⁰ Given the high prevalence of obesity and its many adverse clinical and cost consequences, cost-effective treatments for this chronic condition are imperative.

Interest in medications to reduce weight and improve health in individuals with obesity has increased due to more non-surgical alternatives and data suggesting that newer medications have an acceptable safety profile and may be more effective in promoting weight loss. Limitations of medications for weight loss include side effects that lead to patient discontinuation, and weight regain when stopped. Under a chronic disease framework, clinical experts concluded that long-term anti-obesity medication use would likely be needed, particularly to prevent complications of obesity such as heart disease. This Report reviews four medications approved by the US Food and Drug Administration (FDA): semaglutide (Wegovy®, Novo Nordisk, June 2021), liraglutide (Saxenda®, Novo Nordisk, 2014), phentermine/topiramate (Qysmia®, Vivus, 2012), and bupropion/naltrexone (Contrave®, Currax Pharmaceuticals, 2014). Semaglutide and liraglutide are glucagon-like peptide-1 (GLP-1) receptor agonists that are also approved for diabetes mellitus and given by subcutaneous injection, whereas phentermine/topiramate and bupropion/naltrexone are combination oral agents that work via other mechanisms. Other promising therapies (e.g., tirzepatide) are still under investigation and are therefore not included in the scope of this review.¹¹

For adults without pre-existing diabetes mellitus and either a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbid condition (such as hypertension or dyslipidemia), the four interventions added to usual care all reduced body weight compared to usual care alone, which included standard diet and activity and lifestyle recommendations. Indirect mean and categorical weight loss reduction comparisons across the drugs as well as direct head-to-head evidence between two of the agents (semaglutide and liraglutide) suggest that semaglutide and phentermine/topiramate achieve greater weight loss than liraglutide and bupropion/naltrexone. Semaglutide and liraglutide improved blood sugar and blood pressure compared to usual care, but how they compare to phentermine/topiramate and bupropion/naltrexone is less certain. In

addition, none of these drugs have assessed long-term outcomes in adults without pre-existing diabetes mellitus, and thus there is uncertainty around long-term benefits such as cardiovascular morbidity and mortality.

Few serious harms were reported across all of the trials and interventions, however, patients taking liraglutide, phentermine/topiramate, and bupropion/naltrexone had greater discontinuation due to adverse events than for placebo. Semaglutide appears to have lower rates of discontinuation than liraglutide in one head-to-head trial and than phentermine/topiramate and bupropion/naltrexone from our indirect comparisons. In addition to side effect profiles, additional considerations in comparing drugs include differences in mechanisms of action that may lead to benefits/harms that go beyond their effects on weight loss, uncertainty about whether sustained weight loss leads to decreased clinical endpoints, and if weight regain occurs over time despite continued therapy.

Given the strength of the evidence on weight loss outcomes in the trials and uncertainty around long-term outcomes for adults without pre-existing diabetes mellitus and with obesity or overweight with at least one comorbid condition, Table ES1 presents the ICER evidence ratings comparing each intervention with lifestyle modification to lifestyle modification alone and comparing semaglutide and the other interventions with lifestyle modification.

Table ES1. Evidence Ratings for Treatment of Adults with Obesity

Treatment	Comparator	Evidence Rating
Semaglutide	Lifestyle modification	B+
Liraglutide	Lifestyle modification	B
Phentermine/Topiramate	Lifestyle modification	C++
Bupropion/Naltrexone	Lifestyle modification	C+
Semaglutide	Liraglutide	C+
	Phentermine/topiramate	C+
	Bupropion/naltrexone	C++

Information about ICER’s Evidence Rating Matrix may be found [here](#).

At the current prices and with commonly accepted cost-effectiveness benchmarks, draft results suggest that phentermine/topiramate and bupropion/naltrexone (in addition to lifestyle modification) are cost effective compared with lifestyle modification alone. The cost effectiveness of treatment of obesity with semaglutide or liraglutide, in patients without diabetes mellitus, exceeded commonly used thresholds. Table ES2 presents the incremental results from the base-case cost-effectiveness analyses for each therapy under review.

Table ES2. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained
Semaglutide	Lifestyle modification	\$234,000	\$231,000
Liraglutide	Lifestyle modification	\$506,000	\$496,000
Phentermine/Topiramate	Lifestyle modification	\$9,000	\$9,000
Bupropion/Naltrexone	Lifestyle modification	\$47,000	\$46,000

evLY: equal value life year, QALY: quality-adjusted life year

In summary, among the agents we reviewed, greater weight loss was seen with semaglutide and with phentermine/topiramate; less weight loss was seen with liraglutide and with bupropion/naltrexone. Although few serious harms were noted for all the interventions, semaglutide may have lower rates of discontinuation and, along with liraglutide, may have additional cardiovascular benefits that extend beyond weight loss effects. Phentermine/topiramate and bupropion/naltrexone are substantially less expensive than semaglutide and liraglutide and both meet commonly accepted cost-effectiveness thresholds; both of these combination therapies are actually cost-saving when prescribed generically. Semaglutide does not meet typical cost-effectiveness thresholds but is more effective, less burdensome, and more cost effective than liraglutide.

1. Background

Obesity is a common chronic disease that increases the risk of other conditions such as diabetes mellitus, hypertension, dyslipidemia, cancer, heart disease, and death.^{1,2} Individuals with overweight or obesity face a considerable social stigma that can make them feel judged, shamed, and ostracized, and can affect interactions with family, friends, and even health professionals.³ Because obesity can start in childhood, the stigma can affect social interactions, educational development, relationships, and work.^{5,12} The net effect is that obesity can have a profound impact on all aspects of patients' lives and those of their families and caregivers.

Obesity is defined by the World Health Organization as abnormal or excessive fat accumulation that presents a risk to a person's health.¹³ While not optimal for assessing individuals with high or low muscle mass, body mass index (BMI, weight in kilograms/height in meters²) is commonly used to assess obesity because it is easy to reliably measure and correlates with body fat measurements.^{4,5} More than two-thirds of the United States (US) population have overweight (BMI ≥ 25) or obesity (BMI ≥ 30). The prevalence of obesity among adults has increased over time and was 40-45% in 2017-2018.¹⁴ Among children and adolescents, the prevalence of obesity is almost 20%.⁸ The total number of adults with overweight was estimated at 79 million with another 70 million estimated to have obesity in 2015, and with half the US population projected to have obesity by 2030.^{6,7} The prevalence of obesity varies among racial and ethnic groups, being higher for Hispanic adults and highest among non-Hispanic Black women.^{8,9} Screening adults for obesity is recommended by the US Preventive Services Task Force.¹⁵ Given the prevalence of obesity and its impact on health, the direct medical costs of obesity are staggering, estimated to be \$260 billion in the US in 2016.¹⁰ The financial impact of obesity on individuals includes not only direct medical costs but also indirect costs of lower wages and greater work loss and disability.^{16,17}

The stigma of obesity in society includes negative perceptions that attribute the problem to an individual's inability to control caloric intake and physical activity. However, it is recognized that energy balance dysregulation is the result of interactions among complex genetic factors associated with the body's mechanisms that control energy balance and contribute to developing obesity.^{18,19} An individual's lifestyle choices also are impacted by societal, economic, and cultural factors, which have contributed to the rise in obesity. This complexity supports the idea that treating obesity and its consequences must consider the potential range of causes that contribute to any one individual with obesity.

The goal of therapy for obesity is to broadly prevent, treat, or reverse its complications, including its impact on quality of life.^{20,21} Patients cite a variety of reasons for wanting to lose weight including improved health, self-esteem, and body image. Treatments to promote weight loss are intended to improve health and prevent the health risks associated with obesity (e.g., diabetes, hypertension, dyslipidemia, heart disease, cancer, fatty liver, osteoarthritis, sleep apnea) and ultimately improve

quality of life and longevity.^{5,22} Observational studies support an association between weight loss and reductions in mortality.⁴ Initial weight loss treatments focus on lifestyle interventions that variably combine healthful nutrition, increased physical activity, and behavioral modifications.^{23,24} Though helpful for some, weight loss is usually modest and regaining weight over time occurs in the vast majority of individuals. Earlier generation medications also had modest effects on weight loss, and some were found to pose significant health risks. The introduction of surgical procedures to promote weight loss demonstrated that, for severe obesity, significant weight loss was possible and was associated with decreased weight-related complications.²⁵ This supports the notion that successfully managing obesity as a chronic condition can lead to long-term health benefits.

For individuals who have not achieved desired weight loss with lifestyle changes, there are multiple pharmacotherapy options indicated to promote weight loss and prevent complications of obesity. Pharmacotherapy is often considered first-line before more invasive weight loss techniques are considered (e.g., bariatric surgery). Currently, approved medications by the US Food and Drug Administration (FDA) include the single agents: phentermine (1959), orlistat (Xenical®, H2 Pharma, 2007), liraglutide (Saxenda®, Novo Nordisk, 2014), and semaglutide (Wegovy®, Novo Nordisk, June 2021), and the combination drugs: phentermine/topiramate (Qysmia®, Vivus, 2012) and bupropion/naltrexone (Contrave®, Currax Pharmaceuticals, 2014).

Semaglutide and liraglutide are glucagon-like peptide-1 (GLP-1) receptor agonists that are also approved for diabetes mellitus due to their effect in stimulating insulin production. Their weight loss effect is mediated in part by decreasing hunger and delaying gastric emptying.¹⁸ Both are given by subcutaneous injection with liraglutide administered daily and semaglutide weekly. The other FDA-approved medications are administered by mouth and taken daily. Because orlistat results in modest weight loss and causes intestinal side effects, it is less commonly used for initial medication management and is not reviewed in this Report. Phentermine is an amphetamine-like medication that suppresses appetite and is approved for short-term use (less than 12 weeks). It is also available in combination with topiramate, a carbonic anhydrase inhibitor used to treat seizures. The combination of bupropion and naltrexone works in the brain to decrease hunger.¹⁸ Bupropion is an inhibitor of norepinephrine and dopamine and is an antidepressant and anti-anxiety medication. Naltrexone is an opioid antagonist and blocks the effect of opioid pain medications. Since phentermine, topiramate, bupropion, and naltrexone are available as single agents, clinicians may also use them “off label” alone and in various combinations for weight loss.

There are a host of other more invasive treatments including endoscopic surgical procedures and devices placed into the stomach to promote early satiety. Though these may also be used for individuals who have not achieved desired weight loss with lifestyle changes, patients and experts felt that the limited time duration of weight loss and/or invasive nature of these procedures would make them less comparable to medications that could be taken for longer periods.

Practical issues in using medications for weight loss are modest weight reduction, potential side effects, long-term safety, durability of treatment effect, and concerns about insurance coverage. Consequently, there is a need to understand the comparative benefits and costs of the newer branded medications for individuals interested in weight loss after not achieving their goals with initial lifestyle modification. Because semaglutide appears to promote greater weight loss than other FDA-approved medications, there has been considerable interest among patients and providers despite being administered as an injection and more costly.

Finally, a number of newer medications that promote weight loss are being investigated. An oral version of semaglutide has been approved for the treatment of diabetes mellitus and is under investigation for use in weight loss. Another medication, tirzepatide, is both a GLP-1 receptor agonist and also a glucose-dependent insulinotropic polypeptide receptor agonist, and has been approved for treatment of diabetes mellitus. Data on weight loss with tirzepatide have been published,¹¹ and these results are discussed in [Supplement A3](#).

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Semaglutide	GLP-1 receptor agonist	Subcutaneous	2.4 mg once weekly
Liraglutide	GLP-1 receptor agonist	Subcutaneous	3 mg once daily
Phentermine/Topiramate	Sympathomimetic amine/ GABA receptor modulation	Oral	7.5-15 mg/46-92 mg daily
Bupropion/Naltrexone	Opioid antagonist/NE and DA inhibitor	Oral	32 mg/360 mg daily

CA: carbonic anhydrase, DA: dopamine, GABA: gamma-aminobutyric acid, GLP-1: glucagon-like peptide-1, mg: milligram, NE: norepinephrine

2. Patient and Caregiver Perspectives

Discussions with individual patients and patient organizations identified important insights and perspectives. Common themes emphasized included: the considerable physical and mental burden on patients with obesity; the broad recognition that the social stigma associated with obesity can begin at a young age and affect an individual throughout their life; the need for better treatment options; the impact on all aspects of life including education, work and social/family relationships; the importance of measuring treatment outcomes that are most meaningful to patients; and the affordability of increasingly expensive treatments that may not be covered by health insurance.

Patients and clinicians emphasized that obesity is a serious, chronic disease with important health consequences affecting both physical and mental well-being. Individuals with obesity are at increased risk of chronic health conditions such as high blood pressure or cholesterol, diabetes mellitus, heart disease, sleep apnea, arthritis, immobility, depression, and cancer. As a result, obesity is associated with reduced disease-free life and increased risk of premature death.²⁶

Despite these risks, patients and advocates said that societal biases further the perception that those living with obesity are not able to make the personal lifestyle choices to manage weight. This simplistic focus on “blame the patient” overlooks considerable evidence that the causes of obesity are complex and multifactorial. The resulting social stigma associated with obesity is widely felt by individuals with obesity, begins at a young age, and affects individuals throughout their lives. This stigma and bias can lead to anxiety, depression, and behaviors that make self-care harder, and may impact willingness to engage with health care providers around weight loss and the consequences of obesity.

We also heard that there are diverse perspectives about obesity that broadly reflect the many individuals with obesity and the variety of underlying factors that contribute to obesity and its management. Though many individuals with obesity are interested in weight loss, the cycle of weight loss and gain, the many “fad” diets and treatments that offer unrealistic expectations, and the cost of treatments that are often not covered by health insurance all impact perceptions about weight loss. We heard some advocate more for efforts focused on managing the medical issues associated with obesity, especially for those individuals who have suffered through failed treatments, weight cycling, and the psychological harms associated with such prior experiences. Even among those more interested in weight-neutral treatment efforts, there was recognition that more can be done in the health care system to reduce the stigma of obesity and better support individuals interested in weight loss treatment.

Patients and clinicians highlighted that there is a need for new therapeutic options for individuals with obesity who are interested in weight loss treatments, particularly for individuals who have not responded to lifestyle treatments or who responded but then regained lost weight over time. They

emphasized that no one treatment is a panacea, and this reflects the various underlying mechanisms that contribute to obesity as well as the benefits and harms associated with all therapies. Given the wide variety of treatments available for those interested in weight loss treatment, they supported focusing on medical therapies for those who have not responded to lifestyle interventions and are interested in additional treatments. Though patients may also consider invasive surgical and other device interventions while also considering the use of medical therapies, patients felt that many individuals had treatment preferences that made direct comparison of medical and non-medical therapies less important. This also reflected increased interest in medications that provide substantial weight loss to an increasing percentage of users, with weight reduction that is becoming comparable to results associated with some bariatric procedures.

Patients and clinicians also reported that individuals with obesity commonly use medications approved in combination products for weight loss but available as individual drugs in an off-label manner. This reflected that they often saw this route as minimizing side effects when starting treatment and being less costly for patients given the higher costs of approved combination medications that are often not covered by insurers. The net effect is that many patients end up on a combination of medications, but not always using the approved combination products. There was also recognition that the addition of medications, such as the GLP-1 receptor agonists, represents a step forward in the magnitude of weight loss achieved, but they do not work for everyone, and the weight loss achieved is still less than that seen for bariatric surgery for many individuals. Finally, it is acknowledged that most patients will require chronic use to maintain the weight loss achieved, not unlike the need to use medications to manage diabetes mellitus, but there was concern about the safety of long-term use and the willingness of individuals to remain on therapy for many years, especially if it requires considerable out-of-pocket costs to the individual.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone for the management of obesity are detailed in [Section D1](#) of the Supplement.

Scope of Review

We reviewed the clinical effectiveness of the medications plus lifestyle interventions compared to placebo plus lifestyle interventions. For studies evaluating multiple doses or combinations of the medications, we reviewed only the FDA-approved dose and/or combination for the obesity indication. Lifestyle interventions were variably defined in the clinical trials as interventions ranging from diet and exercise counseling to intensive behavioral therapy (IBT) and meal replacement programs. We sought evidence on weight loss outcomes, including percentage weight loss from baseline and proportion of participants achieving 5%, 10%, or 15% body weight loss as well as patient-important outcomes, including functional status, health-related quality of life (HRQoL), and weight regain. We also sought evidence on changes in glycated hemoglobin (A1C), systolic blood pressure (SBP), low density lipoprotein (LDL), and waist circumference. The full scope of the review is available in [Section D1](#) of the Supplement.

Evidence Base

Semaglutide

Evidence informing our review of semaglutide for obesity management was derived from five of the STEP trials. STEP 1, STEP 2, STEP 3, STEP 5, and STEP 8 were selected as studies of interest due to their study design, relevant population, and length of follow-up.²⁷⁻³¹ Additional studies of semaglutide are described in [Section D2](#) and Tables [D8](#), [D13](#), and [D19](#) in the Supplement.

STEP 1, STEP 2, and STEP 5 evaluated subcutaneous semaglutide 2.4 mg plus lifestyle intervention versus placebo plus lifestyle intervention.^{27,28,32} STEP 2 also evaluated subcutaneous semaglutide at 1.0 mg, but we only reviewed evidence for the subcutaneous semaglutide 2.4 mg as it is the approved dose for obesity treatment.²⁸ STEP 3 evaluated subcutaneous semaglutide 2.4 mg plus IBT versus placebo plus IBT.²⁹ STEP 8 evaluated subcutaneous semaglutide 2.4 mg plus lifestyle intervention versus subcutaneous liraglutide 3.0 mg plus lifestyle intervention, and compared both to placebo plus lifestyle intervention.³¹ STEP 8 was open label due to dosing differences between semaglutide and liraglutide, however, active treatment groups were double-blinded to whether they were receiving the intervention or comparable placebo (Table 3.1).

Participants in STEP 1, 3, 5, and 8 included adults with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbid condition.^{27,29-31} History of type 1 or type 2 diabetes mellitus or HbA1C equal to or above 6.5% were exclusion criteria for these trials. Participants in STEP 2 included adults with BMI of ≥ 27 kg/m² diagnosed with type 2 diabetes mellitus and excluded individuals with renal disease (Table 3.1).²⁸

Participants in STEP 1, 3, 5, and 8 trials were of similar age and baseline weight and BMI.^{27,29-31} Participants in STEP 2 who had diabetes mellitus were somewhat older, had lower BMI, and were less likely to be female or White.²⁸ Baseline characteristics for the STEP trials are outlined in Tables 3.1 and 3.3. Outcomes were assessed at week 68 for all STEP trials except STEP 5, which evaluated outcomes at weeks 52 and 104 (Table 3.1).

STEP 4, which was a withdrawal study, was not included in the base evidence review or network meta-analysis (NMA) due to differences in study design and baseline weight loss during a run-in dose escalation period.³¹ However, we did review its unique data regarding weight regain. See additional information regarding this trial in [Section D2](#) of the Supplement.

Table 3.1. Overview of Key Trials of Semaglutide for the Management of Obesity^{27,29,31-37}

	STEP 1		STEP 3		STEP 5		STEP 8		
Study Arms	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	LIR
N	655	1,306	204	407	152	152	85	126	127
Lifestyle Intervention	Monthly counseling, reduced-calorie diet, and increased physical activity		Low calorie meal replacement diet for 8 weeks and IBT visits		Monthly counseling, reduced-calorie diet, and increased physical activity		Monthly counseling, reduced-calorie diet, and increased physical activity		
Mean Age, Years	47	46	46	46	47	47	51	48	49
Female Gender, %	76	73.1	88.2	77.4	74.3	80.9	77.6	81	76.4
Baseline Weight, kg	105.2	105.4	103.7	106.9	106		108.8	102.5	103.7
Baseline BMI, kg/m ²	38	37.8	37.8	38.1	38.5		38.8	37	37.2
Race, White, %	76	74.5	77.5	75.4	93.4	92.8	70.6	74.6	74.8
Pre-Diabetes, %	40.2	45.4	52.9	48.2	46.4		40	34.1	35.4

IBT: intensive behavioral therapy, kg: kilogram, LIR: liraglutide, m: meter, NR: not reported, PBO: placebo, SEM: semaglutide

Liraglutide

Evidence informing our review of liraglutide for obesity management was derived from six of the SCALE Phase III randomized trials, which evaluated subcutaneous liraglutide 3.0 mg versus placebo.³⁸⁻⁴³ STEP 8, described previously, is included in the liraglutide evidence analysis as well.³¹ Additional studies of liraglutide are described in [Section D2](#) and in Tables [D8](#), [D13](#), and [D19](#) of the Supplement.

SCALE (Maintenance), SCALE (Sleep Apnea), SCALE (Obesity and Pre-Diabetes), and SCALE (Type 2 Diabetes) evaluated subcutaneous liraglutide 3.0 mg plus lifestyle intervention versus placebo plus lifestyle intervention.³⁸⁻⁴³ SCALE (IBT) and SCALE (Insulin) evaluated subcutaneous liraglutide 3.0 mg plus IBT versus placebo plus IBT.^{42,43} Participants in SCALE (IBT) included adults ages ≥ 18 with a BMI ≥ 30 kg/m².⁴² Participants in SCALE (Maintenance), SCALE (Sleep Apnea), and SCALE (Obesity and Pre-Diabetes) included adults ages ≥ 18 with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with untreated dyslipidemia or hypertension.^{38,39,41} SCALE (Sleep Apnea) had additional inclusion criteria of individuals with moderate to severe obstructive sleep apnea who were unable or unwilling to use continuous positive airway pressure (CPAP).³⁹ Participants in SCALE (Type 2 Diabetes) included adults ages ≥ 18 with overweight or obesity (BMI ≥ 27 kg/m²) with a diagnosis of type 2 diabetes mellitus treated with diet and exercise alone or one to three oral hypoglycemic medications.⁴⁰ Participants in SCALE (Insulin) included adults ages ≥ 18 with a BMI ≥ 27 kg/m², a diagnosis of type 2 diabetes mellitus, and receiving stable treatment with any basal insulin and ≤ 2 oral hypoglycemic medications.⁴³ All trials except SCALE (IBT) and SCALE (Insulin) excluded individuals with a history of previous surgical treatment of obesity. Additionally, all studies excluded individuals with a recent history of major depressive disorder or a lifetime suicide attempt. Any history of drug-induced obesity or an endocrine disorder that could contribute to obesity (e.g., Cushing syndrome) was also exclusion criteria across all trials. History of multiple endocrine neoplasia and familial medullary thyroid carcinoma were also exclusionary due to the increased risk of medullary cancer of the thyroid with GLP-1 receptor agonists.^{44,45} Participants across all included trials were primarily female, and of similar age and baseline weight and BMI, with some notable differences. SCALE (Sleep Apnea) participants had higher baseline weight and were primarily male and participants in SCALE (Type 2 Diabetes) and SCALE (Insulin) had higher baseline A1C and SBP.^{39,40,43} Baseline characteristics for the SCALE trials are outlined in Tables 3.2 and 3.3.

Outcomes were assessed at week 56 for all SCALE trials except SCALE (Sleep Apnea), which assessed outcomes at week 32. SCALE (Type 2 Diabetes) additionally evaluated some relevant outcomes at week 68.

Table 3.2. Overview of Key Trials of Liraglutide for the Management of Obesity^{38,39,41,42,46-49}

	SCALE Maintenance		SCALE Sleep Apnea		SCALE Obesity and Pre-Diabetes		SCALE IBT	
Study Arms	PBO	LIR	PBO	LIR	PBO	LIR	PBO	LIR
N	210	212	179	180	1,244	2,487	140	142
Lifestyle Intervention	Low-calorie run-in with weekly counseling then reduced-calorie diet, and increased physical activity		Monthly counseling, reduced-calorie diet, and increased physical activity		Monthly counseling, reduced-calorie diet, and increased physical activity		IBT, reduced-calorie diet, and increased physical activity	
Mean Age, Years	46.5	45.9	48.4	48.6	45	45.2	49	45.4
Female Gender, %	78.6	84	27.9	28.3	78.1	78.7	82.9	83.8
Baseline Weight, kg	98.7	100.4	118.7	116.5	106.2	106.2	106.7	108.5
Baseline BMI, kg/m ²	35.2	36	39.4	38.9	38.3	38.3	38.7	39.3
Race, White, %	88.1	80.2	75.4	72.2	85.3	84.7	82.1	78.9
Pre-Diabetes, %	NR	NR	62.6	63.9	60.9	61.4	NR	NR

IBT: intensive behavioral therapy, kg: kilogram, LIR: liraglutide, m: meter, NR: not reported, PBO: placebo

Table 3.3. Overview of Key Trials of Semaglutide and Liraglutide for the Management of Obesity with Diabetes^{28,40,43,50}

	STEP 2		SCALE Type 2 Diabetes		SCALE Insulin	
Study Arms	PBO	SEM	PBO	LIR	PBO	LIR
N	403	404	212	423	198	198
Lifestyle Intervention	Monthly counseling, reduced-calorie diet, and increased physical activity		Monthly counseling, reduced-calorie diet, and increased physical activity		IBT, reduced-calorie diet, and increased physical activity	
Mean Age, Years	55	55	54.7	55	57.6	55.9
Female Gender, %	47.1	55.2	54.2	48	50	45.5
Baseline Weight, kg	100.5	99.9	106.5	105.7	98.9	100.6
Baseline BMI, kg/m ²	35.9	35.9	37.4	37.1	35.3	35.9
Race, White, %	60	58.7	82.5	83.5	90.9	87.9

IBT: intensive behavioral therapy, kg: kilogram, LIR: liraglutide, m: meter, PBO: placebo, SEM: semaglutide

Phentermine/Topiramate

Evidence informing our review of phentermine/topiramate for obesity management was derived from three Phase III studies (EQUIP, EQUATE, and CONQUER). One additional Phase I/II study, OB-204, is described in [Section D2](#) and Tables [D9](#), [D16](#), and [D20](#) of the Supplement.

EQUIP, EQUATE, and CONQUER were multi-center, Phase III randomized controlled trials that evaluated phentermine 15 mg/topiramate 92 mg (high dose) plus lifestyle intervention versus placebo plus lifestyle intervention.⁵¹⁻⁵⁵ EQUIP also evaluated phentermine 3.75 mg/topiramate 23 mg and CONQUER evaluated the phentermine 7.5/topiramate 46 mg dose. EQUATE had seven arms evaluating multiple doses of phentermine and topiramate monotherapy, in addition to phentermine 7.5 mg/topiramate 46 mg. Evidence was reviewed only for phentermine 15 mg/topiramate 92 mg (high dose) and phentermine 7.5 mg/topiramate 46 mg doses (low dose), and the NMA focused solely on the high dose.

The EQUIP, EQUATE, and CONQUER trials included adults ages 18-70, but each trial had varying BMI requirements. EQUIP required that participants have a BMI of at least 35 kg/m² and EQUATE included participants with a BMI of 30-45 kg/m².^{50,51,52,53} The CONQUER trial required that participants have a BMI of 27-45 kg/m² (with no lower BMI limit for patients who have diabetes mellitus) and have at least two of the following comorbidities: SBP 140-160 mmHg (or 130-160 mmHg if diabetic), diastolic blood pressure 90-100 mmHg (or 85-100 mmHg if diabetic), or taking at least two antihypertensive medications.⁵¹ The CONQUER trial additionally included both adults with and without type 2 diabetes mellitus. For the purposes of our clinical review and NMA, and due to the lack of data available in the subgroup of participants without diabetes mellitus, we focused specifically on the diabetes mellitus subgroup in this trial because it comprised the majority of participants (68%).⁵⁶

Having a serious medical condition, obesity of known endocrine origin, stage 2 hypertension, previous surgery for obesity, or a weight change of >5 kg within three months were common exclusion criteria for these trials. Patients in EQUIP and EQUATE were also excluded if they had type 2 diabetes mellitus.^{52,53} Additional exclusion criteria for CONQUER included fasting glucose greater than 13 mmol/L, triglycerides greater than 4.52 mmol/L, use of antidiabetic medication other than metformin, or a history of seizures or serious psychiatric illness.⁵¹

EQUIP and EQUATE trials had similar baseline characteristics, except for BMI and weight.^{50,51,52,53} The BMI requirement was higher in EQUIP than in other trials, meaning that all participants in this trial had severe obesity. As a result, the mean baseline BMI and body weight of participants was higher in this trial compared to other trials in our review.⁵³ Compared to participants in EQUIP and EQUATE, the diabetes mellitus subgroup of CONQUER had a higher mean age and fewer female participants.⁵⁶ Baseline characteristics for these trials are reported in Tables 3.4 and 3.5.

Bupropion/Naltrexone

Evidence to inform our review of bupropion/naltrexone in patients with overweight or obesity was derived from four Phase III randomized controlled trials, COR-I, COR-II, COR-BMOD, and COR Diabetes. Two additional Phase III trials, CVOT Light and Ignite, are described in [Section D2](#) and Tables [D9](#), [D16](#), and [D20](#) of the Supplement.

COR-I, COR-II, and COR Diabetes were multi-center, Phase III randomized controlled trials that evaluated bupropion SR 360 mg/naltrexone SR 32 mg plus lifestyle intervention versus placebo plus lifestyle intervention.⁵⁷⁻⁶² COR-I additionally evaluated a lower dose of bupropion SR 360 mg/naltrexone SR 16 mg, but we only reviewed the higher approved dose of the medication. COR-BMOD was a multi-center, Phase III randomized controlled trial that evaluated bupropion SR 360 mg/naltrexone SR 32 mg plus IBT versus placebo plus IBT.^{63,64}

COR-I, COR-II, and COR-BMOD included adults ages 18-65 years who had a BMI of 30-45 kg/m², or a BMI of 27-45 kg/m² with controlled hypertension and/or dyslipidemia.^{59,61,63} Inclusion criteria for COR Diabetes included patients ages 18-70 years with a BMI of 27-45 kg/m², who were diagnosed with type 2 diabetes mellitus, had an HbA1C between 7-10%, fasting blood glucose <270 mg/dL, fasting triglycerides <400 mg/dL, SBP <145 mmHg, and diastolic blood pressure <95 mmHg.⁵⁷

Having type 1 diabetes mellitus, a serious medical condition, obesity of known endocrine origin, surgery for obesity, a history of seizures, drug, or alcohol abuse, or using medications that affected body weight were common exclusion criteria among the trials. Adults with overweight or obesity in COR-I, COR-II, and COR-BMOD were additionally excluded if they had type 2 diabetes mellitus or a weight change of >4 kg within three months.^{59,61,63} In COR Diabetes, patients were also excluded if they had diabetes mellitus secondary to pancreatitis or pancreatectomy, weight change >5 kg within three months, or used diabetes medication or were not on a stable dose of oral antidiabetic drugs.⁵⁷

Baseline characteristics for COR-I, COR-II, and COR-BMOD trials were similar,^{59,61,63} except participants in COR Diabetes were slightly older in age and less likely to be female.⁵⁷ Baseline data for patients in these trials are reported in Tables 3.4 and 3.5.

Table 3.4. Overview of Key Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity^{52-55,59-64}

	EQUIP		EQUATE			COR-I		COR-II		COR-BMOD	
Study Arms	PBO	P/T (high)	PBO	P/T (low)	P/T (high)	PBO	B/N	PBO	B/N	PBO	B/N
N	514	512	109	107	108	581	583	495	1,001	202	591
Lifestyle Intervention	LSM counseling, reduced-calorie diet, increased physical activity		LSM counseling, reduced-calorie diet, increased physical activity			LSM counseling, reduced-calorie diet, increased physical activity		LSM counseling, reduced-calorie diet, increased physical activity		IBT, reduced-calorie diet, increased physical activity	
Mean Age, Years	43	41.9	45	44.6	44.6	43.7	44.4	44.4	44.3	45.6	45.9
Female Gender, %	82.7	82.8	78.9	79.4	78.7	85	85	84.8	84.6	91.6	89.3
Baseline Weight, kg	115.8	115.2	100	102.2	99.3	99.5	99.7	99.2	100.3	101.9	100.2
Baseline BMI, kg/m ²	42	41.9	36.2	36.6	35.9	36.2	36.1	36.1	36.2	37	36.3
Race, White, %	79.7	80.4	76.1	74.8	81.5	75.7	75	83.6	83.4	73.7	68.5
Pre-Diabetes, %	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

B/N: bupropion/naltrexone, IBT: intensive behavioral therapy, kg: kilogram, LSM: lifestyle modification, m: meter, NR: not reported, PBO: placebo, P/T: phentermine/topiramate

Table 3.5. Overview of Key Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity with Diabetes^{51,56-58}

	CONQUER (Diabetes Subgroup)			COR Diabetes	
Study Arms	PBO	P/T (low)	P/T (high)	PBO	B/N
N	157	67	164	159	265
Lifestyle Intervention	LSM counseling, reduced-calorie diet, increased physical activity			LSM counseling, reduced-calorie diet, increased physical activity	
Mean Age, Years	52.6	52.5	52.1	53.8	53.9
Female Gender, %	71.3	65.6	62.1	52.8	54.3
Baseline Weight, kg	99.3	97.2	103.2	105	106.3
Baseline BMI, kg/m ²	36.2	35.3	37.1	36.3	36.7
Race, White, %	84.7	94	82.9	83	78.1

B/N: bupropion/naltrexone, kg: kilogram, LSM: lifestyle modification, m: meter, PBO: placebo, P/T: phentermine/topiramate

3.2. Results

The most common primary outcome reported was percentage weight loss from baseline to one year after treatment initiation with dose escalation periods ranging from four to 16 weeks. Other outcomes variably included categorical weight loss (participants achieving 5% or 10% weight loss), and changes in metabolic and cardiovascular risk factors such as SBP, A1C, and LDL. As noted in the prior section, trials differed in populations studied (such as participants with or without diabetes mellitus or other conditions and baseline BMI) and intensity of lifestyle modification interventions offered alongside active treatment or placebo (ranging from diet and exercise counseling to IBT). To ensure comparability and generalizability of results, we present trials of participants with obesity alone separately from trials of participants with obesity and diabetes mellitus. Changes in weight, SBP, A1C, and HRQoL as well as harms and discontinuation rates are summarized below, and additional outcomes are available in [Section D2](#) of the Supplement.

Clinical Benefits

For each medication, weight loss outcomes are summarized first followed by other outcomes (e.g., SBP and A1C). HRQoL outcomes are summarized for all drugs at the end of this section. For each medication, results of trials conducted in patients with obesity are presented first, followed by trials conducted in patients with obesity and diabetes mellitus.

Semaglutide versus Placebo

The efficacy of semaglutide compared with placebo for the management of obesity in patients without diabetes mellitus was evaluated in three Phase III trials (STEP 1, 3, and 5).^{27,29,35} In the STEP 1, 3, and 5 trials, participants in the subcutaneous semaglutide 2.4 mg arm consistently achieved greater percent weight loss at one year (-15.6%, -16.5%, and -15.8%, respectively) versus placebo (-2.8%, -5.8%, and -3.3%, respectively).^{27,29,35} Similarly, for the co-primary outcomes of proportion of participants who achieved at least 5% weight loss, at least 10% weight loss, and at least 15% weight loss, a greater proportion of participants in the semaglutide arm achieved each categorical outcome compared to participants in the placebo arm. Participants in the semaglutide arms of STEP 1, 3, and 5 trials also had greater improvements in SBP from baseline (-6.2 mmHg, -5.6 mmHg, and -6 mmHg, respectively) compared to those in the placebo arms (-1.1 mmHg, -1.6 mmHg, and -1 mmHg, respectively).^{27,29,35} In the STEP 1, 3, and 5 trials, the absolute change in percentage A1C (change in A1C) from baseline improved in the semaglutide arm (-0.45%, -0.51%, and -0.5%, respectively) compared to the placebo arm (-0.15%, -0.27%, and -0.2%, respectively).^{27,35} The absolute change in percentage A1C for STEP 8 improved for the semaglutide arm (-0.2%) compared to an increase in A1C for the placebo arm (0.1%).^{29,31} See Table 3.6 for detailed results.

The efficacy of semaglutide for the management of obesity and type 2 diabetes mellitus was evaluated through one Phase III trial (STEP 2).²⁸ Participants in the subcutaneous semaglutide 2.4

mg arm achieved greater percent weight loss at one year (-9.6%) versus placebo (-3.4%), but the magnitude of weight loss appeared less than in the trials of participants without diabetes mellitus. Similarly, for the co-primary outcomes of proportion of participants who achieved at least 5% weight loss and at least 10% weight loss, a greater proportion of participants in the semaglutide arm achieved each categorical outcome compared to participants in the placebo arm. Participants in the semaglutide arm also had modest improvement in SBP (-3.6 mmHg) compared to those in the placebo arm (-0.5 mmHg). Change in A1c from baseline was consistent across both the semaglutide and placebo arms (-0.4% vs. -0.4%). See Table 3.8 for detailed results.

One trial, STEP 4, reported weight regain after discontinuation. STEP 4 had a crossover design including a 20-week run-in semaglutide dose escalation prior to randomization to either continuing subcutaneous semaglutide 2.4 mg or switching to placebo.³¹ Prior to randomization, all participants achieved a mean weight loss of -10.6% in the 20-week run-in period. After randomization, participants in the subcutaneous semaglutide 2.4 mg arm achieved additional weight loss (-7.9%) compared to participants in the placebo arm who experienced weight regain (6.9%). More participants who switched to placebo experienced weight regain (81.2%) compared to those who continued on semaglutide (12.3%). See [Table D13](#) in the Supplement for detailed results.

Semaglutide versus Liraglutide

The efficacy of subcutaneous semaglutide versus subcutaneous liraglutide with a placebo comparator for the management of obesity was evaluated in one Phase III trial (STEP 8).³¹ Participants in the semaglutide 2.4 mg arm achieved greater weight loss at one year (-15.8%) versus liraglutide 3.0 mg (-6.4%) and placebo (-1.9%). Similarly, for the co-primary outcomes of proportion of participants who achieved at least 5% weight loss, at least 10% weight loss, and at least 15% weight loss, a greater proportion of participants in the semaglutide arm achieved each categorical outcome compared to participants in the liraglutide and placebo arms. Participants in the semaglutide arm also had greater improvements in SBP from baseline (-5.7 mmHg) compared to participants in the liraglutide arm (-2.9 mmHg), and participants in both the semaglutide and liraglutide arms had greater improvement compared to those in the placebo arm, who had a modest increase in SBP (3.2 mmHg). Minimal changes in A1C were seen in all arms of the trial. See Table 3.6 for detailed results.

Table 3.6. Results of Key Trials of Semaglutide for the Management of Obesity^{27,29,31-36,65}

	STEP 1		STEP 3		STEP 5		STEP 8		
Study Arms	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	LIR
N	577	1,212	189	373	129	149	78	117	117
% Weight Loss from Baseline to One Year, Mean (SE)	-2.8 (0.3) [†]	-15.6 (0.3) [†]	-5.8 (0.4) [†]	-16.5 (0.5) [†]	-3.3 (0.6) [†]	-15.8 (0.8) [†]	-1.9 (1.1) [†]	-15.8 (0.9) [†]	-6.4 (0.9) [†]
Participants with at Least 5% Weight Loss, n (%)	182 (31.5)	1,047 (86.4)	90 (47.6)	323 (86.6)	38 (29.5)	132 (88.6)	23 (29.5)	102 (87.2)	68 (58.1)
Participants with at Least 10% Weight Loss, n (%)	69 (12)	838 (69.1)	51 (27)	281 (75.3)	17 (13.2)	102 (68.5)	12 (15.4)	83 (70.9)	30 (25.6)
Change in SBP from Baseline, mmHg, Mean (SE)	-1.1 (0.5) [†]	-6.2 (0.4) [†]	-1.6* (1.1)	-5.6* (0.7)	-1* (1.2) [‡]	-7* (1.1) [†]	3.2* (1.5) [†]	-5.7* (1.2) [†]	-2.9* (1.2) [†]
Change in A1C from Baseline, %, Mean (SE)	-0.15* (0.01) [†]	-0.45* (0.01) [†]	-0.27* (0.01) [†]	-0.51* (0.02) [†]	-0.2* (0.02) [†]	-0.5* (0.03) [†]	0.1* (0.02) [†]	-0.2* (0.03) [†]	-0.1* (0.03) [†]

A1C: glycated hemoglobin, LIR: liraglutide, mmHg: millimeters of mercury, PBO: placebo, SBP: systolic blood pressure, SE: standard error, SEM: semaglutide

*The number of patients for this outcome may differ from the primary analysis population.

[†]SE manually derived from standard deviation or 95% CIs.

Liraglutide versus Placebo

The efficacy of liraglutide compared with placebo for the management of obesity was evaluated in four Phase III trials in the SCALE clinical trial program (Maintenance, Sleep Apnea, Obesity and Pre-Diabetes, IBT).^{38,39,41,42} In the Maintenance, Obesity and Pre-Diabetes, and IBT trials, participants in the subcutaneous liraglutide 3.0 mg arm consistently achieved greater percent weight loss at one year (-6.2%, -8%, and -7.4%, respectively) versus placebo (-0.2%, -2.6%, and -4%, respectively).^{38,41,42} Similarly, for the co-primary outcomes of proportion of participants who achieved at least 5% weight loss and at least 10% weight loss, a greater proportion of participants in the liraglutide arm achieved each categorical outcome compared to participants in the placebo arm. Changes in SBP varied across trials with liraglutide demonstrating modest improvements relative to placebo, except in the Maintenance trial in which participants in both the liraglutide and placebo arms experienced an increase in SBP from baseline (0.2 mmHg and 2.8 mmHg, respectively).³⁸ Across all four SCALE trials, greater improvements in change in A1C were consistently demonstrated in the liraglutide arm compared to the placebo arm, although the results varied between studies.^{38,39,41,42} See Table 3.7 for detailed results.

The efficacy of subcutaneous liraglutide compared with placebo for the management of obesity with diabetes mellitus was evaluated in two Phase III trials in the SCALE clinical trial program (Type 2 Diabetes, Insulin).^{40,43} In both the SCALE (Type 2 Diabetes) and SCALE (Insulin) trials, participants in the liraglutide 3.0 mg arm had greater percent weight loss at one year (-5.9% and -5.8%, respectively) compared to placebo (-2% and -1.5%, respectively). Similarly, liraglutide demonstrated a greater proportion of participants who achieved at least 5% or 10% weight loss

compared to placebo. Liraglutide also demonstrated greater improvements in SBP compared to placebo. Across both trials, improvements in A1C were greater in the liraglutide arms (-1.3% and -1.1%, respectively) compared to the placebo arms (-0.3% and -0.6%, respectively). See Table 3.8 for detailed results.

Table 3.7. Results of Key Trials of Liraglutide for the Management of Obesity^{38,39,41,42,46-49,65}

	SCALE Maintenance		SCALE Sleep Apnea‡		SCALE Obesity and Pre-Diabetes		SCALE IBT	
Study Arms	PBO	LIR	PBO	LIR	PBO	LIR	PBO	LIR
N	188	194	178	175	1,220	2,432	130	141
% Weight Loss from Baseline to One Year, Mean (SE)	-0.2† (0.5)*	-6.2† (0.5)*	N/A	N/A	-2.6 (0.2)*	-8 (0.1)*	-4 (0.6)*	-7.4 (0.7)*
Participants with 5% Weight Loss, n (%)	41 (21.8)	98 (50.5)	33 (18.5)	81 (46.3)	331 (27.1)	1,537 (63.2)	50 (38.8)	87 (61.5)
Participants with 10% Weight Loss, n (%)	12 (6.3)	51 (26.1)	3 (1.7)	41 (23.4)	129 (10.6)	805 (33.1)	26 (19.8)	43 (30.5)
Change in SBP from Baseline, mmHg, Mean (SE)	2.8† (0.7)*	0.2† (0.8)*	0† (1)	-3.4† (0.9)	-1.5† (0.4)*	-4.2† (0.2)*	-0.6† (NR)	-2.8† (NR)
Change in A1C from Baseline, %, Mean (SE)	0.1† (0.03)*	-0.1† (0.03)*	-0.2† (0)	-0.4† (0)	-0.06† (0.01)*	-0.3† (0.01)*	-0.06† (0.02)*	-0.16† (0.03)*

A1C: glycated hemoglobin, LIR: liraglutide, mmHg: millimeters of mercury, N/A: not applicable, NR: not reported, PBO: placebo, SBP: systolic blood pressure, SE: standard error

*SE manually derived from standard deviation or 95% CIs.

†The number of patients for this outcome may differ from the primary analysis population.

‡Timepoint is at Week 32 for all outcomes.

Table 3.8. Results of Key Trials of Semaglutide and Liraglutide for the Management of Obesity with Diabetes Mellitus ^{28,40,43,50,65}

	STEP 2		SCALE Type 2 Diabetes		SCALE Insulin	
Study Arms	PBO	SEM	PBO	LIR	PBO	LIR
N	376	388	211	412	193	191
% Weight Loss from Baseline to One Year, Mean (SE)	-3.4 (0.4)	-9.6 (0.4)	-2 (0.3)*	-5.9 (0.3)*	-1.5 (0.4)	-5.8 (0.4)
Participants with 5% Weight Loss, n (%)	107 (28.5)	267 (68.8)	45 (21.4)	224 (54.3)	46 (24)	100 (51.8)
Participants with 10% Weight Loss, n (%)	31 (8.2)	177 (45.6)	14 (6.7)	104 (25.2)	13 (6.6)	44 (22.8)
Change in SBP from Baseline, mmHg, Mean (SE)	-0.5† (0.8)	-3.9† (0.7)	-0.4† (0.9)*	-2.8† (0.7)*	-1.6† (0.9)	-5.6† (0.9)
Change in A1C from Baseline, %, Mean (SE)	-0.4† (0.1)	-0.4† (0.1)	-0.3† (0.06)*	-1.3† (0.04)*	-0.6† (NR)	-1.1† (NR)

A1C: glycated hemoglobin LIR: liraglutide, mmHg: millimeters of mercury, NR: not reported, PBO: placebo, SBP: systolic blood pressure, SE: standard error, SEM: semaglutide

*SE manually derived from standard deviation or 95% CIs.

†The number of patients for this outcome may differ from the primary analysis population.

Phentermine/Topiramate versus Placebo

In the EQUIP trial, participants in the phentermine 15 mg/topiramate 92 mg arm achieved greater weight loss at one year (-10.9%) than participants in the placebo arm (-1.6%).^{53,55} For the co-primary outcome of proportion of participants who lost at least 5% of their weight, more participants in the phentermine/topiramate arm achieved this outcome compared to participants in the placebo group. Similarly, more participants in the high-dose treatment arm achieved 10% weight loss compared to the placebo arm (Table 3.9).

One-year outcomes were not available in the EQUATE trial, whose timepoints went out to only 28 weeks.

Participants in the diabetes mellitus subgroup of the CONQUER trial receiving phentermine 15 mg/topiramate 92 mg treatment (high dose) and phentermine 7.5 mg/topiramate 46 mg (low dose) achieved a greater weight improvement at one year (-8.8% and -6.8%, respectively) than participants in the placebo arm (-1.9%).^{51,56} Categorical weight loss of at least 5% and 10% were not assessed in this diabetes mellitus subgroup population. See Table 3.10 for detailed results.

In terms of secondary outcomes, in the EQUIP trial, SBP decreased by 2.9 mmHg in the high-dose phentermine/topiramate arm and increased by 0.9 mmHg in the placebo arm (Table 3.9).⁵³ In the CONQUER diabetes mellitus subgroup, patients in the high-dose phentermine/topiramate arm and low-dose phentermine/topiramate arm experienced HbA1C decreases of 0.4% compared to the

placebo decreases of 0.1%.⁵¹ Similarly, in patients with diabetes mellitus in CONQUER, SBP decreased by 4.2 mmHg in the phentermine 15 mg/topiramate 92 mg group, by 2.9 mmHg in the phentermine 7.5 mg/topiramate 46 mg group, and by 2.1 mmHg in the placebo group (Table 3.10).⁵⁶

Bupropion/Naltrexone versus Placebo

In the COR-I, COR-II, and COR-BMOD trials of adults with obesity, participants in the bupropion 360 mg/naltrexone 32 mg (high dose) arm achieved greater weight loss at one year (-6.1%, -6.4%, and -9.3%, respectively), than participants in the placebo arm (-1.3%, -1.2%, and -5.1%, respectively).^{59-61,63,64} For the co-primary outcome of participants who lost at least 5% of their weight, a greater proportion of participants in the intervention arm achieved this outcome compared to placebo. A similar pattern was observed for the secondary outcome of proportion of participants who achieved 10% weight loss between the arms. See Table 3.9 for detailed results.

Participants in the bupropion 360 mg/naltrexone 32 mg arm in the COR Diabetes trial achieved greater percent weight loss at one year (-5%) than participants in the placebo arm (-1.8%).^{57,58} For the co-primary outcome of proportion of participants who lost at least 5% of their weight, more participants in the bupropion/naltrexone arm achieved this outcome compared to participants in the placebo group. Additionally, more participants in the treatment arm achieved 10% weight loss than in the placebo arm (Table 3.10).

In COR-I, SBP decreased by 0.1 mmHg in participants receiving the intervention and by 1.9 mmHg in participants receiving placebo (Table 3.9).^{57,58,59,60} A similar pattern was observed in the COR-BMOD trial, where SBP decreased by 1.3 mmHg in the bupropion/naltrexone group versus 3.9 mmHg in the placebo group.⁶³ In the COR-II trial, SBP increased by 0.6 mmHg in the treatment group and decreased by 0.5 mmHg in the placebo group (p=0.039).⁶¹ None of these trials assessed HbA1C levels.

In the COR Diabetes trial, change from baseline in HbA1C was -0.63% in the treatment group, and -0.14% in the placebo arm.⁵⁷ Participants receiving the treatment experienced no change in SBP, while participants receiving placebo experienced a mean decrease in SBP of 1.1 mmHg. See Table 3.10 for detailed results.

Table 3.9. Results of Key Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity^{53,55,59-64}

Study Arms	EQUIP		COR-I		COR-II		COR BMOD	
	PBO	P/T (high)	PBO	B/N	PBO	B/N	PBO	B/N
N	498	498	511	471	456	702	193	482
% Weight Loss from Baseline to One Year, Mean (SE)	-1.6 (0.4)	-10.9 (0.4)	-1.3 (0.3)	-6.1 (0.3)	-1.2 (0.3)	-6.4 (0.3)	-5.1 (0.6)	-9.3 (0.4)
Participants with 5% Weight Loss, n (%)	86 (17.3)	332 (66.7)	84 (16)	226 (48)	80 (17.1)	354 (50.5)	82 (42.5)	320 (66.4)
Participants with 10% Weight Loss, n (%)	37 (7.4)	235 (47.2)	38 (7)	116 (25)	26 (5.7)	199 (28.3)	39 (20.2)	200 (41.5)
Change in SBP from Baseline, mmHg, Mean (SE)	0.9 (0.6)*	-2.9 (0.6)*	-1.9 (0.4)	-0.1 (0.4)	-0.5 (0.4)	0.6 (0.3)	-3.9 (0.7)	-1.3 (0.5)
Change in A1C from Baseline, %, Mean (SE)	NR	NR	NR	NR	NR	NR	NR	NR

A1C: glycated hemoglobin, B/N: bupropion/naltrexone, mmHg: millimeters of mercury, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SBP: systolic blood pressure, SE: standard error

*SE manually derived from standard deviation or 95% CIs.

Table 3.10. Results of Key Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity with Diabetes Mellitus^{51,56-58}

Study Arms	CONQUER (Diabetes Subgroup)			COR Diabetes	
	PBO	P/T (low)	P/T (high)	PBO	B/N
N	157	67	164	159	265
% Weight Loss from Baseline to One Year, Mean (SE)	-1.9 (0.6)*	-6.8 (0.9)*	-8.8 (0.6)*	-1.8 (0.4)	-5 (0.3)
Participants with 5% Weight Loss, n (%)	NR	NR	NR	30 (18.9)	118 (44.5)
Participants with 10% Weight Loss, n (%)	NR	NR	NR	9 (5.7)	49 (18.5)
Change in SBP from Baseline, mmHg, Mean (SE)	-2.1 (1.1)	-2.9 (1.6)	-4.2† (1)	-1.1 (0.9)	0 (0.7)
Change in A1C from Baseline, %, Mean (SE)	-0.1† (0.05)*	-0.4† (1.5)*	-0.4† (0.6)*	-0.14† (0.09)	-0.63† (0.07)

A1C: glycated hemoglobin, BN: bupropion/naltrexone, mmHg: millimeters of mercury, NR: not reported, PBO: placebo, PT: phentermine/topiramate, SBP: systolic blood pressure, SE: standard error

*SE manually derived from standard deviation or 95% CIs.

†The number of patients for this outcome may differ from the primary analysis population.

HRQoL

Clinical trial participants for all interventions were assessed for improvements in physical function and mental HRQoL using a variety of instruments: Short Form 36v2 Health Survey (SF-36v2), Impact of Weight on Quality of Life (IWQOL) Lite Clinical Trials Version, Patient Health Questionnaire (PHQ-9), and Inventory of Depressive Symptomatology – Self Report (IDS-SR). SF-36v2 consists of 36 questions across eight domains, including physical functioning. Additionally, SF-36v2 provides two aggregated scores: the physical component summary (PCS) and mental component summary (MCS). For the SF-36v2 and IWQOL-Lite-CT instruments, an increase in score is representative of an improvement in health status (positive is better). The PHQ-9 and IDS-SR and reflect depressive symptom severity; a decrease in score in these measures indicates an improvement in depressive symptoms (lower is better). The instruments and their results among the interventions are described in more detail and presented in Supplement [Section D2](#) (Tables [D17](#) and [D18](#)).

Semaglutide

Physical functioning was assessed in the STEP 1, STEP 2, and STEP 3 trials using the SF-36v2 Physical Functioning Score.²⁷⁻²⁹ STEP 1 and 3 also assessed the mean change in baseline of the SF-36v2 PCS. STEP 1 and 2 also assessed physical function utilizing the IWQOL-Lite-CT instrument.^{27,28} Overall, semaglutide resulted in greater improvement in the physical component across all HRQoL instruments compared to placebo, indicating the intervention resulted in greater improvement in health status for physical patient-reported outcomes.

STEP 1, 2, and 3 trials all reported baseline SF-36v2 MCS scores, but only STEP 1 and 3 reported the change from baseline to week 68. STEP 2 reported estimated treatment differences. In STEP 1, participants in the semaglutide arm experienced improvement in SF-36 MCS scores (1.5) versus placebo, which had a reduction in score (-2.1). Conversely, in STEP 3, participants in both treatment arms experienced decreased SF-36 MCS, although there was a smaller decrease in the semaglutide arm (-0.8) compared to placebo (-2.9).

Liraglutide

The SCALE (Sleep Apnea, Obesity and Pre-Diabetes, IBT, and Insulin) trials assessed physical patient-reported outcomes utilizing the SF-36v2 PCS instrument.^{39,41-43} The IWQOL-Lite-CT instrument assessed physical function score in the SCALE (Type 2 Diabetes, Obesity and Pre-Diabetes, IBT, and Insulin) studies.⁴⁰⁻⁴³ Overall, liraglutide resulted in greater improvement in the physical component across all HRQoL instruments compared to placebo, indicating the intervention resulted in greater improvement in health status for physical patient-reported outcomes. The one exception was SCALE (IBT), which reported slightly less improvement in SF-36v2 PCS scores for liraglutide (3.4) compared to placebo (3.8).

Four studies for liraglutide, SCALE (Sleep Apnea, Obesity and Pre-Diabetes, IBT, and Insulin) trials also evaluated the mental component utilizing the SF-36v2 MCS instrument with minimal improvements compared to baseline in the liraglutide arm for the SCALE (Sleep Apnea and Obesity and Pre-Diabetes) trials (1.4 and 0.2, respectively), less improvement in the SCALE (Sleep Apnea) placebo arm (0.9), and a decrease in health quality in the SCALE (Obesity and Pre-Diabetes) placebo arm (-0.9).^{39,41} The SCALE (IBT and Insulin) trials reported a decrease in SF-36v2 scores across both the liraglutide and placebo arms of the trial, indicating a decreased mental health status.

Phentermine/Topiramate

Physical function outcomes were not assessed. Depression was assessed in the EQUATE and EQUIP trials using the PHQ-9 instrument. For both trials, a greater improvement in this measure was observed in the high-dose phentermine/topiramate arms, compared to the placebo arms. In EQUATE, participants in the high-dose and low-dose phentermine/topiramate arms improved by 1.1 and 1.3 points, respectively, while participants in placebo improved by 0.5 points.^{52,54} Depression scores in the EQUIP trial improved more from baseline in the high-dose phentermine/topiramate group (1.5), compared to the placebo group (1.3).^{53,55} PHQ-9 was not assessed in the diabetes mellitus subgroup of the CONQUER trial.

Bupropion/Naltrexone

HRQoL was assessed using the IWQOL-Lite, an obesity-specific instrument and the IDS-SR, which assesses depressive symptoms. In COR-I, COR-II, and COR-BMOD, patients in the bupropion/naltrexone group showed a greater improvement in the IWQOL-LITE physical function and total scores than patients in the placebo group.^{59-61,63,64} However, changes in depression scores were not consistent across trials. In COR-I and COR-II, patients in the placebo arm reported a greater improvement in their depressive symptoms (-0.7 and -0.5, respectively) compared to the high-dose bupropion/naltrexone arm (-0.3) (lower is better).⁵⁹⁻⁶¹ In COR-BMOD, patients in the treatment arm reported a 0.1 increase from baseline in IDS-SR score, meaning their depressive symptoms worsened, while patients in placebo reported no change.^{63,64} In the COR Diabetes trial, patients in the bupropion/naltrexone treatment arm reported no change in depression score, while patients in the placebo arm reported that their mean score improved by 1.6.^{57,58}

NMA Results of Percentage Weight Loss from Baseline at One Year

We conducted NMAs of trials including participants with obesity alone separately from trials of participants with obesity and diabetes mellitus and excluded trials that included IBT as an adjunct to medication. The primary outcome NMAs are reported below, and additional outcomes are available in [Supplement D1](#).

Participants with Obesity Alone

For the trials of the medications conducted in participants with obesity without diabetes mellitus that included standard diet and exercise counseling and reported percentage weight loss at one year, we present the results of the baseline risk-adjusted random effects model, given its better fit for the model compared to the unadjusted model in Table 3.11. All medications, in combination with diet and exercise counseling, showed statistically significantly greater mean weight loss than placebo with diet and exercise counseling at one year. Compared to placebo, the interventions demonstrated 4.6-13.7% mean greater weight loss. Semaglutide demonstrated the greatest percentage weight loss at one year and was superior to all other medications in our review for this outcome. Phentermine/topiramate (high dose) demonstrated greater weight loss than liraglutide and bupropion/naltrexone, however, liraglutide was not statistically more effective in demonstrating weight loss than bupropion/naltrexone (Table 3.11).

Table 3.11. NMA Results of Medications for the Management of Obesity, Mean Percentage Weight Loss from Baseline at One Year (95% CI)

Semaglutide				
-4.6 (-2.4 to -7.2)	Phentermine/ Topiramate*			
-8.7 (-7.3 to -10.4)	-4.1 (-1.9 to -6.3)	Liraglutide		
-9.1 (-7.2 to -11.5)	-4.5 (-2.2 to -6.9)	-0.4 (-2.3 to +1.3)	Bupropion/ Naltrexone	
-13.7 (-12.6 to -15.1)	-9.1 (-7.1 to -11)	-5.0 (-3.9 to -6.1)	-4.6 (-3.0 to -6.0)	Placebo

Legend: Each cell represents estimated absolute differences in percentage weight loss and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo.

Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

Participants with Obesity and Diabetes Mellitus

For the trials of the medications conducted in participants with obesity and diabetes mellitus (using the approved obesity indication dose) that reported percentage weight loss at one year, we present the results of the baseline risk-adjusted random effects model, given its better fit for the model compared to the unadjusted model in Table 3.12. All medications, in combination with diet and exercise counseling, showed statistically significantly greater mean weight loss than placebo with diet and exercise counseling at one year among participants with obesity with diabetes mellitus, although the magnitude of the weight loss was somewhat lower than in trials of participants with obesity alone, especially for semaglutide. Compared to placebo, the medications demonstrated 2.9-7.6% mean greater weight loss at one year. Semaglutide demonstrated a greater percentage weight loss among the medications, however, these differences were not statistically significant. Phentermine/topiramate (high dose) demonstrated greater weight loss than liraglutide and

bupropion/naltrexone, however, the results were only statistically significant compared to bupropion/naltrexone. Liraglutide was not statistically more effective in demonstrating weight loss than bupropion/naltrexone (Table 3.12).

Table 3.12. NMA Results of Medications for the Management of Obesity with Diabetes Mellitus, Mean Percentage Weight Loss from Baseline at One Year (95% CI)

Semaglutide				
-0.9 (-6.3 to +6.2)	Phentermine/ Topiramate*			
-3.9 (-9.3 to +3.7)	-2.9 (-0.05 to -5.8)	Liraglutide		
-4.7 (-10.3 to +2.8)	-3.8 (-0.4 to -7.1)	-0.9 (-3.8 to +2.1)	Bupropion/ Naltrexone	
-7.6 (-1.7 to -11.9)	-6.7 (-4.2 to -9.2)	-3.7 (-1.7 to -6)	-2.9 (-0.4 to -5.6)	Placebo

Legend: Each box represents estimated absolute differences in percentage weight loss and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo.

Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

NMA Results of Change in SBP from Baseline at One Year

Participants with Obesity Alone

For the trials of the medications conducted in participants with obesity without diabetes mellitus that included standard diet and exercise counseling and reported change in SBP at one year, we present the results of the baseline risk-adjusted random effects model, given its better fit for the model compared to the unadjusted model in Table 3.11. All medications, in combination with diet and exercise counseling, showed statistically significantly greater improvements in SBP than placebo with diet and exercise counseling at one year except bupropion/naltrexone, which was comparable to placebo. Compared to placebo, the interventions demonstrated 3.8-7.1 mmHg improvements in SBP. Semaglutide demonstrated the greatest improvement in SBP at one year and was superior to all other medications in our review except for phentermine/topiramate (high dose) for this outcome. Phentermine/topiramate (high dose) and liraglutide both demonstrated greater improvements in SBP than bupropion/naltrexone, however, the interventions were statistically equivalent (Table 3.13).

Table 3.13. NMA Results of Medications for the Management of Obesity, Mean Change in SBP from Baseline at One Year (95% CI)

Semaglutide				
-2.9 (-6.2 to 0.4)	Phentermine/ Topiramate*			
-3.3 (-5.3 to -1.2)	-0.4 (-3.6 to 2.9)	Liraglutide		
-6.3 (-7.9 to -4.7)	-3.4 (-6.3 to -0.6)	-3.1 (-4.7 to -1.4)	Placebo	
-7.1 (-9.8 to -4.4)	-4.2 (-7.9 to -0.6)	-3.9 (-6.8 to -1.0)	-0.8 (-3.0 to 1.3)	Bupropion/ Naltrexone

Legend: Each box represents estimated absolute differences in SBP and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

Participants with Obesity and Diabetes Mellitus

For the trials of the medications conducted in participants with obesity and diabetes mellitus and reported change in SBP at one year, we present the results of the baseline risk-adjusted random effects model, given its better fit for the model compared to the unadjusted model in Table 3.13. Semaglutide and liraglutide, in combination with diet and exercise counseling, showed statistically significantly greater improvements in SBP than placebo with diet and exercise counseling at one year, while phentermine/topiramate (high dose) and bupropion/naltrexone did not. Compared to placebo, semaglutide and liraglutide demonstrated 4.3 mmHg and 3.4 mmHg improvements in SBP, respectively (Table 3.14).

Table 3.14. NMA Results of Medications for the Management of Obesity and Diabetes Mellitus, Mean Change in SBP from Baseline at One Year (95% CI)

Semaglutide				
-0.9 (-4.2 to 2.5)	Liraglutide			
-3.5 (-8.9 to 2.1)	-2.7 (-6.8 to -1.6)	Phentermine/ Topiramate*		
-4.3 (-1.2 to -7.2)	-3.4 (-1.6 to -5.2)	-0.7 (-4.4 to 2.8)	Placebo	
-5.3 (-1.4 to -9.2)	-4.4 (-1.3 to -7.6)	-1.8 (-6.3 to 2.6)	-1.1 (-4.6 to 1.5)	Bupropion/ Naltrexone

Legend: Each box represents estimated absolute differences in SBP and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

Harms

Adverse events reported in the trials are detailed below by medication. It is worth noting that three of the medications carry black box warnings and the fourth has a Risk Evaluation and Mitigation Strategies in place. The GLP-1 medications, semaglutide and liraglutide, carry a black box warning for thyroid carcinoma and bupropion/naltrexone carries a warning for suicidality.

Phentermine/topiramate has a Risk Evaluation and Mitigation Strategy in place for a risk of birth defects. These outcomes were not observed in any of the trials but relate to real-world data and should be taken into consideration when prescribing.

Semaglutide

The most frequent adverse events in the STEP trials for semaglutide were gastrointestinal-related symptoms, including nausea, constipation, and diarrhea.²⁷⁻³⁶ Beyond gastrointestinal events, semaglutide appeared relatively well-tolerated. Rates of adverse events and serious adverse events were higher in the semaglutide arm compared to placebo, except STEP 5, which had a higher rate of serious adverse events in the placebo arm (11.8%) versus the semaglutide arm (7.9%). The higher rate of serious adverse events in the placebo arm of STEP 5 seems to be a chance event associated with events that are not expected to be associated with the intervention within the placebo arm, including COVID-19 infections, foot deformity, jaw and rib fractures, and several occurrences of cancer.^{35,36}

Across all trials, there were higher rates of discontinuation due to adverse events in the semaglutide arms compared to placebo, and discontinuation was most often attributed to gastrointestinal events. In STEP 8, participants in the liraglutide arm were more likely to discontinue due to adverse events (12.6%) compared to both the semaglutide and placebo arms (3.2% and 3.5%, respectively) (safety analysis set).³¹ STEP 2, which evaluated participants with obesity and diabetes mellitus, did not exhibit any significant differences in harms compared to other trials in the STEP clinical trial program, which evaluated participants with obesity without diabetes mellitus.²⁸ See Table 3.15 for detailed harms results.

There were several areas of focus for safety in the STEP clinical trial program due to therapeutic experience with GLP-1 receptor agonists and regulatory feedback and requirements. These included gastrointestinal disorders, gallbladder-related disorders, cardiovascular disorders, and psychiatric disorders. As expected, there were higher rates of gastrointestinal disorders in semaglutide arms as compared to placebo. Gallbladder-related disorders and cardiovascular disorders were higher in the semaglutide arm compared to placebo across all trials. Psychiatric disorder event rates were higher in semaglutide arms versus placebo arms in the STEP 2, STEP 3, and STEP 5 trials.^{28,29,35} In the STEP 8 trial, there were higher rates of psychiatric disorder events in the liraglutide arm (15%) compared to the semaglutide (5.6%) and placebo arms (10.6%).³¹ See Supplement [Table D33](#) for detailed safety focus area results.

Table 3.15. Harms in Key Trials of Semaglutide for the Management of Obesity or Obesity with Diabetes Mellitus²⁷⁻³⁶

	STEP 1		STEP 2*		STEP 3		STEP 5		STEP 8		
Study Arms	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	LIR
N	655	1,306	402	403	204	407	152	152	85	126	127
Any AE, n (%)	566 (86.4)	1,171 (89.7)	309 (76.9)	353 (87.6)	196 (96.1)	390 (95.8)	136 (89.5)	146 (96.1)	81 (95.3)	120 (95.2)	122 (96.1)
SAE, n (%)	42 (6.4)	128 (9.8)	37 (9.2)	40 (9.9)	6 (2.9)	37 (9.1)	18 (11.8)	12 (7.9)	6 (7.1)	10 (7.9)	14 (11)
AEs Leading to Discontinuation, n (%)	20 (3.1)	92 (7)	14 (3.5)	25 (6.2)	6 (2.9)	24 (5.9)	7 (4.6)	9 (5.9)	3 (3.5)	4 (3.2)	16 (12.6)
GI Disorders Leading to Discontinuation, n (%)	5 (0.8)	59 (4.5)	4 (1)	17 (4.2)	0 (0)	14 (3.4)	NR	NR	1 (1.2)	1 (0.8)	8 (6.3)
Nausea, n (%)	114 (17.4)	577 (44.2)	37 (9.2)	136 (33.7)	45 (22.1)	237 (58.2)	NR	NR	19 (22.4)	77 (61.1)	75 (59.1)
Constipation, n (%)	62 (9.5)	306 (23.4)	22 (5.5)	70 (17.4)	50 (24.5)	150 (36.9)	NR	NR	20 (23.5)	49 (38.9)	40 (31.5)
Diarrhea, n (%)	104 (15.9)	412 (31.5)	48 (11.9)	86 (21.3)	45 (22.1)	147 (36.1)	NR	NR	22 (25.9)	35 (27.8)	23 (18.1)

AE: adverse event, GI: gastrointestinal, LIR: liraglutide, NR: not reported, PBO: placebo, SAE: serious adverse event, SEM: semaglutide

*Included participants with obesity and diabetes mellitus.

Liraglutide

Like semaglutide, the most frequent adverse events in the SCALE trials for liraglutide compared with placebo were gastrointestinal-related symptoms, including nausea, constipation, and diarrhea.^{38-43,46,48-50} The frequency of any adverse events was similar between liraglutide and placebo across all trials, with the exception of the SCALE (Obesity and Pre-Diabetes) trial, in which participants in the liraglutide arm experienced a higher rate of any adverse events (80.3%), regardless of causality, compared to participants in the placebo arm (63.3%).⁴¹ Rates of discontinuation due to adverse events were higher in the liraglutide arms compared to placebo. SCALE (Type 2 Diabetes) and SCALE (Insulin), which both included participants with obesity and diabetes mellitus, exhibited higher rates of serious adverse events compared to trials in the SCALE clinical trial program, which evaluated participants with obesity without diabetes mellitus.^{40,42} Across all SCALE trials, there were generally higher rates of gallbladder-related and pancreatic adverse events in the intervention arm compared to placebo. See Table 3.16 for detailed harms results.

Table 3.16. Harms in Key Trials of Liraglutide for the Management of Obesity and Obesity with Diabetes Mellitus^{38-43,46,48-50}

	SCALE Maintenance		SCALE Sleep Apnea		SCALE Obesity and Pre-Diabetes		SCALE IBT		SCALE Type 2 Diabetes*		SCALE Insulin*	
Study Arms	PBO	LIR	PBO	LIR	PBO	LIR	PBO	LIR	PBO	LIR	PBO	LIR
N	210	212	179	176	1,242	2,481	140	142	212	422	197	195
Any AE, n (%)	186 (88.6)	194 (91.5)	124 (69.3)	141 (80.1)	786 (63.3)	1,992 (80.3)	124 (88.6)	136 (95.8)	182 (85.8)	392 (92.9)	175 (88.8)	180 (92.3)
SAE, n (%)	5 (2.4)	9 (4.3)	6 (3.4)	6 (3.4)	62 (5)	154 (6.2)	2 (1.4)	6 (4.2)	21 (9.9)	52 (12.3)	19 (9.6)	16 (8.2)
AE Leading to Discontinuation, n (%)	18 (8.6)	18 (8.5)	NR	NR	47 (3.8)	240 (9.7)	6 (4.3)	12 (8.5)	7 (3.3)	39 (9.2)	6 (3)	15 (7.7)
Nausea, n (%)	36 (17.1)	101 (47.6)	12 (6.7)	47 (26.7)	183 (14.7)	997 (40.2)	25 (17.9)	68 (47.9)	29 (13.7)	138 (32.7)	23 (11.7)	58 (29.7)
Constipation, n (%)	26 (12.4)	57 (26.9)	6 (3.4)	21 (11.9)	108 (8.7)	495 (20)	26 (18.6)	43 (30.3)	13 (6.1)	68 (16.1)	17 (8.6)	28 (14.4)
Diarrhea, n (%)	26 (12.4)	38 (17.9)	14 (7.8)	29 (16.5)	115 (9.3)	518 (20.9)	23 (16.4)	31 (21.8)	27 (12.7)	108 (25.6)	30 (15.2)	45 (23.1)

AE: adverse event, LIR: liraglutide; NR: not reported, PBO: placebo, SAE: serious adverse event

*Included participants with obesity and diabetes mellitus.

Phentermine/Topiramate

Adverse events of any cause in the EQUIP, EQUATE, and CONQUER trials were mostly mild to moderate in severity. Rates of any adverse events were relatively high among all arms (73-86%), with highest rates in the high-dose phentermine/topiramate arm, followed by the low-dose phentermine/topiramate arm, and the placebo arm.^{52-54,56} Adverse reactions that occurred more frequently in the high-dose and low-dose phentermine/topiramate treatment groups included paresthesia, nausea, dry mouth, constipation, and headache. EQUIP and CONQUER also assessed psychiatric adverse events, such as insomnia, anxiety, and depression, which were more common in the high-dose and low-dose phentermine/topiramate arms,^{52,53} with the exception of depression in the CONQUER trial, where the incidence of depression in the low-dose intervention arm (3%) was similar to the placebo arm (3.2%).⁵⁶

Serious adverse reactions were relatively low among all trials and arms (0-6%). In the EQUIP trial, participants in all arms reported serious adverse events at the same rate (2.5%),⁵³ while in the EQUATE trial, more participants in the high-dose treatment arm (1.9%) and low-dose treatment arm (0.9%) reported more serious adverse events than in the placebo arm (0%).⁵² In the CONQUER trial, incidence of serious adverse events was 3.7% in the high-dose phentermine/topiramate arm, 6% in the low-dose phentermine/topiramate arm, and 3.2% in the placebo arm.⁵⁶ Serious adverse events that occurred infrequently in the phentermine/topiramate arms were chest pain, nephrolithiasis, appendicitis, blurred vision, humerus fracture, and myelogenous leukemia. Among all trials, discontinuation due to adverse events occurred most frequently in the high-dose arm (16-21%), followed by the low-dose arm (9-15%), and placebo (7-8%). See Table 3.17 for more details on harms.

Table 3.17. Harms in Key Trials of Phentermine/Topiramate for the Management of Obesity and Obesity with Diabetes Mellitus

	EQUIP		EQUATE			CONQUER (Diabetes Subgroup)*		
Study Arms	PBO	P/T (high)	PBO	P/T (low)	P/T (high)	PBO	P/T (low)	P/T (high)
N	513	511	109	106	108	157	67	164
Any AE, n (%)	374 (72.9)	432 (84.5)	87 (79.8)	85 (80.2)	90 (83.3)	125 (79.6)	54 (80.6)	141 (86)
SAE, n (%)	13 (2.5)	13 (2.5)	0 (0)	1 (0.9)	2 (1.9)	5 (3.2)	4 (6)	6 (3.7)
AE Leading to Disc., n (%)	43 (8.4)	82 (16)	8 (7.3)	16 (15.1)	23 (23.1)	13 (8.3)	6 (9)	31 (18.9)
Paresthesia, n (%)	10 (1.9)	96 (18.8)	4 (3.7)	17 (16)	25 (23.1)	6 (3.8)	5 (7.5)	29 (17.7)
Dry Mouth, n (%)	19 (3.7)	87 (17)	0 (0)	14 (13.2)	20 (18.5)	6 (3.8)	5 (7.5)	22 (13.4)
Headache, n (%)	52 (10.1)	61 (11.9)	14 (12.8)	16 (15.1)	17 (15.7)	9 (5.7)	3 (4.5)	18 (11)
Constipation, n (%)	35 (6.8)	72 (14.1)	9 (8.3)	7 (6.6)	17 (15.7)	10 (6.4)	10 (14.9)	29 (17.7)
Nausea, n (%)	24 (4.7)	37 (7.2)	5 (4.6)	9 (8.5)	8 (7.4)	8 (5.1)	1 (1.5)	13 (7.9)
Insomnia, n (%)	25 (4.9)	40 (7.8)	6 (5.5)	13 (12.3)	11 (10.2)	8 (5.1)	5 (7.5)	23 (14)
Anxiety, n (%)	6 (1.2)	19 (3.7)	NR	NR	NR	NR	NR	NR
Depression, n (%)	6 (1.2)	24 (4.7)	NR	NR	NR	5 (3.2)	2 (3)	10 (6.1)

AE: adverse event, Disc.: discontinuation, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SAE: serious adverse event

*Included participants with obesity and diabetes mellitus.

Bupropion/Naltrexone

Any adverse events in COR-I, COR-II, COR-BMOD, and COR Diabetes occurred at a higher rate in the bupropion/naltrexone arms (83-90%) than in placebo (67-75%).^{57,59,61,63,64} Nausea, dry mouth, headache, constipation, and upper respiratory tract infection occurred more frequently in the treatment arms compared to placebo. Occurrence of psychiatric events, such as insomnia, anxiety, depression, and stress, varied among all trials. Insomnia occurred more frequently in the bupropion/naltrexone group versus placebo in COR-I, COR-II, and COR-BMOD. Rates of anxiety were higher in the intervention arms than in placebo arms in COR-II and COR-BMOD but were lower than in the placebo arm in COR-I. Depression occurred at a higher rate in the treatment groups in all studies except COR-BMOD. Participants in the bupropion/naltrexone group in COR-BMOD also experienced less stress than participants in the placebo arm.

In COR-I, COR-II and COR-BMOD, serious adverse events were more frequent in the intervention arms (2-4%) versus the placebo arm (1%).⁵⁹⁻⁶⁴ In COR Diabetes assessing participants with obesity and diabetes mellitus, serious adverse events were more common in the placebo arm (4.7%) than in the treatment arm (3.9%).^{57,58} Serious adverse events that occurred infrequently in the

bupropion/naltrexone arm were cholecystitis, cardiac failure, and seizures. Discontinuation due to adverse events occurred more frequently in the bupropion/naltrexone arms (20-29%) than in the placebo arms across the trials (10-15%). See Table 3.18 for more details on harms.

Table 3.18. Harms in Key Trials of Bupropion/Naltrexone for the Management of Obesity and Obesity with Diabetes Mellitus⁵⁷⁻⁶⁴

Study Arms	COR-I		COR-II		COR-BMOD		COR Diabetes*	
	PBO	B/N	PBO	B/N	PBO	B/N	PBO	B/N
N	569	573	492	992	200	584	169	333
Any AE, n (%)	390 (68.5)	476 (83.1)	370 (75.2)	852 (85.9)	133 (66.5)	487 (83.4)	144 (85.2)	301 (90.4)
SAE, n (%)	8 (1.4)	9 (1.6)	7 (1.4)	21 (2.1)	1 (0.5)	22 (3.8)	13 (4.7)	8 (3.9)
AE leading to Disc., n (%)	56 (9.8)	112 (19.5)	68 (13.8)	241 (24.3)	25 (12.4)	150 (25.4)	26 (15.4)	98 (29.4)
Death, n (%)	0 (0)	1 (0.2)	NR	NR	0 (0)	0 (0)	NR	NR
Dry mouth, n (%)	11 (1.9)	43 (7.5)	13 (2.6)	90 (9.1)	6 (3)	47 (8)	5 (3)	21 (6.3)
Headache, n (%)	53 (9.3)	79 (13.8)	43 (8.7)	174 (17.5)	35 (17.5)	139 (23.8)	15 (8.9)	46 (13.8)
Constipation, n (%)	32 (5.6)	90 (15.7)	35 (7.1)	189 (19.1)	28 (14)	141 (24.1)	12 (7.1)	59 (17.7)
URTI, n (%)	64 (11.2)	57 (9.9)	55 (11.2)	86 (8.7)	NR	NR	16 (9.5)	26 (7.8)
Nausea, n (%)	30 (5.3)	171 (29.8)	34 (6.9)	290 (29.2)	21 (10.5)	199 (34.1)	12 (7.1)	141 (42.3)
Insomnia, n (%)	29 (5.1)	43 (7.5)	33 (6.7)	97 (9.8)	12 (6)	51 (8.7)	9 (5.3)	37 (11.1)
Anxiety, n (%)	12 (2.1)	9 (1.6)	21 (4.3)	48 (4.8)	7 (3.5)	30 (5.1)	2 (1.2)	18 (5.4)
Depression, n (%)	6 (1.1)	3 (0.5)	8 (1.6)	13 (1.3)	5 (2.5)	2 (0.3)	3 (1.8)	2 (0.6)
Stress, n (%)	NR	NR	NR	NR	4 (2)	3 (0.5)	NR	NR

AE: adverse event, B/N: bupropion/naltrexone, Disc.: discontinuation, NR: not reported, PBO: placebo, SAE: serious adverse event, URTI: upper respiratory tract infection

*Included participants with obesity and diabetes mellitus.

†N=202.

‡N=591.

NMA Results of Discontinuation

For the outcome of discontinuation due to adverse events, we conducted an NMA of trials including participants with obesity alone and excluded trials of participants with obesity and diabetes mellitus. The discontinuation NMA included a wider set of trials than in the efficacy NMAs and did not exclude trials that included IBT programs in addition to the interventions. The NMA of discontinuation due to adverse events is reported below, and the network diagram is presented in the [Supplement](#).

Participants with Obesity Alone

For the trials of the medications conducted in participants with obesity without diabetes mellitus and reported discontinuation due to adverse events, we present the results of the unadjusted random effects model in Table 3.19, given its better fit for the model compared to the baseline risk adjusted model. Discontinuation rates due to adverse events were higher for all medications compared to placebo. Semaglutide may have lower discontinuation rates than liraglutide, phentermine/topiramate, and bupropion/naltrexone, however, these results were not statistically significant (Table 3.19).

Table 3.19. NMA Results of Medications for the Management of Obesity, Odds Ratio of Discontinuation Rates due to Adverse Events (95% CI)

Semaglutide				
0.7 (0.3-1.3)	Liraglutide			
0.8 (0.3-1.5)	1.1 (0.5-2.2)	Bupropion/ Naltrexone		
0.7 (0.2-1.5)	1.0 (0.4-2.3)	0.9 (0.4-2.1)	Phentermine/ Topiramate*	
1.7 (0.9-2.8)	2.4 (1.4-4.0)	2.2 (1.3-3.7)	2.4 (1.3-5.2)	Placebo

Legend: Each box represents the estimated odds ratio of discontinuation due to adverse events and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

Subgroup Analyses and Heterogeneity

We sought evidence on obesity management in subgroups of interest such as in individuals with higher or lower baseline BMI, pre-diabetes, or previous weight loss surgery, however, data were generally not available or were provided to ICER as confidential. In the STEP 1 and 2 trials of semaglutide, SCALE Obesity and Pre-Diabetes trial of liraglutide, and EQUIP trial of phentermine/topiramate in adults with obesity, percentage weight loss was generally consistent across BMI subgroups corresponding to obesity classes I/II/III, suggesting a benefit across the range of obesity severity included in these trials. In a post-hoc analysis of the STEP 1, 3, and 4 trials of semaglutide (which enrolled 40-50% of participants with pre-diabetes), improvements in A1C and blood glucose were comparable or better among participants with pre-diabetes than among the overall study population, suggesting a benefit in glycemic status consistent with the drug's mechanism of action.³⁷

Uncertainty and Controversies

Though pharmacy claims data suggest that many individuals who take medications for weight loss do not use them for long periods of time, experts and patients we spoke with highlighted that weight regain after stopping treatment is common. This points to the need for long-term use of these medications. All key trials reported outcomes over approximately one year follow-up. Few comparative trials have examined longer-term outcomes making the benefits and harms of these medications over prolonged periods uncertain. For individuals without diabetes mellitus, heart disease, arthritis, sleep apnea, or cancer, studies have not shown whether weight loss prevents disease morbidity and mortality. Studies of treatments for obesity in individuals undergoing weight loss surgery for severe obesity demonstrate decreased incidence of cardiovascular- and cancer-related outcomes and lower mortality.^{4,25,66} However, these results primarily come from observational studies and the benefit in individuals without diabetes mellitus and lower baseline weights is less clear. Thus, there is a need for studies examining long-term outcomes in individuals without diabetes mellitus who are chronically using weight loss medications.⁶⁷

We primarily used indirect quantitative methods (NMAs) to compare semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone to each other because there was only a single head-to-head study of semaglutide and liraglutide. Differences in study populations, lifestyle interventions offered, and escalation schedules that led to different follow-up intervals all contribute to indirect analyses having more uncertainty than if the therapies had been compared directly.

All of the pivotal Phase III randomized controlled trials compared the active agents to placebo among patients receiving lifestyle interventions. As a result, the studies assessed the additive benefit of the drugs in addition to lifestyle interventions that varied among the studies. Because we expect that medications when used in routine clinical practice will more commonly be given with

less intensive lifestyle interventions, our primary analyses included trials with standard lifestyle interventions and may represent the best evidence for the efficacy of the active therapies. Other trials compared drugs to placebo along with more intensive lifestyle interventions that included IBT or structured meal programs. These trials also demonstrated benefit of the drugs compared to placebo, but in general, the amount of weight loss was slightly less than seen in the trials with standard lifestyle interventions.

These trials examined the relative benefits of the individual and fixed dose combination agents as single interventions. The drugs that make up the phentermine/topiramate and bupropion/naltrexone combinations are also approved for other indications as individual drugs at somewhat different doses. We heard from experts that these individual drugs are used singly or in various combinations in an “off-label” manner. Clinicians said such use may mitigate side effects and be less costly to patients. Semaglutide and liraglutide are FDA-approved for treatment of diabetes mellitus at lower doses, and while these doses may be associated with less weight loss than the doses used in our primary outcome analyses, these lower doses may be used, especially in those with co-existing diabetes mellitus, because they may be better covered by insurers and result in fewer out-of-pocket expenses to patients.

We only compared results of individual drugs or approved fixed dose combinations. Using multiple drugs that work through different mechanisms may achieve synergistic effects. For example, tirzepatide, which is a GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist, is currently being studied in individuals with obesity and may provide greater weight loss than seen with GLP-1 agents alone. In addition to their weight loss properties, semaglutide and liraglutide as GLP-1 receptor agonists have also been shown to decrease blood sugar in individuals with pre-diabetes and diabetes mellitus, and to decrease major adverse cardiovascular events among individuals with diabetes mellitus. It is not known whether GLP-1 receptor agonists provide benefits to individuals with obesity that go beyond their weight loss effects compared to other approved weight loss drugs with different mechanisms of action. At present, this remains uncertain for individuals without diabetes mellitus using GLP-1 receptor agonists for weight loss and warrants future investigation.

There is limited information available about the relative benefits and harms of these drugs in important subgroups including patients with lower BMIs. Similarly, for those with BMIs of greater than 40 where weight loss surgery is an option, the relative benefits and harms of these drugs compared to weight loss surgery is uncertain. Moreover, experts discussed that these medications are being used in individuals after weight loss surgery to treat or prevent weight regain, and the effects of their use here is also uncertain.

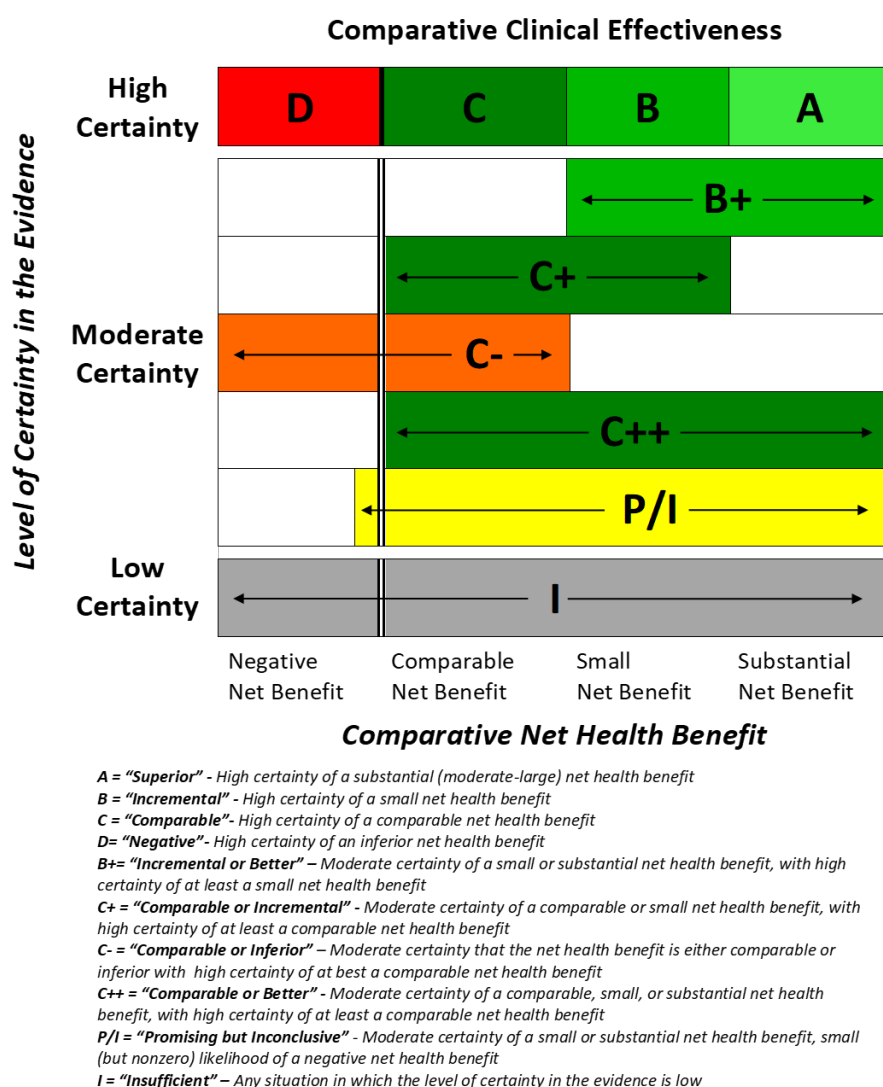
Trials of weight loss medications include populations that are underrepresented in terms of the percentage of men and minority groups. Weight reductions seen in these trials among men and women appeared similar. Since most trials included mostly White patients and given the large

impact of obesity in Black Americans and other racial and ethnic groups, there is a need for more studies evaluating the outcomes of the various medications in these populations. For example, a post-hoc analysis of liraglutide trials showed similar weight reduction across racial and ethnic groups.⁶⁸

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided [here](#).

Figure 3.1. ICER Evidence Rating Matrix



Results from the clinical trials and from our NMAs demonstrate that semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone improve weight loss outcomes of patients with obesity compared to usual care (that includes standard lifestyle management). The magnitude of the weight loss appears to be greater for semaglutide and phentermine/topiramate than for liraglutide and bupropion/naltrexone based on the one head-to-head trial of semaglutide and liraglutide and our indirect NMA results. Other outcomes show that semaglutide and liraglutide improved blood sugar, blood pressure, and physical function compared to usual care. Blood pressure was lower with phentermine/topiramate than usual care. Blood sugar results were not reported in the phentermine/topiramate and bupropion/naltrexone trials for patients without diabetes mellitus.

Semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone appeared to have few serious harms reported from the trials and use for other indications. Discontinuation due to adverse events from our indirect NMA was higher for each intervention compared to placebo. Patients taking liraglutide, phentermine/topiramate, and bupropion/naltrexone may have higher discontinuation rates due to adverse events than for semaglutide.

There is uncertainty about the relative benefit and safety among the four medications due to differences in the trials with regards to their size, patient characteristics, concomitant lifestyle interventions, outcomes assessed, and duration of follow-up that the indirect nature of the NMAs do not fully capture. For all of the drugs, there is a lack of long-term efficacy and safety data that includes whether sustained weight loss leads to decreased clinical endpoints and if weight regain may occur over time despite continued therapy as has been seen with weight loss surgery.⁶⁹ Differences among the medications in their mechanisms of action may also lead to differences in clinical endpoints, such as heart disease, that go beyond their effects on weight loss. For example, semaglutide and liraglutide have been shown to reduce cardiovascular disease endpoints in patients with type 2 diabetes mellitus,⁷⁰ but this is uncertain for individuals with obesity without diabetes mellitus.

In summary, for adults with obesity who have not had sufficient weight loss with lifestyle interventions alone and are interested trying weight loss medications, we assessed the benefits and harms of these four medications added to lifestyle modification compared to standard lifestyle modification alone and to each other. As such:

- We consider the evidence for the net health benefit of semaglutide added to lifestyle modification compared to lifestyle modification alone to be *incremental or better* (“B+”), demonstrating a moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit. This rating is based upon demonstration of substantial short-term weight loss from multiple high-quality studies with few serious harms, but higher rates of discontinuation due to adverse events than placebo, uncertainty

about long-term ability to sustain weight loss, and whether the degree of weight loss in this population results in improved clinical outcomes.

- We consider the evidence for the net health benefit of liraglutide added to lifestyle modification compared to lifestyle modification alone to be *incremental* (“B”), demonstrating a high certainty of a small net health benefit. This rating is based upon demonstration of small to moderate short-term weight loss from multiple high-quality studies with few serious harms; our expectation is that even if the weight loss were sustained, the benefits would only be incremental.
- We consider the evidence for the net health benefit of phentermine/topiramate added to lifestyle modification compared to lifestyle modification alone to be *comparable or better* (“C++”), demonstrating a moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit. This rating is based upon demonstration of moderate to substantial short-term weight loss from a limited number of trials with few serious harms, but higher rates of discontinuation due to adverse events than placebo, uncertainty about long-term ability to sustain weight loss, and whether the degree of weight loss seen translates into improved clinical outcomes given the limited data from clinical process measures.
- We consider the evidence for the net health benefit of bupropion/naltrexone added to lifestyle modification compared to lifestyle modification alone to be *comparable or incremental* (“C+”), demonstrating a moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit. This rating is based upon demonstration of small to moderate short-term weight loss from several trials with few serious harms, but higher rates of discontinuation due to adverse events than placebo, uncertainty about long-term ability to sustain weight loss, and whether the degree of weight loss seen translates into improved clinical outcomes given the limited data from clinical process measures.
- We consider the evidence for the net health benefit of semaglutide compared to liraglutide and phentermine/topiramate to be *comparable or incremental* (“C+”), and compared to bupropion/naltrexone to be *comparable or better* (“C++”). The rating comparing semaglutide to liraglutide is based upon greater weight loss and fewer adverse reactions leading to discontinuation with semaglutide, but uncertainty about long-term ability to sustain weight loss and, given the same mechanism of action, whether the incremental amount of weight loss results in improved clinical outcomes in this population. The rating comparing semaglutide to phentermine/topiramate is based upon similar weight loss and fewer adverse reactions leading to discontinuation, but differences in the number and quality of the trials, differences in mechanisms of action that may impact clinical outcomes, and uncertainty about long-term ability to sustain weight loss. The rating comparing

semaglutide to bupropion/naltrexone is based upon greater weight loss and fewer adverse reactions leading to discontinuation with semaglutide, but differences in mechanisms of action that may impact clinical outcomes, and uncertainty about long-term ability to sustain weight loss.

Table 3.20. Evidence Ratings of Medications for Obesity Management

Treatment	Comparator	Evidence Rating
Semaglutide	Lifestyle modification	B+
Liraglutide	Lifestyle modification	B
Phentermine/Topiramate	Lifestyle modification	C++
Bupropion/Naltrexone	Lifestyle modification	C+
Semaglutide	Liraglutide	C+
	Phentermine/topiramate	C+
	Bupropion/naltrexone	C++

4. Long-Term Cost Effectiveness

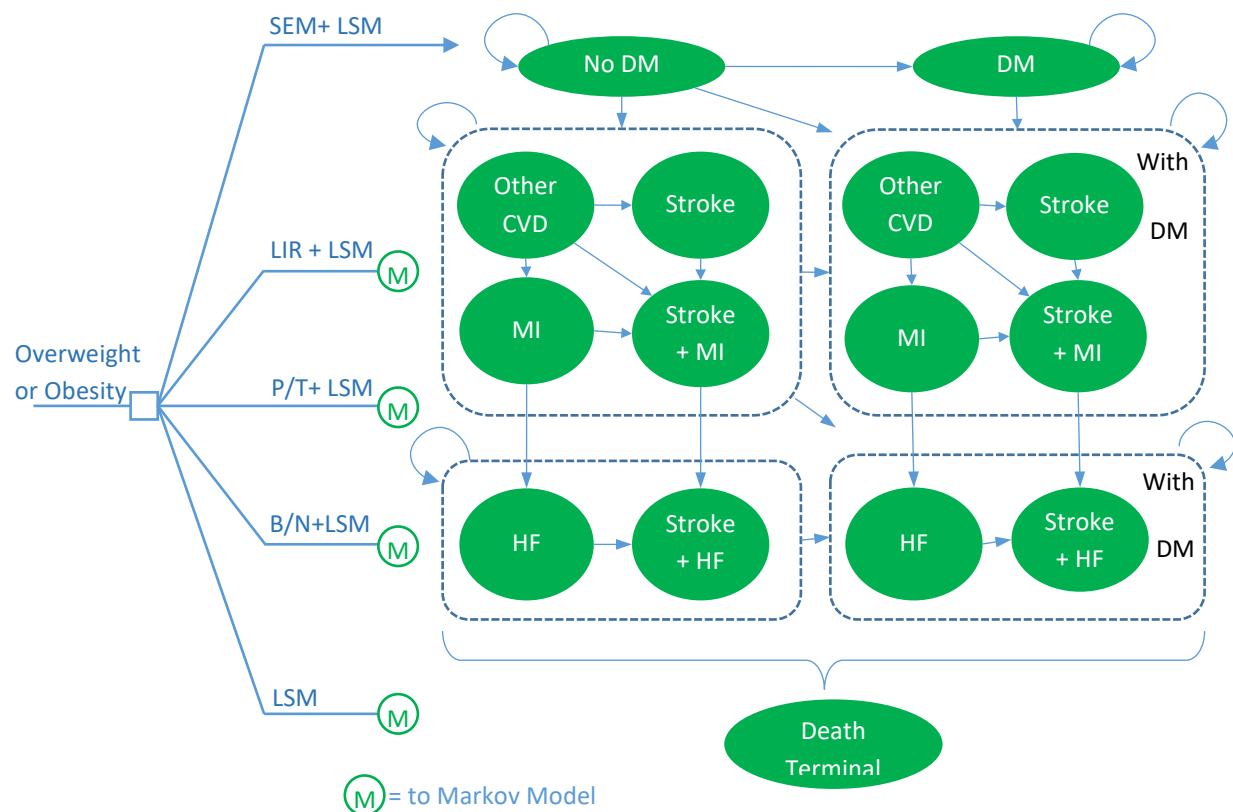
4.1. Methods Overview

The primary aim of this analysis was to estimate the cost effectiveness of semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone compared to standard lifestyle modification and to each other for life-long weight management in the treatment of overweight and obesity. The base-case analysis comparatively evaluated each therapy option in adults with a BMI ≥ 30 kg/m², or ≥ 27 kg/m² with at least one weight-related comorbidity, who are actively seeking medical management for weight loss. Additional scenarios were evaluated as described in Section 4.3. Consistent with clinical trials and real-world evidence on users of medications for weight management, the patient cohort modeled was 80% female with an average age of 45 years, BMI of 38 kg/m², SBP of 125 mmHg, and HbA1C of 5.7% without confirmed diabetes mellitus.

We built a Markov state transition model informed by key clinical trials, prior relevant economic models, systematic literature reviews, and input from diverse stakeholders (patients, advocacy groups, clinicians, payers, researchers, and manufacturers of these agents) from the health care sector perspective (i.e., focused on direct medical care costs) using a lifetime time horizon. The model cycle length was one year, and all costs and outcomes were discounted at a rate of 3% per year.

As shown in the model diagram Figure 4.1 on the following page, simulated patients entered the model through their medication regimen to the initial Markov state “No DM.” From the first cycle onward, patients could remain in the starting state, or transition to any of four non-heart-failure cardiovascular comorbid health states (myocardial infarction, stroke, stroke plus myocardial infarction, or other cardiovascular disease) with or without developing diabetes mellitus. Other cardiovascular disease included peripheral artery disease, angina, and transient ischemic attack. Myocardial infarction was a prerequisite to developing heart failure because of the strong causal association between obesity and heart failure mediated by myocardial changes.⁷¹ At any state in the model, patients could transition to the terminal “Death” state.

Figure 4.1. Model Diagram



CVD: cardiovascular disease, DM: diabetes mellitus, HF: heart failure, LM: lifestyle management, LIR: liraglutide, MI: myocardial infarction, B/N: bupropion/naltrexone, P/T: phentermine/topiramate, SEM: semaglutide

Average BMI reduction with therapy was the primary factor used to estimate differences in cardiovascular comorbidity and risk of progression to diabetes mellitus. The annual risk of developing cardiovascular conditions at the beginning of each cycle was calculated using a published risk equation model based on BMI, presence of diabetes mellitus, population demographics, and clinical characteristics. Specifically, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline risk equation was used to calculate the 10-year risk of non-heart-failure cardiovascular conditions.⁷² The resulting 10-year risks were then used to calculate the annual probability of a cardiovascular event and updated in each cycle of the model using the equation $P[t]=1-e^{(-r^t)}$. BMI was included as a time-varying input in the risk calculation for each cycle.

The risk of a cardiovascular event was calculated for each combination of patient factors (e.g., male vs. female, smokers vs. nonsmokers, and active hypertension treatment vs. no hypertension treatment, diagnosis of diabetes mellitus vs. no diabetes mellitus, age, and BMI) and the weighted average was used to calculate overall risk. Cardiovascular event risks were then further stratified

into specific stroke, myocardial infarction, and other cardiovascular disease event probabilities given proportion of each condition observed in a US population.⁷³⁻⁷⁶

The HbA1C-lowering effect of semaglutide, liraglutide, and bupropion/naltrexone was expected to delay the onset of diabetes mellitus.^{77,78} Therefore, we calculated the annual incidence of diabetes mellitus for each cycle using BMI and HbA1C data.⁷⁹ Furthermore, weight loss from medication therapy may result in hypertension remission. We therefore incorporated an association between BMI and hypertension to allow for a decreased prevalence of hypertension as BMI decreased.^{80,81}

Although we did not explicitly include some conditions that are known to be associated with weight loss, the anticipated benefit of weight loss in reducing the onset of such conditions was implicitly captured. For example, the impact of weight loss on sleep apnea is captured by the mortality benefits mediated by the cardiovascular conditions. Chronic kidney disease was not included as a separate Markov state in the base-case simulation. However, most chronic kidney disease is likely to result from diabetes mellitus or hypertension. Including costs and quality of life changes from studies with a broad selection of patients with diabetes mellitus, we implicitly addressed the influence of the chronic kidney disease on the cost-effectiveness decision. Chronic kidney disease resulting from hypertension was not captured in the model, as we assumed that hypertension management would be similar among patients with or without weight loss. Improvements in lipids were not explicitly included in the model. The ACC/AHA risk equations for cardiovascular risk account for either changes in weight or LDL, but not both. Therefore, including changes to lipids in the model would likely double count the cardiovascular benefits from treatment. Overall, our model indirectly captured the impact of weight loss in delaying the onset of diabetes mellitus. Supplement [Section E1](#) details additional rationale behind our choice of health states in the base case.

Health gains in the model were mainly derived from increased utility in those with improved BMI associated with enhanced daily functioning, decreased risk of developing diabetes mellitus/cardiovascular disease, and reduced complications/comorbidities. The estimated utility gains from enhanced daily functioning included improvements in conditions such as sleep apnea, gastroesophageal reflux disease, and osteoarthritis as well as improved mobility and self-image.

Scenario Analyses

In order to address several uncertainties, we conducted multiple scenario analyses:

- Societal perspective, including labor costs
- Evaluation of patients with a starting BMI of ≥ 40 kg/m² (i.e., weight class III with average BMI of 50 kg/m²)
- Use of generic phentermine/topiramate and bupropion/naltrexone
- Patient population consisting of a similar proportion of men and women

- Evaluation of a “Drug X” with the effect on weight loss seen in the SUPPORT 1 trial of tirzepatide and pricing of semaglutide for overweight and obesity and effects on blood pressure and diabetes mellitus similar to semaglutide.

4.2. Key Model Assumptions and Inputs

Model Assumptions

Several assumptions were required to estimate the cost effectiveness of treatments for obesity. These assumptions were based on clinical expert opinion, a review of the available evidence and published models, and the investigators’ experience with developing similar models. The key model assumptions and rationales for each assumption are listed in Table 4.1. Additional model assumptions are described in the [Supplement](#).

Table 4.1. Key Model Assumptions

Assumption	Rationale
Cardiovascular risk equations provide the best estimate of treatment benefit on cardiovascular outcomes.	Certain drug treatments may have benefits unrelated to weight loss achieved or changes in HbA1C. In the absence of strong evidence for the effects of medications on cardiovascular risk in patients with obesity and without diabetes mellitus, we did not include such a benefit. Should evidence emerge supporting additional benefits, the model can be updated to include these benefits. The potential benefits on cardiovascular outcomes of delays in diabetes mellitus onset from therapies that directly reduce A1C, beyond those associated with weight reduction, provided sufficient evidence exists, will be considered in the model.
Patients continue to receive the treatment or lifestyle modification throughout the model time horizon.	Expert opinion suggests that since obesity is increasingly considered to be a chronic metabolic disease that requires long-term management to affect outcomes, long-term drug treatment is required for most individuals. After stopping therapy, weight regain is common.
Treatment discontinuation is included in the model prior to the first model cycle; longitudinal changes in the persistence and adherence to medications were not considered in the model.	Including the impact of poor long-term persistence requires the addition of several “discontinuation” health states, thereby increasing model complexity. Further, there is no information on the impact of short-term treatment on cardiovascular outcomes, especially after discontinuation of the treatment.

HbA1C: glycated hemoglobin

Model Inputs

The key model inputs are listed in Table 4.2. The clinical inputs for the model were weighted over time and by associated probabilities of cardiovascular disease (myocardial infarction, stroke, other cardiovascular disease), heart failure, and diabetes mellitus. Weight change resulting from treatment was determined from an NMA of trials conducted as part of this review evaluating the four obesity drug therapies of interest. The risk of myocardial infarction, stroke, and other cardiovascular disease was obtained from a risk equation model.⁸¹⁻⁸³ Risk of heart failure and diabetes mellitus was determined from a systematic review of the literature and published risk equations.⁸⁴⁻⁸⁸

BMI and weight trajectory over time were used as model inputs to assess cardiovascular risk. Percent weight change (and thus BMI change, assuming no change in height) from baseline at year one and maximum percent weight change by the end of the second year were incorporated into the model. We assumed patients received the maintenance dose continuously, the medication maintained long-term effectiveness, and there was no additional weight change beyond the maximum weight reduction until the end of the model time horizon in the base case.

The impact of weight loss on mortality was incorporated as reduction of fatal cardiovascular events, as estimated from a review of existing literature and a direct extraction of general population all-cause mortality from the Human Mortality Database US-specific life tables.^{89,90}

Table 4.2. Key Model Inputs*

Parameter	Input	Source
Clinical Inputs		
Absolute Difference in % Weight Change, SEM vs. LSM	-13.7%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, SEM vs. LSM	-0.30	STEP 1 ³²
Absolute Difference in % Weight Change, LIR vs. LSM	-5.0%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, LIR vs. LSM	-0.20	SCALE (Maintenance) ³⁹
Absolute Difference in % Weight Change, P/T vs. LSM	-9.1%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, P/T vs. LSM	0.00	EQUATE ^{51,55,56}
Absolute Difference in % Weight Change, B/N vs. LSM	-4.6%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, B/N vs. LSM	-0.13	STEP 1 and STEP 2 ^{28,32}
Baseline Risk of CV Event, Female Non-Smoker without Treated HTN	0.04	Framingham Risk Calculation Coefficient
Baseline Risk of CV Event, Male Smoker with Treated HTN	0.23	Framingham Risk Calculation Coefficient
Multiplier for Probability of MI from CV Risk	0.22	Framingham Risk Calculation Coefficient
Multiplier for Probability of Stroke from CV Risk	0.23	Framingham Risk Calculation Coefficient
Multiplier for Probability of Other CV Disease from CV Risk	0.55	Framingham Risk Calculation Coefficient
HbA1C Effect on the Annual Incidence of DM	$8.49 \times 10^{-6} \exp(1.58 \times \text{HbA1C})$	Exponential regression from Edelman et al. ⁷⁹
BMI Effect on the Annual Incidence of DM	$1.97 \times 10^{-2} \exp(0.101 \times \text{BMI})$	Exponential regression from Edelman et al. ⁷⁹
Comorbidity Annual Cost Inputs		
Cost Other CV Disease	\$14,279	Scully 2017 ⁹¹
Cost Acute Stroke	\$17,316	HCUP ⁹²
Cost Post Stroke	\$6,500	Kazi 2019 ⁹³
Cost Acute MI	\$26,034	HCUP ⁹²
Cost Post MI	\$3,117	Kazi 2016 ⁹⁴
Cost HF	\$15,605	Patel 2021 ⁹⁵
Cost DM	\$11,425	ADA 2018 ⁹⁶
Quality of Life Inputs		
Utility with Normal BMI†	$0.9442 - 0.0007 \times \text{Age}$	Sullivan 2006 ⁹⁷
Disutility per BMI Unit Increase	-0.0033	Kim 2022 ⁹⁸ , Pi-Sunyer 2015 ⁴¹
Multiplicative Utility – Other CV Disease	0.959	Sullivan 2006 ⁹⁷
Disutility – Acute Stroke	-0.190	Matza 2015
Multiplicative Utility – Post-Stroke	0.943	Sullivan 2006 ⁹⁷
Disutility – Acute MI	-0.150	Matza 2015
Multiplicative Utility – Post-MI	0.955	Sullivan 2006 ⁹⁷
Multiplicative Utility – HF	0.930	
Multiplicative Utility – DM	0.962	

BMI: body mass index, B/N: bupropion/naltrexone, CV: cardiovascular, DM: diabetes mellitus, HbA1C: glycated hemoglobin, HF: heart failure, HTN: hypertension, ICER: Institute for Clinical and Economic Review, LIR: liraglutide, LSM: lifestyle modification, NMA: network meta-analysis, P/T: phentermine/topiramate, SEM: semaglutide

*This cardiovascular model does not include inputs of anti-obesity medication changes in blood pressure, lipids, sleep apnea, cancer, and physical inactivity (e.g., immobility or osteoarthritis).

†Midpoint of the normal BMI range of 18.5-25 kg/m².

Starting utility was derived from age-specific utility values for patients with the characteristics of the target population.⁹⁷ A utility gain was applied for each unit of weight loss due to treatment. The linear association between weight gain and utility loss was extracted from a recent cost-effectiveness analysis and trial data.^{41,98}

For comorbidities associated with higher BMI, we used consistent health state utility values across all evaluated treatments. Health state disutilities due to cardiovascular comorbid conditions, diabetes mellitus, and heart failure were derived from systematic literature reviews, utility-specific patient preference research articles cited in prior cost-effectiveness assessments, and manufacturer-submitted data. A multiplicative approach was used to apply the health utility value changes for each of the Markov states. To address the significant decrease in the health utility for acute event management, we applied daily disutilities for acute myocardial infarction and acute stroke management for 30 days, an anticipated duration influenced by the significant loss of mobility and self-care. Subcutaneous injections of GLP-1 receptor agonists are expected to have a small impact on the overall health state utility compared to the impact of chronic conditions. Thus, we did not include a utility decrease for the subcutaneous administration of semaglutide or liraglutide.

For estimates of net pricing, drug costs, and discounts, data are available from both the SSR Health pricing database and US Department of Veterans Affairs Federal Supply Schedule Service (FSS) database. Since SSR discount/rebate data were not available for semaglutide for weight loss, phentermine/topiramate for the most recent quarter, and bupropion/naltrexone for the most recent quarter, we opted to use the net price from the US FSS database.

Table 4.3. Drug Costs

Drug	List Price		Rebates/ Discounts from WAC	Model Inputs from FSS Data	
	Year One Annual WAC	Year 2+ Annual WAC		Year One Annual Net	Year 2+ Annual Net
Semaglutide	\$17,597	\$17,597	22.6%*	\$13,618	\$13,618
Liraglutide	\$15,795	\$16,424	28.4%†	\$11,309	\$11,760
Phentermine/ Topiramate	\$2,382	\$2,429	39.7-57.8%*	\$1,355	\$1,465
Bupropion/ Naltrexone	\$7,393	\$7,612	72.5%*	\$2,034	\$2,095

FSS: Federal Supply Schedule, WAC: wholesale acquisition cost

*Rebates taken from FSS due to no available net price evidence in SSR Health for the most recent year.

†Rebates taken from SSR Health.

Standard lifestyle modification, consisting of diet and physical activity recommendations, was a background health care intervention across all treatment arms of the model. The cost of lifestyle modification was identified by review of prior economic outcome assessment studies.

Cost of care for cardiovascular comorbid conditions was identified from targeted literature reviews. The acute care costs of myocardial infarction and stroke were identified from a Healthcare Cost and Utilization Project National Inpatient Sample database online query. Long-term care costs for post-myocardial infarction, post-stroke, other cardiovascular disease, heart failure, and diabetes mellitus were identified from review of prior economic outcome assessments.

Productivity costs, such as due to patient absenteeism or presenteeism, and caregiver costs were identified from a review of prior economic assessments and were used to calculate the indirect costs of the cardiovascular conditions in question under the modified societal perspective.^{96,99-101}

4.3. Results

Base-Case Results

The discounted total life years gained, QALYs gained, evLYs gained, and total costs over the lifetime horizon are shown for each of the obesity treatment strategies in Table 4.4. Incremental values compared to lifestyle modification are presented in Table 4.5. Undiscounted base-case results are presented in [Supplement E](#).

Table 4.4. Discounted Base-Case Results

Treatment	Drug Cost	Non-Drug Cost	Total Cost	Life Years	QALYs	evLYs
Semaglutide	\$282,600	\$105,800	\$388,400	21.04	17.85	17.86
Liraglutide	\$250,200	\$134,800	\$385,000	20.86	17.36	17.37
Phentermine/Topiramate	\$40,300	\$142,400	\$182,800	20.85	17.40	17.41
Bupropion/Naltrexone	\$51,500	\$142,700	\$194,200	20.82	17.28	17.29
Lifestyle Modification*	\$11,400	\$167,300	\$178,700	20.70	16.95	16.95

evLY: equal value life year, QALY: quality-adjusted life year

*Reference for evLY calculation for all active treatments.

Table 4.5. Select Discounted Incremental Results for the Base Case

Incremental Values vs. Lifestyle Modification						
Treatment	Drug Cost	Non-Drug Cost	Total Cost	Life Years	QALYs	evLYs
Semaglutide	\$271,100	-\$61,500	\$209,700	0.34	0.90	0.91
Liraglutide	\$238,800	-\$32,500	\$206,300	0.16	0.41	0.42
Phentermine/Topiramate	\$28,900	-\$24,900	\$4,100	0.15	0.45	0.46
Bupropion/Naltrexone	\$40,100	-\$24,600	\$15,500	0.13	0.33	0.34
Lifestyle Modification*	--	--	--	--	--	--

evLY: equal value life year, QALY: quality-adjusted life year

*Reference for incremental calculation for all active treatments.

Incremental cost per QALY, life year gained, and evLY gained over the lifetime horizon are shown in Table 4.6 for each of the obesity treatment strategies.

Table 4.6. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per Life Year Gained	Cost per QALY Gained	Cost per evLY Gained
Semaglutide	Lifestyle modification	\$615,000	\$234,000	\$231,000
Liraglutide	Lifestyle modification	\$1,262,000	\$506,000	\$496,000
Phentermine/Topiramate	Lifestyle modification	\$26,000	\$9,000	\$9,000
Bupropion/Naltrexone	Lifestyle modification	\$122,000	\$47,000	\$46,000
Semaglutide	Liraglutide	\$19,000	\$7,000	\$7,000
	Phentermine/topiramate	\$1,107,000	\$463,000	\$459,000
	Bupropion/naltrexone	\$909,000	\$343,000	\$341,000

evLY: equal value life year, QALY: quality-adjusted life year

Sensitivity Analyses

The model was sensitive to several inputs, including the disutility per BMI change, effectiveness of each treatment in weight loss, baseline HbA1C, and cost of diabetes mellitus. Disutility per BMI change was most important for semaglutide and liraglutide. The cost of diabetes mellitus management was most impactful for phentermine/topiramate and bupropion/naltrexone. Varying the weight-lowering effect of each treatment compared to lifestyle management and varying the baseline HbA1c had a considerable influence across all four treatment options. The full one-way sensitivity analysis results are shown in the [Supplement](#). Probabilistic sensitivity analysis results in are shown in Table 4.7.

Table 4.7. Results of Probabilistic Sensitivity Analysis by Cost per QALY Gained

Treatment	Comparator	Cost Effective at \$50,000 per QALY Gained	Cost Effective at \$100,000 per QALY Gained	Cost Effective at \$150,000 per QALY Gained	Cost Effective at \$200,000 per QALY Gained
Semaglutide	Lifestyle modification	0.0%	0.0%	1.6%	9.5%
Liraglutide	Lifestyle modification	0.0%	0.0%	0.0%	0.0%
Phentermine/Topiramate	Lifestyle modification	64.4%	85.3%	92.2%	95.1%
Bupropion/Naltrexone	Lifestyle modification	20.5%	53.9%	73.2%	82.2%
Semaglutide	Phentermine/topiramate	0.0%	0.0%	0.0%	0.0%
	Bupropion/naltrexone	0.0%	0.0%	0.0%	0.4%

QALY: quality-adjusted life year

Scenario Analyses

Conducting the analysis from a societal perspective had some impact on estimates of cost effectiveness. These results are shown in Tables 4.8 and 4.9. Table 4.10 presents scenarios with use of an additional Drug X, use of generic phentermine/topiramate, and use of generic

bupropion/naltrexone. The incremental cost-effectiveness ratio for the lifetime weight management with Drug X versus lifestyle modification is \$147,000 per QALY gained at the annual Drug X cost of \$13,618. The lifetime drug cost for generic phentermine/topiramate was \$14,200 (compared to \$40,300 for branded therapy in the base case) and for generic bupropion/naltrexone was \$25,100 (compared to \$51,500 for branded therapy in the base case).

Table 4.8. Discounted Results from the Societal Perspective

Treatment	Drug Cost	Non-Drug Cost	Total Cost	Life Years	QALYs	evLYs
Semaglutide	\$282,600	\$144,900	\$427,500	21.04	17.85	17.86
Liraglutide	\$250,200	\$183,000	\$433,200	20.86	17.36	17.37
Phentermine/Topiramate	\$40,300	\$192,600	\$233,000	20.85	17.40	17.41
Bupropion/Naltrexone	\$51,500	\$193,300	\$244,800	20.82	17.28	17.29
Lifestyle Modification*	\$11,400	\$225,500	\$236,900	20.70	16.95	16.95

evLY: equal value life year, QALY: quality-adjusted life year

*Reference for evLY calculation for all active treatments.

Table 4.9. Discounted Incremental Results from the Societal Perspective

Incremental Values vs. Lifestyle Modification						
Treatment	Drug Cost	Non-Drug Cost	Total Cost	Life Years	QALYs	evLYs
Semaglutide	\$271,200	-\$80,600	\$190,600	0.34	0.90	0.91
Liraglutide	\$238,800	-\$42,500	\$196,300	0.16	0.41	0.42
Phentermine/Topiramate	\$28,900	-\$32,900	-\$3,900	0.15	0.45	0.46
Bupropion/Naltrexone	\$40,100	-\$32,200	\$7,900	0.12	0.33	0.34
Lifestyle Modification*	--	--	--	--	--	--

evLY: equal value life year, QALY: quality-adjusted life year

*Reference for incremental calculation for all active treatments.

Table 4.10. Scenario Analysis Results (Drug X and Generic Combination)

Treatment	Drug Cost	Non-Drug Cost	Total Cost	Life Years	QALYs	evLYs
Drug X	\$285,500	\$83,200	\$368,700	21.18	18.25	18.26
Generic P/T	\$14,200	\$142,400	\$156,600	20.85	17.40	17.41
Generic B/N	\$25,100	\$142,700	\$167,800	20.82	17.28	17.29
LSM	\$11,400	\$167,300	\$178,700	20.70	16.95	16.95
Incremental Value vs. LSM						
Drug X	\$274,100	-\$84,100	\$190,000	0.48	1.30	1.31
Generic P/T	\$2,700	-\$24,900	-\$22,100	0.15	0.45	0.46
Generic B/N	\$13,700	-\$24,600	-\$10,900	0.12	0.33	0.34
Incremental Cost Effectiveness (QALY) Ratio vs. LSM				Cost/LY Gained	Cost/QALY Gained	Cost/evLY Gained
Drug X				\$392,000	\$147,000	\$146,000
Generic P/T				Generic P/T less costly, more effective		
Generic B/N				Generic B/N less costly, more effective		

B/N: bupropion/naltrexone, evLY: equal value life year, LSM: lifestyle modification, LY: life year, P/T: phentermine/topiramate, QALY: quality-adjusted life year

Threshold Analyses

The annualized prices required to achieve thresholds of \$50,000 to \$200,000 per QALY gained are presented in Table 4.11.

Table 4.11. QALY-Based Threshold Analysis Results

	Annual Net Price	Annualized Price to Achieve \$50,000 per QALY Gained	Annualized Price to Achieve \$100,000 per QALY Gained	Annualized Price to Achieve \$150,000 per QALY Gained	Annualized Price to Achieve \$200,000 per QALY Gained
Semaglutide	\$13,618	\$5,342	\$7,587	\$9,832	\$12,077
Liraglutide	\$11,760	\$2,587	\$3,607	\$4,611	\$5,614
Phentermine/Topiramate	\$1,465	\$2,396	\$3,530	\$4,664	\$5,797
Bupropion/Naltrexone	\$2,094	\$2,142	\$2,990	\$3,839	\$4,687
Lifestyle Modification	Reference				

QALY: quality-adjusted life year

Model Validation

Model validation followed standard practices in the field. All mathematical functions in the model were tested to assess face validity and to ensure consistency with the Report. We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, the model was subjected to internal and external review to evaluate the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. We also identified a publication that evaluated semaglutide and other drugs for medication-assisted treatment of weight loss.⁹⁸ This recently published model differed from ours in structure and inputs, including having additional Markov states and differences in the handling of multiple comorbidities, a two-year treatment period instead of lifetime, a 30-year time horizon instead of lifetime, handling excess mortality due to obesity in a different manner, using a higher cost of semaglutide, and having different utility inputs. When we changed our model inputs to resemble theirs (i.e., higher semaglutide unit cost, utility inputs, two-year treatment, and 30-year time horizon), our incremental cost-effectiveness estimate comparing semaglutide to lifestyle modification (\$113,200) approached their reported estimate comparing semaglutide to diet and exercise (\$122,549). The remaining difference in these incremental cost-effectiveness estimates could likely be explained by a much shorter 30-year life expectancy in all treatments reported in their model.

Finally, a targeted literature search was conducted to review mortality and cardiovascular events from real-world evidence and to compare the real-world data with those predicted by the model. The average remaining life expectancy of a 45-year-old US female is 38.08 years.¹⁰² In one study, class I obesity shortened life expectancy by approximately 3.5 years in middle-aged women.¹⁰³ Our model estimate was comparable to this real-world data, with an expected remaining median survival of 34 years and a predominantly female population taking semaglutide. Our model produced estimates for the cumulative incidence of cardiovascular conditions of 59.5% in patients receiving lifestyle management. The cumulative estimated incidence in patients receiving semaglutide was 52.1%. These model findings reflect the lifetime cardiovascular risk estimates from real-world studies in patients with an average age of 45 years living with major risk factors or obesity.^{104,105}

[Supplement E7](#) contains additional information about model validation results.

Uncertainty and Controversies

In 2013, the American Medical Association recognized obesity as a chronic disease.¹⁰⁶ As a result, long-term weight management includes both weight loss and maintenance of weight reduction. However, medications for weight management are often not covered or require a stepped approach to care, with access granted only after lifestyle changes and other treatments have failed.¹⁰⁷ Where medications are covered, restrictions may be imposed on the duration of treatment (e.g., through day supply/quantity limits or reauthorization criteria). The Government Accountability Office showed that, between 2008 and 2017, 78.4% of first treatment episodes users had a medication duration of 91 days or less.¹⁰⁷ However, after discussions with several experts in our scoping discussions, most stated that lifetime treatment with medications is now the preferred

approach to managing obesity and overweight, given weight regain after discontinuation and the need for long-term use to prevent comorbid disease and mortality. As a result of this input, we decided to evaluate lifetime treatment with medications as the base-case analysis.

Another important uncertainty in the model was that the medications used for weight management often had multiple effects on the body in addition to weight loss. To limit the complexity of the cost-effectiveness model and to prevent the double-counting of treatment benefits, we limited the long-term effects of treatments for weight management to cardiovascular risk and delays in the onset and/or diagnosis of diabetes mellitus (in patients starting in the model without diabetes) due to the effect of medications on A1C. As a result, there may be additional benefits with certain therapies that were not captured in the model. For example, GLP-1 receptor agonists have been shown to improve cardiovascular risk to a greater extent than expected by changes to HbA1c and weight loss alone in patients with diabetes mellitus.^{27,41} These effects of GLP-1 receptor agonists have not yet been well elucidated in patients without diabetes mellitus, the starting population within the base-case model.

The long-term benefits of preventing other comorbidities including cancer, chronic kidney disease, osteoarthritis, and sleep apnea were not explicitly modeled in the base case. Though obesity is associated with cancer risk, a clear causal relationship has not been established between weight loss and the extent to which cancer-specific outcomes change. The short-term quality-of-life gains from decreased pain from osteoarthritis and improved sleep were included as a general improvement in health-related utility associated with changes in BMI. With regard to chronic kidney disease, the costs and disutility of chronic kidney disease secondary to diabetes mellitus and heart failure were implicitly captured in the model. The impact of treatment on chronic kidney disease risk arising from overweight and obesity independent of the effects on diabetes mellitus and heart failure could not be quantified and was not included in the base case. Similarly, the cardiovascular benefits of reduced sleep apnea were already implicitly included in the equation used to estimate cardiovascular risk. However, the potential cost savings arising from a reduced need for osteoarthritis or sleep apnea treatments with substantial weight loss were believed to be small relative to the costs of cardiovascular conditions and diabetes mellitus and were not included in the base-case simulation. To further explore the potential impact of comorbid conditions partially included or excluded from the base-case analysis, we tested the potential impact of weight loss on cancer risk and chronic kidney disease using add-on “Comorbidity X” Markov states. These scenario analyses did not significantly alter the incremental cost-effectiveness ratios, alleviating concerns about the effects of these comorbidities on the cost effectiveness of weight management strategies.

Bupropion is an approved treatment for smoking cessation, which may also improve cardiovascular risk. Additionally, smoking cessation can lead to weight gain.¹⁰⁸ Since we wanted to evaluate the

impact of these treatments on weight loss alone, the potential benefits of bupropion for patients wanting to quit smoking were not included in the model.

The key drivers of cost effectiveness in our model were health state utility, effectiveness of medication in reducing weight, and factors associated with prevention of diabetes mellitus, such as reduction in HbA1C with treatment and baseline HbA1C. Cardiovascular benefits of GLP-1 receptor agonists that appear to extend beyond their impact on weight loss and HbA1C improvements have been shown in patients with diabetes mellitus. Although not evaluated in our model, additional cardiovascular benefits, if present for GLP-1 receptor agonists in patients without diabetes mellitus, could result in improved cost effectiveness of treatment with semaglutide and liraglutide. Decision on the order of cost effectiveness will be subject to the cost of tirzepatide, achieving larger QALYs gained with a significant decrease in BMI compared to the currently available weight management strategies.

There are several important limitations in this analysis. As described in the methods section, we were not able to include the full impact of weight loss on chronic kidney disease and other conditions for which weight loss may be beneficial, such as a number of cancers. Also, the equations used in our model were developed to determine the associations among patient-related factors, including weight and first cardiovascular events. These equations may have limitations when attempting to predict the impact of medication-assisted treatment for weight loss, especially in the case of medications that have complex actions on the body.

4.4. Summary and Comment

We conducted an analysis of the cost effectiveness of medication assisted therapy for weight loss, administered over an individual's lifetime, using a Markov health state transition model. All medication therapies added to lifestyle modification conferred health gains as compared to lifestyle modification alone in accordance with their incremental weight loss and corresponding cardiovascular and metabolic benefits. Draft results suggest that at current estimates of net price, neither semaglutide nor liraglutide were cost effective given commonly accepted cost-effectiveness thresholds. In contrast, phentermine/topiramate and bupropion/naltrexone (both in addition to lifestyle modification) were cost effective given commonly accepted thresholds owing to their comparatively smaller net acquisition costs. At the current prices and with accepted cost-effectiveness benchmarks, phentermine/topiramate and bupropion/naltrexone (both in addition to lifestyle modification) were cost effective compared with lifestyle modification alone. Weight management with semaglutide over a lifetime time horizon did not achieve commonly accepted cost-effectiveness thresholds. Semaglutide offers survival benefit and cardiovascular risk reduction, improving effectiveness by 0.90 QALYs.

When treatments were compared with each other, phentermine/topiramate plus lifestyle modification was less costly and more effective than bupropion/naltrexone plus lifestyle

modification. However, for patients not achieving desired weight loss or unable to tolerate phentermine/topiramate, bupropion/naltrexone may be a cost-effective alternative. Semaglutide (plus lifestyle modification) was more effective and more costly than both phentermine/topiramate and bupropion/naltrexone but did not meet commonly accepted cost-effectiveness thresholds for either comparison. As such, semaglutide might be considered in patients not achieving desired weight loss or unable to tolerate phentermine/topiramate or bupropion/naltrexone, but only with a significant discount.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	Not applicable
Magnitude of the lifetime impact on individual patients of the condition being treated	Obesity is a chronic disease that usually begins early in life and can continue throughout the course of a patient's life broadly affecting physical, psychosocial, and emotional health. As such it can affect educational achievement, workplace opportunities and performance assessments, and personal relationship.
There is uncertainty about how short-term mild to moderate weight loss translates into long-term benefits in preventing obesity related disease morbidity and mortality	Though evidence from trials of semaglutide, liraglutide, phentermine/topiramate, bupropion/naltrexone in patients with obesity showed sustained weight loss and few serious side effects over short-term follow-up, the long-term benefits of the chronic use of these medications remains uncertain. This relates to the ability to maintain use over long periods given evidence for weight regain upon discontinuation, the benefits of mild to moderate weight loss on clinical outcomes, and potential differences in the medications underlying mechanisms that may be associated with other beneficial or harmful aspects on clinical outcomes beyond any sustained weight loss.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	New medications for obesity that lead to sustained weight loss and improve the symptoms and complications of obesity may help improve quality of life across a range of different outcomes including social interactions with family, friends and other relations, educational achievement and work opportunities and performance. However, it is uncertain whether semaglutide, liraglutide, phentermine/topiramate, bupropion/naltrexone will improve these outcomes.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Though children and adolescents with obesity often require care that involves family members and other caregivers, this report focused on adults with obesity. Even among adults with obesity, its impact may fall not only on the patient, but also on caregivers. As such, new medications that promote sustained weight loss offer the possibility of improving the quality of life for caregivers as well as for patients.
Patients' ability to manage and sustain treatment given the complexity of regimen	The potential of medications such as phentermine/topiramate and bupropion/naltrexone, which are oral therapies and do not require the daily or weekly injections with using liraglutide or semaglutide may decrease the complexity of care. All four medications may be less complex to use on a long-term basis than constant attention to diet and physical activity.
Society's goal of reducing health inequities	Obesity disproportionately impacts certain racial and ethnic groups, and thus the need for improved treatment options. However, the costs of medications for obesity, which are often not covered by health insurance, may exacerbate existing health inequities by selectively limiting access of these medications to those patients who are able to afford them. Additionally, ICER calculated the Health Improvement Distribution Index, looking at the relative proportion of any health gains from treatment of overweight with one or more comorbidities and obesity for the following groups who have a higher prevalence of overweight with comorbidities and obesity than the general US population. ¹⁰⁹ <ul style="list-style-type: none"> • African American/Black female: 1.3 • Hispanic: 1.1
These medications offer new mechanisms of action that may allow more patients to achieve meaningful weight loss among those who have failed other treatments or may wish to avoid surgical therapies	Semaglutide and liraglutide, GLP-1 receptor agonists, represent medications that reflect research in which improved understanding of the mechanisms of disease have led to new therapies.

6. Health-Benefit Price Benchmarks

ICER does not provide health-benefit price benchmarks as part of draft Reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft Report will match the health-benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Using results from the cost-effectiveness model, we estimated the potential budget impact of adding semaglutide to current lifestyle modification for US adults with BMI ≥ 30 or 27.0 kg/m² \leq BMI < 30 kg/m² with one or more weight-related comorbidities. In accordance with the [Reference Case](#), semaglutide is treated as an intervention in the budget impact analysis, as it has been on the market for less than two years as of posting of the corresponding model analysis plan. In contrast, liraglutide, phentermine/topiramate, and bupropion/naltrexone are treated as comparators, as they have been on the market for two years or more.

For potential budget impact analyses, we used semaglutide's list price and net price and three threshold prices (at \$50,000, \$100,000, and \$150,000 per QALY) compared to lifestyle modification alone. These additional analyses on semaglutide threshold prices were conducted to inform budgetary impact estimations aligned with notions of semaglutide's cost effectiveness as calculated within the cost-effectiveness analyses. Potential budget impact is defined as the total differential cost of using semaglutide rather than the relevant existing therapies for the treated population, calculated as intervention costs minus any offsets in these costs from averted health care events or other resource utilization. All costs were undiscounted and estimated over a five-year time horizon.

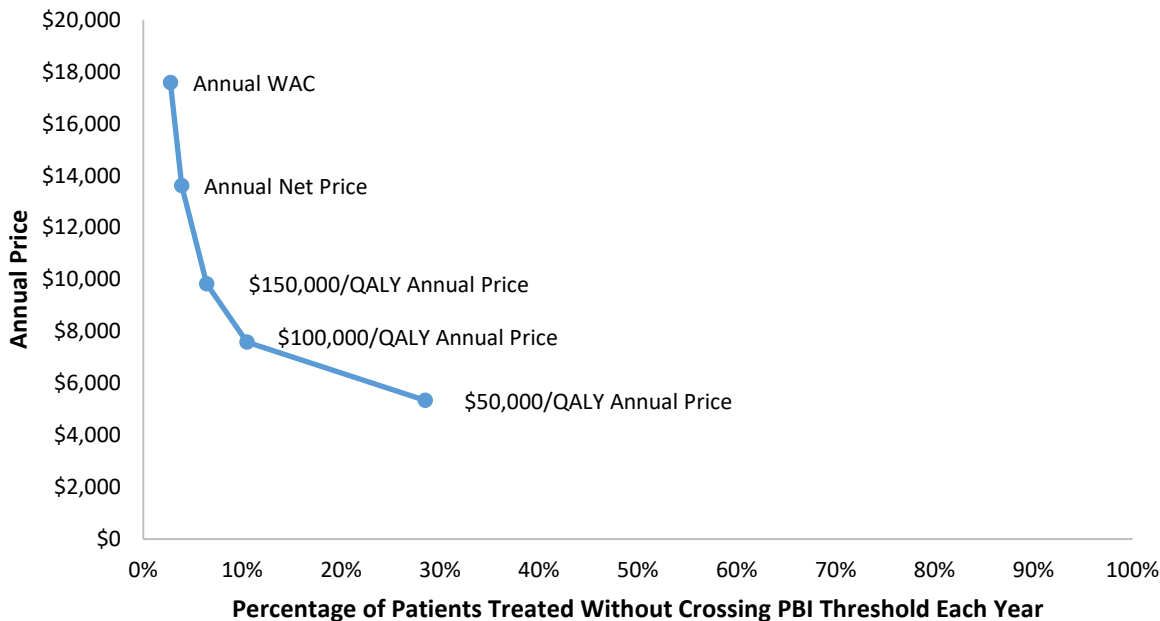
To estimate the size of the potential candidate populations for treatment, we used the US adult population and prevalence of overweight and obesity given specific weight-related comorbidities or biomarkers as reported within National Health and Nutrition Examination Survey (NHANES) datasets over the 2017-2018 and 2019-March 2020 data collection cycles.¹¹⁰ Accordingly, we estimated a combined prevalence value for US adults with BMI ≥ 30 kg/m² (41.96%) or 27.0 kg/m² \leq BMI < 30 kg/m² with one or more weight-related comorbidities (11.57%) at 53.53%. To quantify the number of these patients eligible for semaglutide therapy, we identified two cohorts: those currently on medication treatment for weight management and those seeking medication treatment for weight management. Accordingly, we estimated that 1.3% of all US adults in the prevalent cohort receive medication, with another 1.3% seeking medication therapy but not currently receiving it. These estimates were derived from electronic health record data on 2.2 million adults eligible for weight loss medication from eight geographically dispersed health care systems across the US, and from manufacturer data submissions, respectively.^{111,112} Applied to the projected US adult population over 2022-2026, we estimated 3,700,000 adults would be eligible for treatment with semaglutide. For this analysis, we assumed that 20% of these patients would initiate treatment with semaglutide in each of the five years (~740,000 per year), for a total of 100% of the cohort being treated with semaglutide at the end of five years.

Of the 1.3% of individuals on medication therapy at baseline, 53%, 30%, and 17% are assigned to liraglutide, phentermine/topiramate, and bupropion/naltrexone, respectively.¹¹² The remaining individuals seeking medication therapy are assigned to lifestyle modification alone at baseline. In our potential budget impact analyses, semaglutide draws market share proportionally from each of the model comparators over the five-year time horizon.

7.2. Results

At semaglutide’s estimated net price of \$13,618.22 per year, 3.88% of eligible patients could be treated within five years (assuming 20% uptake each year) without crossing the ICER potential budget impact threshold of \$777 million per year. In contrast, 2.74%, 6.42%, 10.48%, and 28.51% of eligible patients could be treated within five years without crossing the ICER potential budget impact threshold at the annual price to reach list price (\$17,597.48), \$150,000 per QALY (\$9,800), \$100,000 per QALY (\$7,600), and \$50,000 per QALY (\$5,300), respectively. The modest percentages were primarily driven by the large population eligible for treatment with semaglutide. Figure 7.1. depicts the potential budgetary impact of semaglutide at the annual list price, net price, and three threshold prices compared to lifestyle modification alone.

Figure 7.1. Budgetary Impact of Semaglutide in US Adults Seeking or Using Medication Therapy for Weight Management with BMI ≥30 or 27.0 kg/m²≤BMI<30 kg/m² with One or More Weight-Related Comorbidities



PBI: potential budget impact, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Obesity: BMI is the most common way that obesity is defined in clinical practice. Overweight is considered a BMI of 25 kg/m² to 29.9 kg/m². Obesity is considered a BMI of 30 kg/m² or greater. It is further subclassified as level I (30 kg/m² to 34.9 kg/m²), level II (35 kg/m² to 39.9 kg/m²), or level III (40 kg/m² or more).

Pre-diabetes: The clinical trials assessed patients for pre-diabetes using slightly different criteria. Pre-diabetes is defined by the American Diabetes Association based on an HbA1C result of 5.7%-6.4% (39-47 mmol/mol), a fasting glucose of 100-125 mg/dL (5.6-6.9 mmol/L), or a two-hour oral glucose tolerance test of 140-mg-199 mg/dL (7.8-11.0 mmol/L).¹¹³

Important outcomes in the pivotal trials studied include:

Percentage weight loss: This primary outcome in most studies represents the mean percentage point change in weight at follow-up relative to the baseline body weight.

Categorical weight loss (≥5%): This is a co-primary outcome in many studies and represents the percentage of individuals who achieve at least a ≥5% change in body weight from baseline to follow-up assessment. Greater weight loss can be assessed using ≥10%, ≥15%, or higher percentages.

Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT): The IWQOL was the first quality of life instrument specifically developed to assess individuals with obesity.¹¹⁴ It measures those aspects of quality of life that were identified by individuals with moderate or severe obesity to be of greatest concern. Eight domains assessed include health, social/interpersonal, work, mobility, self-esteem, sexual life, activities of daily living, and comfort with food. Originally a 74-item instrument, the IWQOL-Lite is a shorter, 31-item, self-reported version that consists of a total score and scores on each of five scales: Physical Function, Self-Esteem, Sexual Life, Public Distress, and Work.¹¹⁵ The IWQOL-Lite Clinical Trials Version (IWQOL-Lite-CT), was developed and validated for use in clinical trials.^{116,117} It is a 20-item measure used to assess weight-related physical and psychosocial functioning in three composite scores (physical, physical function, and psychosocial) and a total score. The range of possible scores for the IWQOL-Lite-CT is 0-100. For the IWQOL-Lite-CT, an increase in score is representative of an improvement in health status.

Short Form-36 v2® Health Survey, Acute Version (SF-36): The SF-36 is a generic quality of life measure widely used to assess patient-reported functional outcomes.¹¹⁸ It includes 36 questions across eight domains (physical functioning, role limitations due to physical health problems, body

pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health). Additionally, the SF-36 domains can be aggregated into two scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). For the SF-36, an increase in score is representative of an improvement in health status.

Patient Health Questionnaire (PHQ-9): The PHQ-9 is a self-administered instrument to measure symptoms of depression.¹¹⁹ It was derived from the PRIME-MD diagnostic instrument for common mental disorders. Each item asks the individual to rate daily symptoms from "0" (not at all) to "3" (nearly every day). A higher score indicated worse depressive symptoms.

Inventory of Depressive Symptomatology (Self-Report) (IDS-SR): The IDS-SR is a 30-item questionnaire measuring depressive symptoms. Each item has four statements that reflect various degrees of symptom severity, scored on a four-point scale from 0 to 3.¹²⁰ A higher score indicated worse depressive symptoms.

A2. Potential Cost-Saving Measures in Obesity Management

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see <https://icer.org/our-approach/methods-process/value-assessment-framework/>). These services are ones that would not be directly affected by semaglutide, liraglutide, phentermine/topiramate, and/or bupropion/naltrexone (e.g., need for obstructive sleep apnea treatment), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of obesity beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for individuals with obesity that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Future Therapies

In June 2022, results from the SURMOUNT-1 trial of tirzepatide were published.¹¹ Tirzepatide is both a GLP-1 receptor agonist and also a glucose-dependent insulinotropic polypeptide receptor agonist. [ICER previously reviewed tirzepatide](#) as a treatment for type 2 diabetes mellitus. The manufacturer of tirzepatide requested that it not be added to this report as the evaluation process was already underway. Tirzepatide is neither an intervention nor a comparator in this Report, however, to provide context, we review the results of SURMOUNT-1 here.

SURMOUNT-1 was a 72-week Phase III trial comparing three doses of tirzepatide and placebo in 2,539 adults without diabetes and with a BMI ≥ 30 or ≥ 27 with one weight-related complication.

Tirzepatide was administered by weekly subcutaneous injection at doses of 5 mg, 10 mg, or 15 mg, with an initial 20-week dose-escalation period.

The mean baseline BMI in the study population was 38. Tirzepatide at doses of 5 mg, 10 mg, and 15 mg resulted in greater percentage reductions in weight than placebo (15.0%, 19.5%, and 20.9% vs. 3.1%, respectively). More patients achieved categorical weight reduction targets as well. For example, a $\geq 5\%$ target was achieved by 85.1%, 88.9%, and 90.9% of patients, respectively, with tirzepatide versus 34.5% with placebo. A $\geq 25\%$ target was achieved by 15.3%, 32.3%, and 36.2% of patients with tirzepatide versus 1.5% with placebo.

Patients treated with tirzepatide also experienced improvements in physical functioning, decreases in systolic and diastolic blood pressure, improvements in lipids, and decreases in fasting insulin levels.

Most adverse events with tirzepatide were gastrointestinal in nature and discontinuation for adverse events occurred in more patients treated with tirzepatide than placebo (4.3%, 7.1%, and 6.2% vs. 2.6%, respectively). Gastrointestinal adverse events were typically worse at initiation or dose escalation of tirzepatide, with improvement over time.

B. Patient Perspectives: Supplemental Information

B1. Methods

In developing and executing this Report, we received valuable input from individual patients and patient organizations throughout the scoping and evidence development process. We received public comments on our draft scoping document from the Obesity Action Coalition. We also conducted a focus group with six patients that was arranged through the Obesity Action Coalition. These interviews with patients helped to illustrate the diversity of experiences of patients living with obesity as well as highlighted the health outcomes that were most important to them.

C. Clinical Guidelines

Veterans' Health Administration/Department of Defense

Clinical Practice Guideline for the Management of Adult Overweight and Obesity¹²¹

The Evidence-Based Practice Work Group of the Department of Veterans Affairs and the Department of Defense released updated guideline recommendations in 2020. These recommendations updated a prior evidence review released in 2014. A number of key elements of weight loss and management were highlighted. Obesity is recognized as a chronic disease requiring long-term management. Shared decision-making involving patients and providers is seen as a fundamental aspect of weight management. Managing obesity involves addressing all of the factors that may be involved for a given patient. This may include assessing whether medications or treatments for other conditions may exacerbate weight issues for a patient. Lifestyle interventions involving comprehensive use of behavioral, dietary, and physical activity components are central to success in reducing and sustaining weight loss. Pharmacotherapy and weight loss surgery should be considered along with comprehensive lifestyle interventions and when instituted they require long-term follow-up.

In terms of pharmacotherapy, the use of FDA-approved medications needs to consider potential side effects as well as patient tolerability and preferences. Weight regain can occur with any medication after discontinuation, so long-term use to maintain weight loss is often needed. Specific pharmacotherapies that can be offered to patients include bupropion/naltrexone, liraglutide, orlistat, or phentermine/topiramate. Eligibility includes patients with a BMI ≥ 30 kg/m² and for those with a BMI ≥ 27 kg/m² who also have obesity-associated conditions. There is insufficient information to recommend phentermine monotherapy or other stimulants for intermittent, short-term, or long-term use.

Canadian Clinical Practice Guideline

Obesity in Adults: A Clinical Practice Guideline⁵

This guideline was funded by the Canadian Institutes of Health Research Strategic Patient-Oriented Research initiative, Obesity Canada's Fund for Obesity Collaboration and Unified initiative, and the Canadian Association of Bariatric Physicians and Surgeons. An executive and steering committee with broad expertise and geographic representation were created. The scope of the guideline was developed by the executive committee. A literature review was performed by the McMaster Evidence Review and Synthesis Team. Guideline recommendations were formulated by the steering committee along with chapter leads and authors. Seven individuals living with obesity

were engaged and one participated on the steering committee. This guideline updated the first Canadian obesity guideline published in 2006.

Key points emphasized that obesity is a common, complex, progressive, and relapsing disease. It is characterized by abnormal or excessive body fat that impairs health. Newer insights into appetite regulation and the underlying mechanisms leading to obesity have opened new approaches for treating this chronic disease. People living with obesity face substantial bias and stigma, and this contributes independently of weight or BMI to morbidity and mortality. Reducing weight bias and stigma, better understanding of the underlying causes of obesity, and supporting patient-centered care can improve the wellbeing of those living with obesity. Obesity care should be based on evidence-based principles of chronic disease management, validate patients' lived experiences, and move beyond the simplistic notion that obesity requires eating less and increasing activity.

In terms of pharmacotherapy, the guideline focuses on individuals with BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with comorbid conditions. Pharmacotherapy is meant to be an adjunctive for weight loss and weight loss maintenance in addition to medical nutrition therapy, physical activity, and psychological interventions. Recommended options include liraglutide 3.0 mg, bupropion/naltrexone, and orlistat. Details of the recommendations are available online in the chapter titled "Pharmacotherapy in Obesity Management." Pharmacotherapy is intended to augment the magnitude of weight loss beyond what can be achieved with health behavior changes alone. It is also emphasized as being important for the prevention of weight regain.

Endocrine Society

Pharmacological Management of Obesity Guideline¹²²

This evidence-based guideline was developed by members of the Endocrine Society, the European Society of Endocrinology, and the Obesity Society. Weight loss is seen as a path to achieving improved health for patients with obesity-associated risk factors and comorbidities. Medications approved for chronic weight management can be useful adjuncts to lifestyle interventions for patients that have not met weight loss goals on their own. Diet, exercise, and behavioral modification are recommended for patients with BMI ≥ 25 kg/m² and should be included with other obesity management interventions. Pharmacotherapy can be considered for those with BMI ≥ 27 kg/m² with comorbidity or BMI over 30 kg/m². Patients with a history of being unable to successfully lose and maintain weight are candidates for weight loss medications. Patients responding well to weight loss (5% or more after three months) should continue with therapy. In addition to addressing medications that can promote weight loss, the guidelines emphasize attention to the use of medications for other conditions that are weight-neutral and avoiding those that are associated with weight gain.

Specific pharmacotherapy recommendations include avoiding sympathomimetic agents such as phentermine in patients with diabetes mellitus and uncontrolled hypertension or a history of heart disease. In patients with type 2 diabetes mellitus who are overweight or have obesity, antidiabetic medications that may promote weight loss such as GLP-1 receptor agonists, or sodium-glucose-linked transporter-2 inhibitors are suggested. Off-label use of medications approved for other conditions is not recommended for the sole purpose of weight loss.

National Institute for Health and Care Excellence (NICE)

Obesity: Identification, Assessment, and Management Clinical Guideline¹²³

NICE released recommendations for managing obesity in 2014. Areas of focus for this guideline included identification, assessment, and management of obesity. Interventions assessed included lifestyle, behavioral, physical activity, dietary, pharmacological, and surgical interventions. In terms of lifestyle interventions, multi-component ones are considered treatment of choice, and should include behavioral change strategies that can support increased physical activity and improved eating habits.

Pharmacological treatment is recommended only after dietary, exercise, and behavioral approaches have been initiated. One should consider drug treatment of interested individuals who have not reached their target weight loss. Pharmacological treatments may be continued to maintain weight loss. For those who have not reached their weight loss target, consideration should be given for stopping the drug. Since weight loss may be slower in individuals who also have type 2 diabetes mellitus, less strict goals and longer duration of therapy may be appropriate. Orlistat should only be prescribed when it is part of an overall plan for managing obesity, should not be co-prescribed with other weight loss drugs, and should not be continued beyond three months if the person has not lost at least 5% of their initial body weight. Phentermine/topiramate was not mentioned in this document, but is listed as being in development.

In December, 2017, NICE released recommendations for bupropion/naltrexone. It was not recommended for managing overweight and obesity in adults alongside a reduced-calorie diet and increased physical activity. In February, 2022, NICE released a draft guideline for the use of semaglutide for weight management. It is an option when given in addition to diet and activity recommendations for individuals with a BMI of at least 35 or 30-34.9 with other comorbid conditions that meet NICE criteria. It can be used for a maximum of two years and needs to be given within a specialist weight management service. Consideration for stopping semaglutide if less than 5% initial weight loss has been achieved after six months of maintenance therapy.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review is adults with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbid condition (such as hypertension, type 2 diabetes mellitus, obstructive sleep apnea, or hyperlipidemia) who are actively seeking medical management for weight loss. Data permitting, we sought to examine the following patient subgroups, including but not limited to:

- BMI categories: 27-29.9, 30-34.9, 35-39.9, or greater than 40 kg/m²
- Pre-diabetes or diabetes mellitus
- Prior bariatric surgery

Interventions

The full list of interventions is as follows:

- Semaglutide
- Liraglutide
- Bupropion and naltrexone in combination
- Phentermine and topiramate in combination

Comparators

We intended to compare each intervention with lifestyle modification to placebo with lifestyle modification. Data permitting, we also compared the interventions to one another.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
 - Quality of life and functional status
 - Anxiety and depression
 - Body image
 - Long-term health outcomes such as cardiovascular disease, cancer, and mortality
 - Weight loss (as measured by % weight loss, categorical weight loss [e.g., 5%, 10%, or 15%], BMI, etc.)
 - Weight re-gain
 - Adverse events including:
 - Side effects
 - Psychological harm
 - Serious adverse events
- Other Outcomes
 - Metabolic profile, such as LDL, hemoglobin A1C, and blood pressure
 - Weight cycling
 - Waist circumference
 - Progression from pre-diabetes to diabetes mellitus or pre-hypertensive to hypertensive
 - Withdrawal or dose reduction in concomitant medications for weight-related comorbidities
 - Subsequent surgical interventions for weight loss
 - Discontinuation due to adverse events

Timing

Evidence on intervention effectiveness were derived from studies of at least 12 weeks duration and evidence on harms from studies of any duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

Table D1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search Strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]).	

Section and Topic	Item #	Checklist item	Reported on Page #
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study Characteristics	17	Cite each included study and present its characteristics.	
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.	
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	

Section and Topic	Item #	Checklist item	Reported on Page #
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing Interests	26	Declare any competing interests of review authors.	
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on treatments for obesity management followed established best research methods.^{124,125} We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹²⁶ The PRISMA guidelines include a checklist of 27 items.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and Emtree terms in EMBASE) as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to

the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see <https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/>). Where feasible and deemed necessary, we also accepted data submitted by manufacturers “in-confidence,” in accordance with ICER’s published guidelines on acceptance and use of such data (<https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/>).

Table D2. Search Strategy of EMBASE Search

	Search Term	Hits
#1	'obesity'/exp OR 'obesity'	715,626
#2	'body weight loss'/exp OR 'body weight loss'	216,099
#3	('obes*' OR 'body mass ind*' OR 'adiposity' OR 'overweight' OR 'over weight' OR 'anti-obesity' OR 'body-weight' OR 'body weight'):ti,ab	1,002,246
#4	#1 OR #2 OR #3	1,302,513
#5	'phentermine plus topiramate'/exp	774
#6	((('phentermine' AND 'topiramate') OR 'phentermine plus topiramate' OR 'qysmia' OR 'qsiva' OR 'VI-0521' OR 'VI0521' OR 'VI 0521'):ti,ab	449
#7	'amfebutamone plus naltrexone'/exp	616
#8	('amfebutamone plus naltrexone' OR 'contrave' OR ('amfebutamone' AND 'naltrexone') OR ('bupropion' AND 'naltrexone') OR 'CID 11556075' OR 'CID11556075' OR 'CID-11556075'):ti,ab	489
#9	'glucagon like peptide 1 receptor agonist'/exp	40,407
#10	'liraglutide'/exp	10,432
#11	('liraglutide' OR 'saxenda' OR 'victoza' OR 'NN 2211' OR 'NN2211' OR 'NN-2211'):ti,ab	6,186
#12	'semaglutide'/exp	2,172
#13	('semaglutide' OR 'ozempic' OR 'wegovy' OR 'NN 9535' OR 'NN9535' OR 'NN-9535'):ti,ab	1,252
#14	('phentermine' OR 'Adipex-P' OR 'Lomaira' OR 'Suprenza'):ti,ab	1,176
#15	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	42,083
#16	#4 AND #15	18,557
#17	#16 NOT ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' OR 'case report' OR 'comment' OR 'congresses' OR 'consensus development conference' OR 'duplicate publication' OR 'editorial' OR 'guideline' OR 'in vitro' OR 'interview' OR 'lecture' OR 'legal cases' OR 'legislation' OR 'letter' OR 'news' OR 'newspaper article' OR 'patient education handout' OR 'periodical index' OR 'personal narratives' OR 'portraits' OR 'practice guideline' OR 'review' OR 'video audio media')/it	13,697
#18	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp	7,709,777
#19	#17 NOT #18	10,962
#20	#19 AND [English]/lim	10,664
#21	#20 NOT [medline]/lim	5,675
#22	#21 AND [01/07/2020]/sd	927

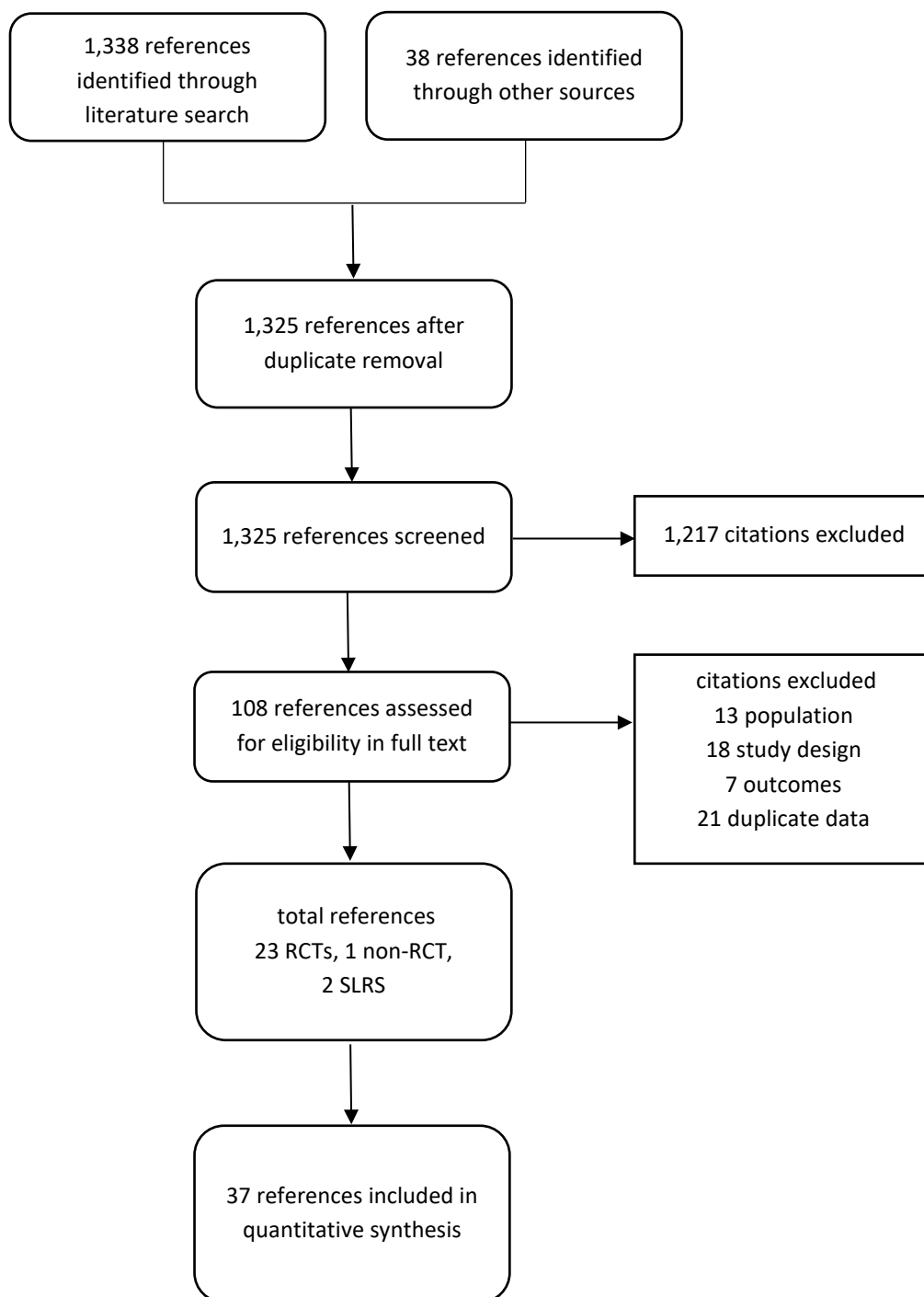
*Search last updated on April 11, 2022.

Table D3. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

	Search Term	Hits
1	exp Obesity/	241,120
2	exp Weight Loss/	46,611
3	exp Overweight/	251,757
4	(obes* or "body mass inde*" or adiposity or overweight or "over weight" or antiobesity or "anti-obesity" or bodyweight or "body weight").ti,ab.	687,798
5	1 or 2 or 3 or 4	747,430
6	((phentermine and topiramate) or "phentermine topiramate" or phenterminetopiramate or qsymia or qsvia or topiramatephentermine or "phentermine-topiramate" or VI0521 or "VI 0521" or "VI-0521").ti,ab.	255
7	((amfebutamone and naltrexone) or (bupropion and naltrexone) or contrave or "bupropion-naltrexone" or CID11556075 or "CID 11556075" or "CID-11556075").ti,ab.	287
8	exp Glucagon-Like Peptides/	11,511
9	exp liraglutide/	2,169
10	(liraglutide or saxenda or victoza or NN2211 or "NN 2211" or "NN-2211").ti,ab.	3,210
11	(semaglutide or ozempic or wegovy or NN9535 or "NN 9535" or "NN-9535").ti,ab.	691
12	(phentermine or Adipex-P or Lomaira or Suprenza).ti,ab.	785
13	6 or 7 or 8 or 9 or 10 or 11 or 12	13,584
14	5 and 13	4,560
15	14 not ("address" or "autobiography" or "bibliography" or "biography" or "case reports" or "comment" or "congress" or "consensus development conference" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "review" or "video-audio media").pt.	3,222
16	15 not (animals not (humans and animals)).sh.	2,264
17	limit 16 to english language	2,211
18	remove duplicates from 17	2,208
19	limit 18 to ed=20200701-20220330	425

*Search last updated on April 11, 2022.

Figure D1. PRISMA Flowchart Showing Results of Literature Search for Medications for Obesity Management



Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force to assess the quality of randomized controlled trials and comparative cohort studies, using the categories “good,” “fair,” or “poor” (see Table D21)¹²⁷ Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention-to-treat analysis is used for randomized controlled trials.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention-to-treat analysis is done for randomized controlled trials.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For randomized controlled trials, intention-to-treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the [ICER Evidence Rating Matrix](#) to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.^{128,129}

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we performed an assessment of publication bias on for semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone using the ClinicalTrials.gov. We scanned the site to identify studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

The results of the studies were summarized in the evidence tables and described narratively in the body of the report. In addition, we evaluated the comparative efficacy of semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone by means of NMA, where feasible. Based on data availability, our NMA evaluated the outcomes of change in body weight and SBP, and categorical weight loss at one year. NMA Supplemental Information below contains a detailed description of the NMA methods. Due to inconsistent or limited data reporting, other outcomes were only described narratively in the body of the Report and in Section D2.

Supplemental NMA Methods

As described in the Report, we conducted random effect NMAs where feasible. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).^{130,131}

NMAs were conducted using a Bayesian framework. For continuous outcomes, the NMA model corresponds to a generalized linear model with identity link.¹³² For binary outcomes (e.g., proportion of patients discontinuing due to adverse events), the NMA model corresponds to a generalized linear model with a logit link.¹³² For all analyses, we included random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) was assumed constant across all treatment comparisons. We used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as “burn-in” and base inferences on an additional 50,000 iterations using three chains. Convergence of chains was

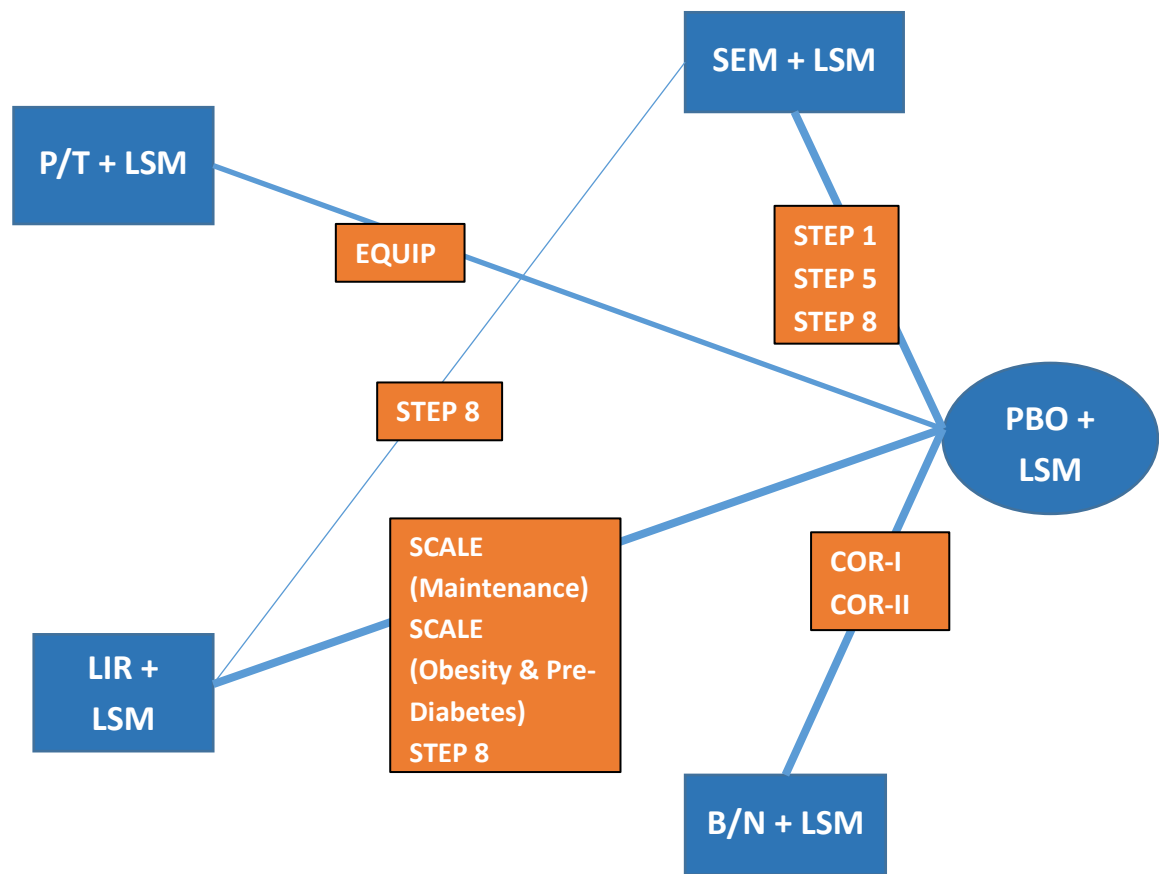
assessed visually using trace plots. Furthermore, for any network where there were “loops” in evidence, we empirically compared the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node splitting approach.¹³²

As there was no evidence of inconsistency, we present the full NMA results in the report. All analyses were conducted using the IndiRect NMA platform (CRG-EVERSANA, 2020™) or R.

Supplemental NMA Results

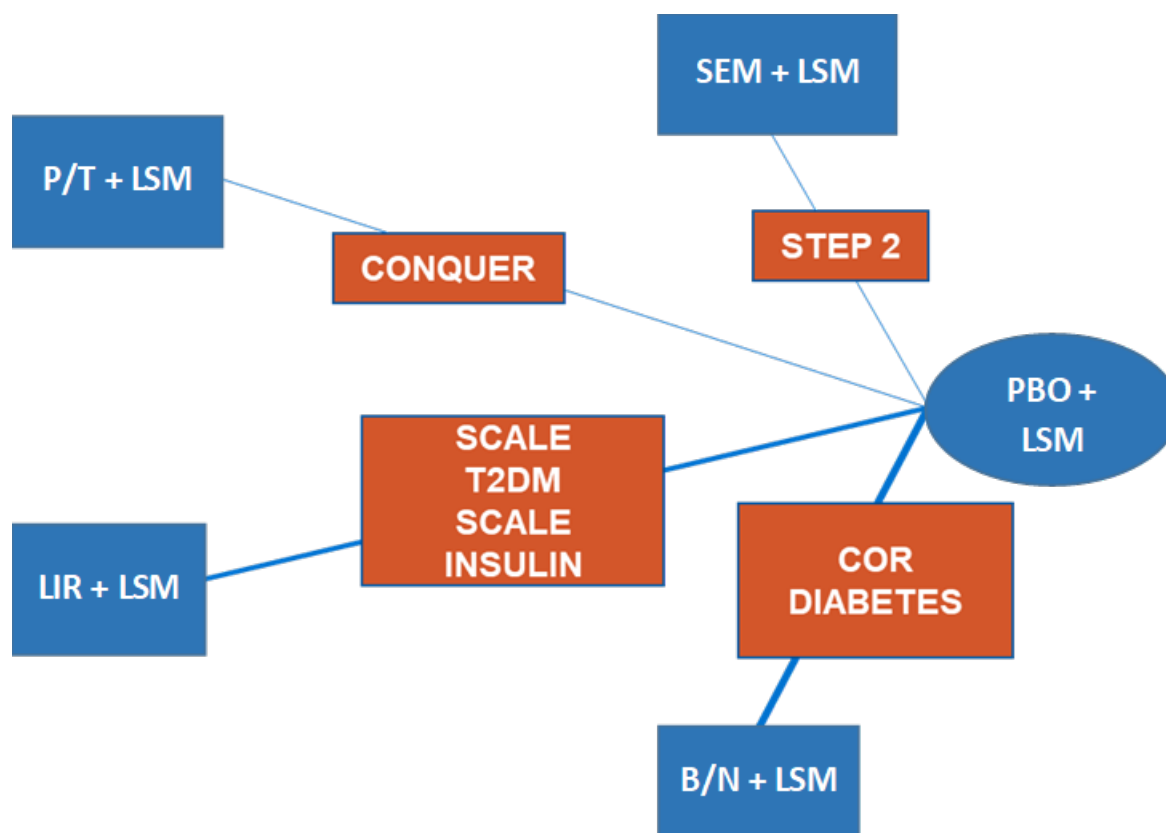
We provide three network diagrams that represents the NMAs in the report (Figures D2, D3, and D4). To interpret the network figures, note that the lines indicate the presence of a trial directly assessing the connecting interventions, with the thickness of the line corresponding to the number of trials. The location of treatments and the distances between them do not have any meaning. The medications are depicted in blue and the trial names are depicted in orange.

Figure D2. Network of Studies Included in the NMAs of Medications for Obesity, Mean Percentage Weight Loss, Change in SBP from Baseline to One Year and Categorical Weight Loss



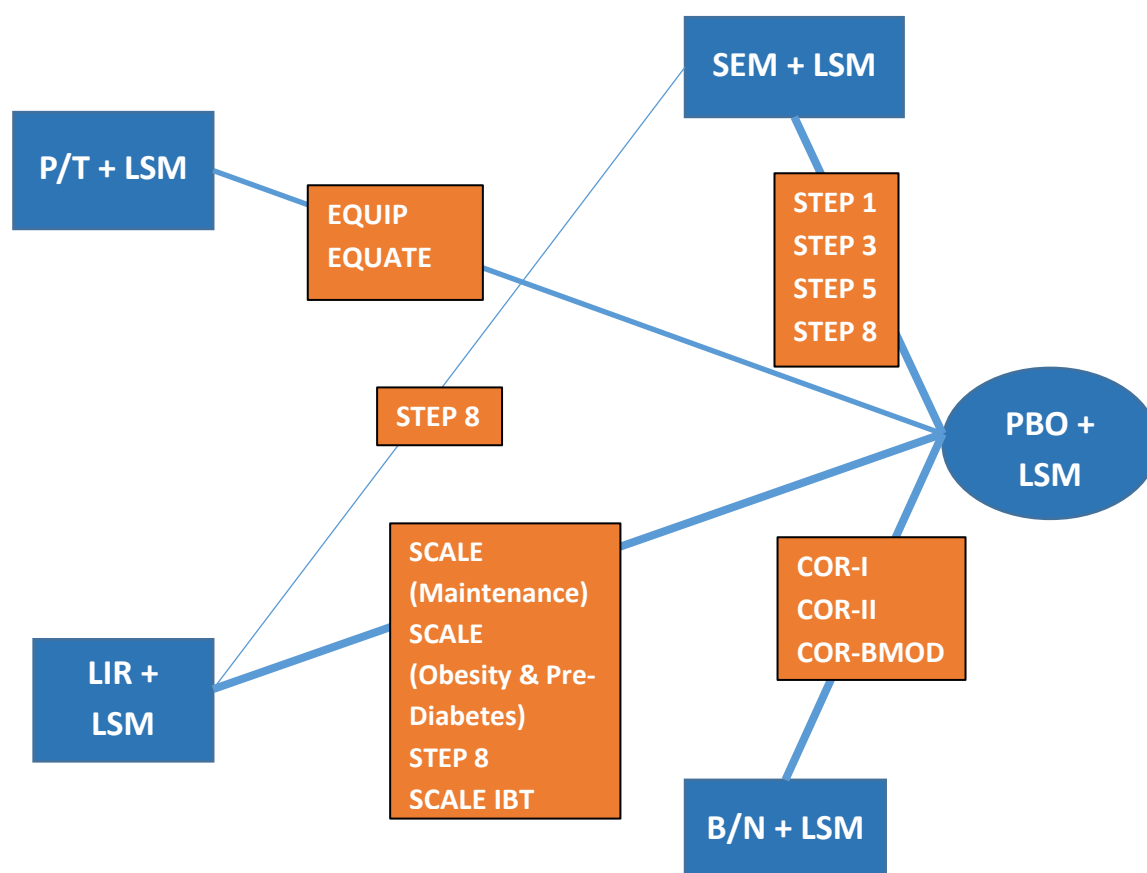
B/N: bupropion/naltrexone, LIR: liraglutide, LSM: lifestyle modification, PBO: placebo, P/T: phentermine/topiramate, SEM: semaglutide

Figure D3. Network of Studies Included in the NMA of Medications for the Management of Obesity with Diabetes Mellitus, Mean Percentage Weight Loss and Mean Change in SBP from Baseline to One Year



B/N: bupropion/naltrexone, LIR: liraglutide, LSM: lifestyle modification, PBO: placebo, P/T: phentermine/topiramate, SEM: semaglutide

Figure D4. Network of Studies Included in the NMAs of Medications for Obesity, Discontinuation Due to Adverse Events



B/N: bupropion/naltrexone, LIR: liraglutide, LSM: lifestyle modification, PBO: placebo, P/T: phentermine/topiramate, SEM: semaglutide

Results of Categorical Weight Loss

We conducted NMAs of trials including participants with obesity alone separately from trials of participants with obesity and diabetes and excluded trials that included IBT as an adjunct to medication. Categorical weight loss NMAs (proportion of patients achieving at least 5% or 10% weight loss) are reported below.

Participants with Obesity Alone

For the trials of the medications conducted in participants with obesity without diabetes that included standard diet and exercise counseling and reported proportion of patients who achieved at least 5% or 10% weight loss at one year, we present the results of the baseline risk-adjusted random effects model, given its better fit for the model compared to the unadjusted model in Tables D4 and D5. All medications, in combination with diet and exercise counseling, showed

statistically significantly greater odds of achieving at least 5% weight loss at one year. Compared to placebo, the interventions demonstrated 4.6-17.3 times the odds of 5% weight loss and 3.6-22.4 times the odds of 10% weight loss. Semaglutide demonstrated the greatest odds of achieving 5% and 10% weight loss at one year and was superior to all other medications in our review for this outcome. Phentermine/topiramate (high dose) demonstrated greater odds than liraglutide and bupropion/naltrexone, however this difference was not statistically significant for the outcome of 5% weight loss. Liraglutide was not statistically more effective in demonstrating at least 5% or 10% weight loss than bupropion/naltrexone (Tables D4 and D5).

Table D4. NMA Results of Medications for the Management of Obesity, Odds Ratio of Likelihood of Achieving at Least 5% Weight Loss at One Year (95% CI)

Semaglutide				
2.0 (0.5 to 10.0)	Phentermine/ Topiramate*			
4.0 (2.4 to 8.0)	2.0 (0.6 to 7.1)	Liraglutide		
4.0 (1.01 to 20.6)	2.0 (0.9 to 4.4)	1.0 (0.3 to 3.4)	Bupropion/ Naltrexone	
17.3 (8.9 to 38.3)	8.6 (3.3 to 22.0)	4.3 (2.5 to 6.7)	4.3 (1.7 to 10.2)	Placebo

Legend: Each box represents estimated odds ratio of achieving 5% weight loss and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

Table D5. NMA Results of Medications for the Management of Obesity, Odds Ratio of Likelihood of Achieving at Least 10% Weight Loss at One Year (95% CI)

Semaglutide				
2.6 (0.95 to 6.2)	Phentermine/ Topiramate*			
5.3 (3.5 to 9.6)	2.1 (1.04 to 5.6)	Liraglutide		
6.3 (2.4 to 15.9)	2.5 (1.2 to 5.3)	1.2 (0.5 to 2.4)	Bupropion/ Naltrexone	
22.4 (13.6 to 36.2)	8.8 (4.7 to 18.1)	4.2 (2.6 to 5.7)	3.6 (2.0 to 6.8)	Placebo

Legend: Each box represents estimated odds ratio of achieving 10% weight loss and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

Participants with Obesity and Diabetes Mellitus

For the trials of the medications conducted in participants with obesity and diabetes mellitus that included standard diet and exercise counseling and reported proportion of patients who achieved at least 5% or 10% weight loss at one year, we present the results of the unadjusted random effects model, given its better fit for the model compared to the baseline-adjusted model in Tables D6 and D7. Data on categorical weight loss in patients with diabetes mellitus was not available for phentermine/topiramate and was therefore not included in the NMA. All medications, in combination with diet and exercise counseling, showed greater odds of achieving at least 5% or 10% weight loss at one year, however, this difference was only statistically significant for liraglutide for the 5% weight loss outcome and semaglutide and liraglutide for the 10% weight loss outcome. Compared to placebo, the interventions demonstrated 2.2-2.7 times the odds of 5% weight loss and 3.3-6.1 times the odds of 10% weight loss. Semaglutide demonstrated the greatest odds of achieving 5% or 10% weight loss at one year, followed by liraglutide.

Table D6. NMA Results of Medications for the Management of Obesity and Diabetes Mellitus, Odds Ratio of Likelihood of Achieving at Least 5% Weight Loss at One Year (95% CI)

Semaglutide			
1.2 (0.4 to 2.9)	Liraglutide		
1.2 (0.4 to 4.8)	1.1 (0.4 to 4.2)	Bupropion/ Naltrexone	
2.7 (0.9 to 4.1)	2.4 (1.0 to 3.6)	2.2 (0.6 to 3.9)	Placebo

Legend: Each box represents estimated odds ratio of achieving 5% weight loss and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

Table D7. NMA Results of Medications for the Management of Obesity and Diabetes Mellitus, Odds Ratio of Likelihood of Achieving at Least 10% Weight Loss at One Year (95% CI)

Semaglutide			
1.6 (0.3 to 6.8)	Liraglutide		
1.8 (0.3 to 12.2)	1.1 (0.2 to 8.1)	Bupropion/ Naltrexone	
6.1 (1.3 to 12.8)	3.7 (1.1 to 8.9)	3.3 (0.5 to 10.8)	Placebo

Each box represents estimated odds ratio of achieving 10% weight loss and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

D2. Additional Clinical Evidence

Evidence Base

Semaglutide versus Placebo

The Report discusses the primary sources of data to inform our review of semaglutide for the management of obesity with and without diabetes mellitus: STEP 1, STEP 2, STEP 3, STEP 5, and STEP 8 trials. STEP 4 and STEP 6 are two additional trials from the STEP clinical trial program that were not included in the Report due to study design (STEP 4) and differences in population (STEP 6). Both studies were multi-center Phase III studies and evaluated subcutaneous semaglutide 2.4 mg plus lifestyle intervention versus placebo plus lifestyle intervention.¹³³⁻¹³⁵ STEP 6 also evaluated subcutaneous semaglutide 1.7 mg, but we only reviewed evidence for the subcutaneous semaglutide 2.4 mg arm as that is the approved dose for obesity treatment.

STEP 4 reported unique data regarding weight regain, in addition to other outcomes of interest. Participants included in this trial were adults with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbid condition.^{133,134} Participants with diabetes mellitus (HbA1C $\geq 6.5\%$) were excluded. The study design included a 20-week run-in period with all participants receiving a dose escalation of subcutaneous semaglutide starting at 0.25 mg and increased every four weeks to the maintenance dose of 2.4 mg at week 16. At week 20, subjects were randomized to either continue semaglutide 2.4 mg or switch to placebo. Due to the withdrawal study design, baseline weight for these participants was different compared to the STEP trials included in the main review. The baseline weight and BMI for all participants prior to the run-in period was 107.2 kg and 38.4 kg/m². At randomization (week 20) baseline weight was 96.5 kg in the semaglutide arm versus 95.4 kg in the placebo arm and baseline BMI was 34.5 kg/m² in the semaglutide arm versus 34.1 kg/m² in the placebo arm (Table D8).

STEP 6 was conducted in Japan and South Korea, with 100% of their participants of Asian ethnicity.¹³⁵ Baseline BMI, body weight, and waist circumference of participants in the STEP 6 trial were lower than that of the other STEP trials. Additionally, due to differences in guidelines, the inclusion criteria were slightly different with STEP 6 requiring eligible participants to be adults aged ≥ 18 in South Korea and ≥ 20 in Japan with a BMI of at least 27 kg/m² with two or more treated or untreated weight-related comorbidities, or a BMI of at least 35 kg/m² with one or more treated or untreated weight-related comorbidity, according to the Japan Society for the Study of Obesity (JASSO) guidelines. STEP 6 did not exclude individuals with diabetes mellitus and at baseline 25% of participants in each arm had diabetes mellitus. Outcomes were assessed at week 68 for both STEP 4 and STEP 6. Baseline characteristics are outlined in Table D8.

Liraglutide versus Placebo

The Report discusses the primary sources of data to inform our review of semaglutide for the management of obesity with and without diabetes mellitus: the SCALE clinical trial program (Maintenance, Obesity & Pre-Diabetes, Sleep Apnea, Type 2 DM, Insulin, and IBT) trials. LOSEIT was a single-center Phase III trial based at the Parker Institute in Denmark, which evaluated subcutaneous liraglutide 3.0 mg plus lifestyle intervention versus placebo plus lifestyle intervention.¹³⁶ Participants included in this trial were adults aged 18 to 74 with BMI ≥ 27 kg/m² with symptomatic knee osteoarthritis and were excluded if they were currently using medications for weight loss or gain, participating in an ongoing weight loss program, or on radiography for end-stage knee osteoarthritis. Prior to randomization, participants engaged in a dietary intervention period for eight weeks and were randomized to liraglutide or placebo if they had achieved at least 5% weight-loss during that eight-week period. Baseline characteristics for BMI, weight, and waist circumference were lower for participants in LOSEIT than those included in the main review. Primary outcomes for this trial were also slightly different from those included in the main review, with absolute changes in body weight and Knee Injury and Osteoarthritis Outcome Score (KOOS) as the co-primary outcomes. The study captured categorical weight loss ($\geq 5\%$ and $\geq 10\%$) as well as change in BMI and waist circumference. Outcomes were assessed at week 52. Baseline characteristics are outlined in Table D8.

Table D8. Overview of Additional Trials of Semaglutide and Liraglutide for the Management of Obesity¹³³⁻¹³⁶

	STEP 4			STEP 6		LOSEIT	
Study Arms	Run-in	PBO*	SEM*	PBO	SEM	PBO	LIR
N	803	268	535	101	199	76	80
Lifestyle Intervention	Monthly counseling, reduced-calorie diet, and increased physical activity			Monthly counseling, reduced-calorie diet, and increased physical activity		Low-calorie run-in with weekly counseling then reduced-calorie diet, and bi-weekly counseling for 8 weeks	
Mean Age, Years	46	46	47	50	52	59.3	59.2
Female Gender, %	79	76.5	80.2	25.7	42.7	64	65
Baseline Weight, kg	107.2	95.4	96.5	90.2	86.9	90.8	96.3
Baseline Weight Loss, %	-10.6 [†]	N/A	N/A	N/A	N/A	N/A	N/A
Baseline BMI, kg/m ²	38.4	34.1	34.5	31.9	32	31.3	32.8
Race, White, %	83.7	84.3	83.4	0	0	NR	NR
Pre-Diabetes, %	NR	NR	NR	25	22	NR	NR

kg: kilogram, LIR: liraglutide, m: meter, N/A: not applicable, NR: not reported, PBO: placebo, SEM: semaglutide

*Baseline data measured at Week 20.

[†]Change from baseline data measured at Week 20.

Phentermine/Topiramate versus Placebo

The Report discusses the primary source of data to inform our review of phentermine/topiramate for the management of obesity: the EQUIP and EQUATE trials. OB-204 was a single-center, double-blind, parallel-group, placebo-controlled, Phase I/II trial that randomized adults with overweight or obesity and moderate-to-severe obstructive sleep apnea syndrome to receive phentermine 15 mg/topiramate 92 mg (n=22), or placebo (n=23) (Table D9).¹³⁷ All participants in each treatment group also received standardized lifestyle modification counseling. Participants were eligible to participate if they were between the ages of 30-65 years, had a BMI of 30-40 kg/m², a diagnosis of moderate-to-severe obstructive sleep apnea syndrome, an apnea-hypopnea index ≥ 15 , and were unable to comply with CPAP treatment. Participants were excluded if they had a sleep disorder other than obstructive sleep apnea syndrome, unstable angina or heart failure, history of myocardial infarction, coronary revascularization, cholecystitis or cholelithiasis, glaucoma, or seizures, used any prescription central nervous system stimulant, experienced a weight change >5 kg, had previous surgery for obesity, had a psychiatric disorder, or were pregnant or breastfeeding. Participants in the OB-204 trial had a mean age of 52 years, and 47% were female. The majority (91%) of participants were White and 9% were Black. The average weight of participants in this trial was 105 kg and mean BMI was 36 kg/m² at baseline. See Table D9 for detailed baseline characteristics.

Bupropion/Naltrexone versus Placebo

The Report discusses the primary sources of data to inform our review of bupropion/naltrexone for the management of obesity: COR-I, COR-II and COR-BMOD. CVOT Light was a multi-center, Phase IIIb trial that randomized participants with overweight or obesity at an increased risk of adverse cardiovascular outcomes to receive bupropion 360 mg/naltrexone 32 mg or placebo.^{138,139} All participants in each treatment arm were also encouraged to participate in an Internet-based weight management program that included resources on healthy eating such as a low-calorie meal plan, exercise, behavioral modifications, weekly lessons, and access to a personal coach. Participants were eligible to participate if they were women over 50 years old, or men over 45 years old, had a BMI of 27-50 kg/m², a waist circumference of ≥ 88 cm for women or ≥ 102 cm for men, and demonstrated an increased risk of adverse cardiovascular outcomes, such as confirmed or high likelihood of cardiovascular disease, or had type 2 diabetes mellitus and at least two of the following: hypertension, dyslipidemia requiring pharmacotherapy, low high-density lipoprotein cholesterol, or were currently smoking tobacco. Participants were excluded if they had a myocardial infarction within four months, severe angina pectoris, NYHA class III or IV heart failure, history of stroke or SBP ≥ 145 mmHg or diastolic blood pressure ≥ 95 mmHg, weight change $>3\%$ within three months, had surgery for obesity, or history of seizures, mania, psychosis, bulimia, or anorexia nervosa. Participants in CVOT Light had a mean age of 61 years, and 55% were female.

The majority (84%) of participants were White and 15% were Black. The average weight of participants in this trial was 106 kg and mean BMI was 37 kg/m² at baseline (Table D9).

Ignite was a multi-center, open-label, Phase IIIb trial that randomized participants for the first 26 weeks to receive bupropion 360 mg/naltrexone 32 mg or usual care.¹⁴⁰ Participants in the treatment arm were additionally required to participate in a comprehensive lifestyle intervention, which consisted of a progressive nutrition and exercise program with personalized goal-setting and tracking tools with a coach or dietitian, while participants in the usual care arm were instructed to follow an exercise prescription and a hypocaloric diet. From 26 weeks through 78 weeks, participants in the bupropion/naltrexone group continued on the medication, while participants in usual care arm were switched to bupropion/naltrexone in addition to the comprehensive lifestyle intervention. For the purposes of our review, we are evaluating efficacy data only up to 26 weeks because of the lack of comparative data beyond that timepoint. Participants were eligible to participate if they were between the ages of 18-60 years, had either a BMI of 30-45 kg/m² or a BMI 27-45 kg/m² with dyslipidemia and/or controlled hypertension. Participants were excluded if they had type 1 or type 2 diabetes mellitus, myocardial infarction within six months, angina pectoris grade III/IV, history of strokes, seizures, bulimia, anorexia nervosa, had surgery for obesity, or had a psychiatric illness including mania, psychosis, or depression. Participants in this trial had a mean age of 47 years and were predominantly female (84%). The majority (76%) of participants were White and 23% were Black. The average weight of participants in this trial was 101 kg and mean BMI was 36 kg/m² at baseline. See Table D9 for detailed baseline characteristics.

Table D9. Overview of Additional Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity¹³⁷⁻¹⁴²

	OB-204		CVOT Light		Ignite	
Study Arms	PBO	P/T (high)	PBO	B/N	PBO	B/N
N	23	22	4,450	4,455	89	153
Lifestyle Intervention	LSM counseling, reduced-calorie diet, and increased physical activity		LSM counseling, reduced-calorie diet, and increased physical activity		LSM counseling, reduced-calorie diet, and increased physical activity	CLI with progressive nutrition and an exercise program, and personalized goal-setting
Mean Age, Years	51.4	53.4	60.9	61.1	47	46.1
Female Gender, %	34.8	59.1	54.4	54.7	86.5	81.7
Baseline Weight, kg	106.9	103.7	106.3	105.6	100.2	101.4
Baseline BMI, kg/m²	35.3	36	37.4	37.2	36.3	36.3
Race, White, %	91.3	90.9	83.1	83.9	71.9	81
Pre-Diabetes, %	NR	NR	NR	NR	NR	NR

B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, kg: kilogram, LSM: lifestyle modification, m: meter, NR: not reported, PBO: placebo, P/T: phentermine/topiramate

Results

For each medication, secondary outcomes from trials in the Report are summarized first, followed by primary outcomes for the additional trials summarized in the supplement. Weight loss outcomes are summarized first, followed by other outcomes (e.g., waist circumference, blood glucose, and LDL cholesterol), where relevant. HRQoL is summarized for all drugs at the end of this section. For each medication, results of trials conducted in patients with obesity are presented first, followed by trials conducted in patients with obesity and diabetes mellitus.

Semaglutide versus Placebo

The efficacy of semaglutide compared with placebo for the management of obesity in patients without diabetes mellitus was evaluated in three Phase III trials (STEP 1, 3, and 5). We were able to obtain percent weight loss at six months through digitizing published graphical data. Participants in the subcutaneous semaglutide 2.4 mg arm achieved greater percent weight loss at six months (-11.7%, -15.4%, and -13.2% respectively) compared to placebo (-2.9%, -7.9%, and -2.6%, respectively).^{27,29,32-36,136} Similarly, at one year, the proportion of participants who achieved at least 15% weight loss and at least 20% weight loss, a greater proportion of participants in the semaglutide arm achieved these categorical outcomes compared to participants in the placebo. Treatment with semaglutide in STEP 1, 3, and 5 trials also resulted in additional clinical benefits in

waist circumference, blood glucose, and LDL cholesterol compared to placebo. Outcomes related to changes in LDL were reported as absolute change from baseline for STEP 3 and as ratio of LDL from baseline for STEP 1 and 5. See Table D10 for detailed results.

The efficacy of semaglutide for the management of obesity and type 2 diabetes mellitus was evaluated through one Phase III trial (STEP 2). We were able to obtain percent weight loss at six months through digitizing published graphical data. Participants in the subcutaneous semaglutide 2.4 mg arm achieved greater percent weight loss at six months (-8.7%) compared to placebo (-2.7%).²⁸ Similarly, at one year, the proportion of participants who achieved at least 15% weight loss and at least 20% weight loss, a greater proportion of participants in the semaglutide arm ([15% WL: 25.8%]; [20% WL: 13.1%]) achieved these categorical outcomes compared to participants in the placebo arm ([15% WL: 3.2%]; [20% WL: 1.6%]). Treatment with subcutaneous semaglutide 2.4 mg was also associated with greater improvements in waist circumference (-9.4 cm) compared to placebo (-4.5 cm). There were no clinical differences between the subcutaneous semaglutide 2.4 mg arm and placebo arm in blood glucose and LDL cholesterol. See Table D12 for detailed results.

STEP 4, which had a crossover design including a 20-week run-in semaglutide dose escalation prior to randomization to either continuing subcutaneous semaglutide 2.4 mg or switching to placebo, assessed the efficacy of semaglutide compared with placebo for the management of obesity.^{133,134} Prior to randomization, all participants achieved a mean weight loss of -10.6% in the 20-week run-in period. We were able to obtain percent weight loss at six months through digitizing published graphical data. Participants who remained on semaglutide continued to experience weight loss at six months (-13.2%) compared to participants who were placed on placebo, who experienced slight weight regain compared to randomization baseline data at week 20 (-9.6% weight loss at six months from baseline). Overall percent weight loss at one year from week 0 (including semaglutide run-in) was -17.8% in the semaglutide arm compared to -5.4% in the placebo arm. For the co-primary outcomes of proportion of participants who achieved at least 5%, 10%, 15%, or 20% weight loss at one year, a greater proportion of participants in the semaglutide arm (88.6%, 78.8%, 63.8%, and 39.2%, respectively) achieved each categorical outcome compared to participants in the placebo arm (47.4%, 20.1%, 8.7%, and 4.4%, respectively). These categorical outcome data are digitized from published graphical data. See Table D13 for detailed results.

STEP 6 evaluated the efficacy of semaglutide compared with placebo for the management of obesity in patients with or without diabetes mellitus. Participants in the subcutaneous semaglutide 2.4 mg arm achieved greater percent weight loss at one year (-13.2%) compared to placebo (-2.1%).¹³⁵ Similarly, for the co-primary outcomes of proportion of participants who achieved at least 5%, 10%, 15%, or 20% weight loss at one year, a greater proportion of participants in the semaglutide arm (83%, 61%, 41%, and 20%, respectively) achieved each categorical outcome compared to participants in the placebo arm (21%, 5%, 3%, and 2%, respectively). See Table D13 for detailed results.

Semaglutide versus Liraglutide

The efficacy of subcutaneous semaglutide versus subcutaneous liraglutide with a placebo comparator for the management of obesity was evaluated in one Phase III trial (STEP 8).³¹ We were able to obtain percent weight loss at six months for the semaglutide and liraglutide arms by digitizing published graphical data. Data on weight loss at six months were not available for the placebo arm. Participants in the semaglutide arm achieved greater percent weight loss at six months (-13.3%) compared to participants in the liraglutide arm (-6.8%). Treatment with semaglutide also resulted in additional clinical benefits in waist circumference, blood glucose, and LDL cholesterol compared to both liraglutide and placebo. Treatment with liraglutide resulted in additional clinical benefits in waist circumference and blood glucose compared to placebo; however, participants in the liraglutide arm experienced an increase in LDL cholesterol from baseline (0.9 mg/dL) compared to semaglutide (-6.5 mg/dL) and placebo (-1.1 mg/dL), which both had reduced LDL cholesterol from baseline. See Table D10 for detailed results.

Table D10. Secondary Outcomes of Key Trials of Semaglutide for the Management of Obesity^{27,29,31-36}

	STEP 1		STEP 3		STEP 5		STEP 8		
Study Arms	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	LIR
N	577	1,212	189	373	129	149	78	117	117
% Weight Loss from Baseline to 6 Months, Mean (SE)	-2.9* (0.2)	-11.7* (0.2)	-7.9 (0.5)†	-15.4* (0.3)†	-2.6 (NR)	-13.2 (NR)	NR	-13.3* (NR)	-6.8* (NR)
Participants with 15% Weight loss, n (%)	28 (4.9)	612 (50.5)	25 (13.2)	208 (55.8)	7 (5.4)	78 (52.3)	5 (6.4)	65 (55.6)	14 (12)
Participants with 20% Weight loss, n (%)	10 (1.7)	388 (32)	7 (3.7)	133 (35.7)	3 (2.3)	52 (34.9)	2 (2.6)	45 (38.5)	7 (6)
Change in Waist Circumference, cm, Mean (SE)	-4.1 (NR)	-13.5 (NR)	-6.3 (NR)	-14.6 (NR)	-4.5 (0.6)†	-14.3 (0.8)†	-2 (1.1)†	-13.2 (0.9)†	-6.6 (0.9)†
Change in Fasting Blood Glucose, mg/dL, Mean (SE)	-0.5 (NR)	-8.4 (NR)	-0.7 (NR)	-6.7 (NR)	1.6§ (NR)	-7.6§ (NR)	3.3 (1.4)†	-8.3 (1.1)†	-4.3 (1.2)†
Change in LDL Cholesterol, mg/dL, Mean (SD)	1.1*‡ (NR)	-3.3*‡ (NR)	2.6* (NR)	-4.7 (NR)	-1.1‡ (NR)	-7.8‡ (NR)	-1.1* (5.6)†	-6.5* (3.1)†	0.9* (2.8)†

cm: centimeter, dL: deciliter, LDL: low-density lipoprotein, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, SBP: systolic blood pressure, SD: standard deviation, SE: standard error, SEM: semaglutide

*The number of patients for this outcome may differ from the primary analysis population.

†SE manually derived from standard deviation or 95% CIs.

‡Change in LDL cholesterol was calculated using ratio of LDL and respective baseline LDL.

§Timepoint for this outcome is at Week 104.

Liraglutide versus Placebo

The efficacy of liraglutide compared with placebo for the management of obesity was evaluated in four Phase III trials in the SCALE clinical trial program (Maintenance, Sleep Apnea, Obesity & Pre-Diabetes, IBT). We were able to obtain percent weight loss at six months by digitizing published graphical data. Participants in the liraglutide arms achieved greater percent weight loss at six months (-7.7%, -5.7%, -8.2%, and -8.4%) compared to participants in the placebo arm (-1%, -1.6%, -2.9%, and -5.4%).^{38,39,41,42,46-49} Data for the co-primary outcome of proportion of participants who achieved at least 15% weight loss at one year were only available for SCALE (IBT), in which a greater proportion of participants in the liraglutide arm (18.1%) achieved the outcome compared to the placebo arm (8.9%). Treatment with liraglutide resulted in additional benefits in waist circumference and blood glucose compared to placebo. Treatment with liraglutide resulted in additional benefits in LDL cholesterol in the Obesity & Pre-Diabetes (-3 mg/dL) and IBT (-1.5 mg/dL) trials compared to placebo (-1 mg/dL and 1.5 mg/dL, respectively). In the Maintenance trial, participants in both the liraglutide and placebo arms experienced an increase in LDL cholesterol from baseline (7.7 mg/dL and 11.6 mg/dL, respectively), although there was a greater increase in the placebo arm. Data on LDL cholesterol were not available for the Sleep Apnea trial. See Table D11 for detailed results.

The efficacy of subcutaneous liraglutide 3.0 mg compared with placebo for the management of obesity with diabetes mellitus was evaluated in two Phase III trials in the SCALE clinical trial program (Type 2 Diabetes, Insulin).^{40,43,50} We were able to obtain percent weight loss at six months through digitizing published graphical data. Participants in the liraglutide arms achieved greater percent weight loss at six months (-6% and -6.4%, respectively) compared to participants in the placebo arm (-2.7% and -2.1%, respectively) (Table D12). Categorical data for proportion of participants who achieved at least 15% weight loss at one year were not available for either study. Treatment with liraglutide resulted in additional benefits in waist circumference and blood glucose compared to placebo. Outcomes related to changes in LDL were reported as absolute change from baseline for SCALE (Type 2 Diabetes) and as ratio of LDL from baseline for SCALE (Insulin). In the Type 2 Diabetes trial, participants in both the liraglutide and placebo arms experienced an increase in LDL cholesterol from baseline (0.6 mg/dL and 5 mg/dL, respectively). Participants in the Insulin trial had a decreased ratio of LDL cholesterol from baseline (0.97 mg/dL) compared to placebo, which remained relatively unchanged from baseline (1.0 mg/dL).

LOSEIT evaluated the efficacy of liraglutide compared with placebo for the management of obesity in patients with or without diabetes mellitus. Data for percent weight loss at one year were not available. For the co-primary outcomes of proportion of participants who achieved at least 5% weight loss and at least 10% weight loss at one year, a great proportion of participants in the liraglutide arm achieved each categorical outcome (35% and 21.3%, respectively) compared to

participants in the placebo arm (17.1% and 9.6%, respectively).¹³⁶ See Table D13 for detailed results.

Table D11. Secondary Outcomes of Key Trials of Liraglutide for the Management of Obesity^{38,39,41,42,46-49}

	SCALE Maintenance		SCALE Sleep Apnea‡		SCALE Obesity & Pre-Diabetes		SCALE IBT	
Study Arms	PBO	LIR	PBO	LIR	PBO	LIR	PBO	LIR
N	206	207	178	175	1,225	2,437	130	141
% Weight Loss from Baseline to 6 Months, Mean (SE)	-1* (0.5)	-7.7* (0.5)	-1.6 (0.3)	-5.7 (0.4)	-2.9 (0.3)	-8.2 (0.2)	-5.4* (0.5)	-8.4* (0.6)
Participants with 15% Weight loss, n (%)	NR	NR	NR	NR	NR	NR	12 (8.9)	26 (18.1)
Change in Waist Circumference, cm, Mean (SE)	-1.2 (0.4)†	-4.7 (0.5)†	-3.1 (0.5)	-6.4 (0.5)	-3.9 (0.2)†	-8.2 (0.1)†	-6.7 (NR)	-9.4 (NR)
Change in Fasting Blood Glucose, mg/dL, Mean (SE)	-3.6 (0.9)†	-9.0 (0.8)†	3.6 (1.8)	-3.6 (1.8)	0.1 (0.3)†	-7.1 (0.2)†	0.2 (NR)	-4.1 (NR)
Change in LDL Cholesterol, mg/dL, Mean (SD)	11.6 (1.6)†	7.7 (1.6)†	NR	NR	-1 (NR)	-3 (NR)	1.5 (NR)	-1.5 (NR)

cm: centimeter, dL: deciliter, LDL: low-density lipoprotein, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, SBP: systolic blood pressure, SD: standard deviation, SE: standard error

*The number of patients for this outcome may differ from the primary analysis population.

†SE manually derived from standard deviation or 95% CIs.

‡Timepoint for all outcomes except percent weight loss is at 32 weeks.

Table D12. Secondary Outcomes of Key Trials of Semaglutide and Liraglutide for the Management of Obesity with Diabetes Mellitus^{28,40,43,50}

	STEP 2		SCALE Type 2 Diabetes		SCALE Insulin	
Study Arms	PBO	SEM	PBO	LIR	PBO	LIR
N	376	388	211	412	193	191
% Weight Loss from Baseline to 6 Months, Mean (SE)	-2.7* (0.2)	-8.7* (0.3)	-2.7* (0.3)‡	-6* (0.3)‡	-2.1* (0.4)	-6.4* (0.4)
Participants with 15% Weight loss, n (%)	12 (3.2)	100 (25.8)	NR	NR	NR	NR
Participants with 20% Weight loss, n (%)	6 (1.6)	51 (13.1)	NR	NR	NR	NR
Change in Waist Circumference, cm, Mean (SE)	-4.5 (0.4)	-9.4 (0.4)	-2.7 (0.4)‡	-6.1 (0.3)‡	-2.6 (NR)	-5.3 (NR)
Change in Fasting Blood Glucose, mg/dL, Mean (SE)	-0.1 (1.8)	-2.1 (1.8)	-0.2 (2.5)‡	-34.3 (1.9)‡	-11.5 (NR)	-18.4 (NR)
Change in LDL Cholesterol, mg/dL, Mean (SD)	0* (NR)†	0* (NR)†	5 (NR)	0.6* (NR)	0.9* (NR)†	-2.8* (NR)†

cm: centimeter, dL: deciliter, LDL: low-density lipoprotein, mg: milligram, NR: not reported, PBO: placebo, SBP: systolic blood pressure, SD: standard deviation, SE: standard error, SEM: semaglutide

*The number of patients for this outcome may differ from the primary analysis population.

†Change in LDL cholesterol was calculated using ratio of LDL and respective baseline LDL.

‡SE manually derived from standard deviation or 95% CIs.

Table D13. Results of Additional Trials of Semaglutide and Liraglutide for the Management of Obesity¹³³⁻¹³⁶

Study Arms	STEP 4		STEP 6		LOSEIT	
	PBO	SEM	PBO	SEM	PBO	LIR
N	250	520	100	193	76	80
% Weight Loss from Baseline to One Year, Mean (SE)	6.9*‡ (0.5) [†]	-7.9*‡ (4) [†]	-2.1 (0.8)	-13.2 (0.5)	NR	NR
Participants with at Least 5% Weight Loss, n (%)	119§ (47.4)	461§ (88.6)	21 (21)	160 (83)	13 (17.1)	28 (35)
Participants with at Least 10% Weight Loss, n (%)	50§ (20.1)	410§ (78.8)	5 (5)	117 (61)	7 (9.6)	17 (21.3)
Participants with at Least 15% Weight Loss, n (%)	22§ (8.7)	332§ (63.8)	3 (3)	79 (41)	NR	NR
Participants with at Least 20% Weight Loss, n (%)	11§ (4.4)	204§ (39.2)	2 (2)	38 (20)	NR	NR

LIR: liraglutide, NR: not reported, PBO: placebo, SEM: semaglutide

*The number of patients for this outcome may differ from the primary analysis population.

[†]SE manually derived from standard deviation or 95% CIs.

[‡]Timepoint for this outcome is Weeks 20-68.

[§]Timepoint for this outcome is Weeks 0-68.

Phentermine/Topiramate versus Placebo

The Report discusses the primary outcome of percentage weight loss at one year and proportion of participants achieving 5% and 10% weight loss in the EQUIP trial. In the EQUIP trial, data on weight loss at six months were not available. For the categorical outcome of at least 15% weight loss at one year, more participants in the phentermine 15 mg/topiramate 92 mg arm achieved this outcome (32%) compared to those in placebo (3%)⁵²⁻⁵⁵ (Table D14). In EQUATE, participants in the high-dose phentermine/topiramate arm experienced the greatest percent weight loss from baseline (-9.2%), followed by the low-dose intervention arm (-8.5%), and placebo (-5.5%). Categorical weight loss of at least 15% at one year was not assessed in the EQUATE trial.

Treatment with phentermine/topiramate in both EQUIP and EQUATE was associated with additional clinical benefits in terms of reductions in waist circumference, blood glucose, and LDL cholesterol at one year. In the EQUIP trial, mean reduction in waist circumference was greater in the treatment arm than placebo (-10.9 cm vs. -3.1cm, respectively).⁵²⁻⁵⁵ Mean reduction in waist circumference in the high-dose and low-dose intervention arms in EQUATE was also greater than placebo (-8.7 cm and -8.8 cm, versus -3.1cm, respectively). In the EQUIP trial, participants receiving phentermine/topiramate experienced a small improvement in their blood glucose levels (-0.6 mg/dL), while participants receiving placebo experienced a slight elevation in blood glucose on average (1.9 mg/dL). Participants in both arms improved LDL cholesterol levels, but the effect was greater in the phentermine/topiramate arm (-8.4 vs. -5.5 mg/dL, respectively). In the EQUATE trial,

mean change from baseline in blood glucose levels in both arms was negligible (-1 to 0 mg/dL change). See Table D14 for detailed results.

In the diabetes mellitus subgroup of the CONQUER trial, data on secondary outcomes such as weight loss at six months, categorical weight loss of at least 15%, and change in waist circumference were not available. All reported outcomes here are from the one-year timepoint. Participants in the diabetes subgroup receiving high-dose and low-dose phentermine/topiramate experienced a greater improvement in their blood glucose levels than participants in the placebo group (-12.6 and -9 vs. -5.4 mg/dL, respectively).^{51,56} Similar trends were observed for LDL cholesterol; high and low-dose phentermine/topiramate was associated with greater improvements in LDL compared to placebo (-2.8 and -3.6 vs. -2.3 mg/dL, respectively). See Table D15 for detailed results.

In the Phase I/II OB-204 trial, efficacy outcomes were assessed at 28 weeks. At that timepoint, participants in the phentermine/topiramate arm achieved a greater percent weight loss (-10.3%) compared to participants in the placebo arm (-4.2%).¹³⁷ Similarly, more participants receiving the intervention achieved target weight loss of at least 5% and 10% body weight than participants receiving placebo. See Table D16 for detailed results.

Bupropion/Naltrexone versus Placebo

Weight loss data at six months were not available in the COR-I trial. In COR-II and COR-BMOD, participants in the bupropion/naltrexone arms experienced greater weight loss than participants in the placebo arms at six months (-6.5% and -9.4% vs. -1.9% and -5.6%, respectively) (Table D14). Similarly, for all three trials, more participants in the treatment arms achieved at least 15% bodyweight at one year compared to the placebo arms.⁶¹⁻⁶⁴

At the one-year timepoint, participants receiving bupropion/naltrexone in the COR-I, COR-II, and COR-BMOD trials experienced greater improvement in waist circumference (-6.2, -6.7, and -10 cm, respectively) than participants receiving placebo (-2.5, -2.1, and -6.8, respectively).⁵⁹⁻⁶⁴ Similarly, participants receiving bupropion/naltrexone achieved greater improvements in blood glucose levels (-3.2, -2.8, and -2.4 mg/dL) versus placebo (-1.3, -1.3, and -1.1, respectively). In COR-I and COR-II, participants in the intervention arms experienced a greater improvement from baseline in their LDL cholesterol (-4.4 and -6.2 mg/dL, respectively), compared to placebo (-3.3 and -2.1 mg/dL, respectively). However, in the COR-BMOD trial, both arms experienced an increase in their LDL cholesterol, with participants in the placebo arm experiencing a greater increase (8.1 mg/dL) than participants in the bupropion/naltrexone arm (5.4 mg/dL). See Table D14 for detailed results.

In the COR Diabetes trial of bupropion/naltrexone for the management of obesity with diabetes mellitus, participants in the intervention arm experienced a greater percent change in their weight at six months (-5.1%) compared to those in the placebo arm (-2%).^{57,58} Categorical weight loss of at least 15% at one year was not available in this trial. At the one-year timepoint, participants in the

treatment arm experienced greater improvements in waist circumference compared to placebo (-5 cm vs. -2.9 cm, respectively), change in blood glucose (-11.9 mg/dL vs. -4 mg/dL, respectively) and change in LDL cholesterol (-1.4 mg/dL vs. 0 mg/dL, respectively). See Table D15 for detailed results.

In CVOT Light, participants in the bupropion 360 mg/naltrexone 32 mg arm achieved greater weight loss at one year (-4.6%) than participants in the placebo arm (-1.8%)^{138,139} (Table D16). The categorical weight loss outcomes of at least 5% and 10% were not assessed in this trial.

In the Ignite trial, since all participants were either switched or continued on open-label bupropion/naltrexone treatment at 26 weeks, we evaluated efficacy outcomes only up to that timepoint.^{140,142} Similar to CVOT Light, participants in the intervention arm achieved a greater weight improvement at 26 weeks (-9.5%) compared to participants in the usual care arm (-0.9%). For the endpoint of proportion of participants who lost at least 5% of and 10% of their weight, more participants in the bupropion/naltrexone treatment arm achieved these outcomes compared to participants in the usual care group. See Table D16 for detailed results.

Table D14. Secondary Outcomes of Key Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity^{52-55,59-64,79}

	EQUIP		EQUATE			COR-I		COR-II		COR BMOD	
Study Arms	PBO	P/T (high)	PBO	P/T (low)	P/T (high)	PBO	B/N	PBO	B/N	PBO	B/N
N	498	498	103	103	103	511	471	456	702	193	482
% Weight Loss from Baseline to 6 Months, Mean (SE)	NR	NR	-1.7 (0.6)	-8.5 (0.6)	-9.2 (0.6)	NR	NR	-1.9* (0.3)	-6.5* (0.2)	-5.6* (0.5)	-9.4* (0.4)
Participants with 15% Weight loss, n (%)	17 (3.4)	161 (32.3)	NR	NR	NR	10 (2)	56 (12)	11 (2.4)	95 (13.5)	21 (10.9)	140 (29.1)
Change in Waist Circumference, cm, Mean (SE)	-3.1 (0.5) [†]	-10.9 (0.5) [†]	-3.3 (0.7)	-8.8* (0.7)	-8.7 (0.7)	-2.5 (0.4)	-6.2 (0.4)	-2.1 (0.5)	-6.7 (0.3)	-6.8 (0.8)	-10 (0.5)
Change in Fasting Blood Glucose, mg/dL, Mean (SE)	1.9 (0.5) [†]	-0.6 (0.5) [†]	-0.1* (0.1)	0* (0.1)	-0.1* (0.1)	-1.3 (0.6)	-3.2 (0.6)	-1.3 (0.6)	-2.8 (0.5)	-1.1 (1)	-2.4 (0.6)
Change in LDL Cholesterol, mg/dL, Mean (SD)	-5.5* (0.9) [†]	-8.4* (0.9) [†]	NR	NR	NR	-3.3* (1.2)	-4.4* (1.2)	-2.1* (1.3)	-6.2* (0.9)	8.1* (2.1)	5.4* (1.4)

B/N: bupropion/naltrexone, cm: centimeter, dL: deciliter, LDL: low-density lipoprotein, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SBP: systolic blood pressure, SD: standard deviation, SE: standard error

*The number of patients for this outcome may differ from the primary analysis population.

[†]SE manually derived from standard deviation or 95% CIs.

Table D15. Secondary Outcomes of Key Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity and Obesity with Diabetes^{51,56-58}

Study Arms	CONQUER (Diabetes Subgroup)			COR Diabetes	
	PBO	P/T (low)	P/T (high)	PBO	B/N
N	157	67	164	159	265
% Weight Loss from Baseline to 6 Months, Mean (SE)	NR	NR	NR	-2* (0.4)	-5.1* (0.3)
Participants with 15% Weight loss, n (%)	NR	NR	NR	NR	NR
Change in Waist Circumference, cm, Mean (SE)	NR	NR	NR	-2.9 (0.6)	-5 (0.5)
Change in Fasting Blood Glucose, mg/dL, Mean (SE)	-5.4 (1.8) [†]	-9 (3.6) [†]	-12.6 (1.8) [†]	-4 (3.4)	-11.9 (2.7)
Change in LDL Cholesterol, mg/dL, Mean (SD)	-2.3* (2.1)	-3.6* (3.2)	-2.8* (2)	0* (2.4)	-1.4* (1.9)

B/N: bupropion/naltrexone, cm: centimeter, dL: deciliter, LDL: low-density lipoprotein, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SBP: systolic blood pressure, SD: standard deviation, SE: standard error

*The number of patients for this outcome may differ from the primary analysis population.

[†]SE manually derived from standard deviation or 95% CIs.

Table D16. Results of Additional Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity¹³⁷⁻¹⁴²

Study Arms	OB-204 [†]		CVOT Light		Ignite [‡]	
	PBO	P/T (high)	PBO	B/N	PBO	B/N
N	23	22	4450	4455	82	71
% Weight Loss from Baseline to One Year, Mean (SE)	-4.2 (1.2)	-10.3 (1.2)	-1.8* (NR)	-4.6* (NR)	-0.9 (0.5)	-9.5 (0.5)
Participants with 5% Weight Loss, n (%)	11 (47.8)	16 (72.7)	NR	NR	10 (12.2)	60 (84.5)
Participants with 10% Weight Loss, n (%)	3 (13)	12 (54.5)	NR	NR	3 (3.7)	30 (42.3)

B/N: bupropion/naltrexone, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SE: standard error

*The number of patients for this outcome may differ from the primary analysis population.

[†]Timepoint for all outcomes is at Week 28.

[‡]Timepoint of interest for all outcomes for this trial is at Week 26.

HRQoL

For each medication, HRQoL data for additional studies included in the Supplement are described in the text below. Additional HRQoL data beyond physical functioning and mental scores for studies from the Report are also discussed in the text below. The Report outlines physical function and mental HRQoL data for studies included in our primary analysis. Data from the Report for physical function and mental HRQoL are outlined in Tables D17 and D18 below.

Semaglutide

HRQoL in STEP 4 was assessed using the SF-36v2 physical function score. During the 20-week run-in period, participants experienced an average score improvement of 2.2 from baseline score. After randomization, from weeks 20 to 68, participants who continued semaglutide experienced a further improvement in physical functioning score (1.0) compared to a decreased score for those who switched to placebo (-1.5). Additionally, improvements were seen in the semaglutide arm for the SF-36v2 Physical Component Summary (0.8) and Mental Component Summary (0.1) compared to decreased scores for both in the placebo arm (-0.9 and -3.4, respectively).¹³³ (Table D30).

Patient reported outcomes for STEP 6 included SF-36v2 physical functioning scores and the IWQOL-Lite-CT physical function score. Participants in the semaglutide arm experienced improvement from baseline in SF-36v2 physical functioning score (0.8) compared to placebo which resulted in a decrease in score (-0.3) (higher is better). Improvements in the IWQOL-Lite-CT physical function score was higher in the semaglutide arm (4.2) compared to placebo (0.8) (higher is better).¹³⁵ See Table D30 for detailed results.

Liraglutide

The SCALE (Sleep Apnea) trial discussed in the Report also assessed patient-reported outcomes related to sleep health using two instruments: Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ). For the FOSQ instrument, a higher score indicates less functional impairment. The ESS assesses daytime sleepiness with a lower score indicating a lower propensity for daytime sleepiness. The change from baseline for both the ESS and FOSQ instruments did not differ significantly between the semaglutide (-2.5 and 1.3, respectively) and placebo arms (-2.3 and 1.1, respectively) (Table D31).^{39,48}

The LOSEIT trial assessed patient-reported outcomes related to knee pain using the KOOS instrument, with higher scores (scale 0-100) indicating improved disease status (positive is better). At week 52, participants in the liraglutide arm reported improvement on the KOOS pain instrument (0.4) compared to placebo arm, which reported a decreased score (-0.6) from baseline. Additionally, participants in the liraglutide arm reported greater improvement in function in activities of daily living (1.4) and knee-related quality of life (3.1) compared to those in the placebo arm (-1.6 and 0.7, respectively). Conversely, change in symptoms had a decreased score in the

liraglutide arm (-1.2) compared to placebo (0.3). Overall, there were no significant differences in change from baseline score for the KOOS instrument and its subsections observed between the liraglutide versus placebo arms.¹³⁶

Phentermine/Topiramate

HRQoL was assessed using the SF-36 instrument, the ESS, and the Pittsburgh Sleep Quality Index in OB-204. Participants in the phentermine/topiramate group demonstrated greater improvement in the SF-36 physical functioning subscale compared to placebo.^{137,141} Additionally, participants receiving phentermine/topiramate had a greater improvement compared to participants receiving placebo in their sleep quality, measured by the ESS (-1.9% vs. -1.8%, respectively), and the PSQI (-3.1% vs. -0.9%, respectively) (Tables D30 and D31).

Bupropion/Naltrexone

In the Ignite trial, HRQoL was assessed with the IWQOL-Lite total score. Participants receiving the intervention had a significant improvement in their quality of life (16.4), while participants receiving usual care slightly decreased in their reported quality of life (-1)^{140,142} (Table D30).

Table D17. Physical Component HRQoL Outcomes of Key Trials^{27-29,32,33,39-43,46,48-50,61-64}

Study Name	Arms	SF-36v2 Physical Functioning Score, Mean Change from Baseline (SE)	SF-36v2 Physical Component Score, Mean Change from Baseline (SE)	IWQOL-Lite-CT Physical Function Score, Mean Change from Baseline (SE)
Semaglutide				
STEP 1	PBO	0.4 (NR)	0.2† (0.3)*	5.3 (NR)
	SEM	2.2 (NR)	2.4† (0.2)*	14.7 (NR)
STEP 2	PBO	1† (0.4)	NR	5.3 (1.1)
	SEM	2.5† (0.4)	NR	10.1 (1)
STEP 3	PBO	1.6 (NR)	2.3 (NR)	NR
	SEM	2.4 (NR)	3 (NR)	NR
Liraglutide				
SCALE (Sleep Apnea)	PBO	NR	1.9 (0.5)	NR
	LIR	NR	3 (0.6)	NR
SCALE (Obesity & Pre-Diabetes)	PBO	NR	2.1 (0.2)*	NR
	LIR	NR	3.6 (0.1)*	NR
SCALE (IBT)	PBO	3.8 (NR)	3.8 (0.6)*	14.1 (NR)
	LIR	4 (NR)	3.4 (0.6)*	14.9 (NR)
SCALE (Type 2 Diabetes)	PBO	NR	NR	8.9 (1.1)*
	LIR	NR	NR	15.2 (0.9)*
SCALE (Insulin)	PBO	2.6 (0.5)*	2.2 (0.5)*	5.7 (NR)
	LIR	2.5 (0.6)*	2.7 (0.5)*	8.2 (NR)
Bupropion/Naltrexone				
COR-II	PBO			8.2 (0.8)
	B/N			14.1 (0.6)
COR-BMOD	PBO			12 (0.8)
	B/N			16.5 (0.5)

B/N: bupropion/naltrexone, IWQOL-Lite-CT: Quality of Life-Lite Clinical Trials Version, LIR: liraglutide, NR: not reported, PBO: placebo, SE: standard error, SEM: semaglutide, SF-36v2: Short Form 36v2 Health Survey

Note: Greyed-out boxes indicate that the HRQoL instrument was not used for any trials within that intervention group.

*SE manually derived from standard deviation or 95% CIs.

†The number of patients for this outcome may differ from the primary analysis population.

Table D18. Mental Component HRQoL Outcomes of Key Trials^{29,33,39,41,46,48,51-64}

Study Name	Arms	SF-36v2 MCS, Mean Change from Baseline (SE)	Depression Score, Mean Change from Baseline (SE)*
Semaglutide			
STEP 1	PBO	-2.1‡ (0.3)†	
	SEM	-1.5‡ (0.2)†	
STEP 3	PBO	-2.9 (NR)	
	SEM	-0.8 (NR)	
Liraglutide			
SCALE (Sleep Apnea)	PBO	0.9 (0.6)	
	LIR	1.4 (0.6)	
SCALE (Obesity & Pre-Diabetes)	PBO	-0.9 (0.3)†	
	LIR	0.2 (0.2)†	
SCALE (IBT)	PBO	-2.2 (0.7)†	
	LIR	-1.2 (0.7)†	
SCALE (Insulin)	PBO	-1.7 (0.5)†	
	LIR	-1.9 (0.6)†	
Phentermine/Topiramate			
EQUIP	PBO		-1.3 (0.2)†
	P/T (low)		-1.2 (0.2)†
	P/T (high)		-1.5 (0.1)†
EQUATE	PBO		-0.5 (0.4)†
	P/T (low)		-1.3 (0.2)†
	P/T (high)		-1.1 (0.4)†
CONQUER	PBO		NR
	P/T (low)		NR
	P/T (high)		NR
Bupropion/Naltrexone			
COR-I	PBO		-0.7 (0.2)
	B/N		-0.3‡ (0.2)
COR-II	PBO		-0.5 (0.3)
	B/N		-0.3 (0.2)
COR-BMOD	PBO		0‡ (0.4)
	B/N		0.1‡ (0.2)
COR-Diabetes	PBO		-1.6 (0.4)
	B/N		0 (0.3)

B/N: bupropion/naltrexone, IDS-SR: Inventory of Depressive Symptomology (Self-Report), LIR: liraglutide, MCS: mental component summary, mg: milligram, NR: not reported, PBO: placebo, PHQ-9: Patient Health Questionnaire, P/T: phentermine/topiramate, SE: standard error, SEM: semaglutide, SF-36v2: Short Form 36v2 Health Survey

Note: Greyed-out boxes indicate that the HRQoL instrument was not used for any trials within that intervention group.

*Phentermine/topiramate studies utilized PHQ-9 for depression score, bupropion/naltrexone utilized IDS-SR for depression score.

†SE manually derived from standard deviation or 95% CIs.

‡The number of patients for this outcome may differ from the primary analysis population.

Harms

Semaglutide versus Placebo

The most frequent adverse events in the STEP 4 and 6 trials for semaglutide were gastrointestinal-related symptoms, including nausea, constipation, and diarrhea.¹³³⁻¹³⁵ Beyond gastrointestinal events, semaglutide appeared relatively well-tolerated. Participants in the semaglutide arms of the STEP 4 and 6 trials experienced more adverse events (81.3% and 86%, respectively) compared to those in the placebo arms (75% and 79%, respectively). Similarly for STEP 4, participants in the semaglutide arm experienced more serious adverse events (SAEs) (7.7%) compared to participants in the placebo arm (5.6%).^{133,134} However, STEP 6 reported a higher rate of serious adverse events in the placebo arm (7%) compared to the semaglutide arm (5%).¹³⁵ One death was reported in each treatment group for STEP 4, but both were determined to be unrelated to study treatment. There were no deaths reported in STEP 6. Notable serious adverse events that occurred included one occurrence of cholecystitis in the STEP 4 intervention arm, five occurrences of cholelithiasis in the STEP 4 intervention arm (two occurrences in the placebo arm) and two occurrences in the STEP 6 intervention arm, one occurrence of nephrolithiasis in the STEP 4 intervention arm, and one occurrence of ureterolithiasis in the STEP 4 intervention arm and one occurrence in the STEP 6 intervention arm (one occurrence in the placebo arm). Rates of discontinuation due to adverse events were higher in the semaglutide arms for both STEP 4 and STEP 6 (2.4% and 3%, respectively) compared to placebo arm (2.2% and 1%, respectively). Gastrointestinal events were the most common reported reason for discontinuing due to adverse events. See D19 for detailed harms results.

Liraglutide versus Placebo

The most common adverse events reported in LOSEIT included gastrointestinal events, with a total of 264 events in the liraglutide arm versus 144 events in the placebo arm.¹³⁶ Participants in the liraglutide arm experienced more adverse events (96%) compared to those in the placebo arm (93%). Rates of serious adverse events were similar between both the liraglutide (9%) and placebo arms (8%) (Table D19). Gastrointestinal serious adverse events occurred in one participant from the liraglutide arm (ileus leading to surgery) and one participant from the placebo arm (cholecystitis). There were no deaths reported in the trial. Rates of discontinuation due to adverse events were higher in the liraglutide arm (10 patients) compared to placebo arm (four patients). Gastrointestinal events were the most common reported reason for discontinuing due to adverse events.

Table D19. Harms in Other Trials of Semaglutide and Liraglutide for the Management of Obesity¹³³⁻¹³⁶

	STEP 4			STEP 6		LOSEIT	
Study Arms	Run-in*	PBO†	SEM†	PBO	SEM	PBO	LIR
N	902	268	535	101	199	76	80
Any AE, n (%)	760 (84.3)	201 (75)	435 (81.3)	80 (79)	171 (86)	71 (93)	77 (96)
SAE, n (%)	21 (2.3)	15 (5.6)	41 (7.7)	7 (7)	10 (5)	6 (8)	7 (9)
AEs Leading to Discontinuation, n (%)	48 (5.3)	6 (2.2)	13 (2.4)	1 (1)	5 (3)	4 (5.3)	10 (12.5)
GI Disorders Leading to Discontinuation, n (%)	NR	NR	NR	0 (0)	4 (2)	2 (2.6)	8 (10)
Nausea, n (%)	NR	13 (4.9)	75 (14)	4 (4)	35 (18)	NR	NR
Constipation, n (%)	NR	17 (6.3)	62 (11.6)	3 (3)	52 (26)	NR	NR
Diarrhea, n (%)	NR	19 (7.1)	77 (14.4)	6 (6)	32 (16)	NR	NR

AE: adverse event, GI: gastrointestinal, LIR: liraglutide, NR: not reported, PBO: placebo, SAE: serious adverse event, SEM: semaglutide

*Timepoint for harms is at Weeks 0-20.

†Timepoint for harms is at Weeks 20-68.

Phentermine/Topiramate versus Placebo

In OB-204, most treatment-emergent adverse events were mild to moderate in severity, and the incidence of any adverse events was higher in the phentermine/topiramate arm (91%) than in the placebo arm (78%).^{137,141} Adverse reactions that occurred more frequently in the intervention arm than in the placebo arm included dry mouth (50% vs. 0%), dysgeusia (27% vs. 0%), and sinusitis (23% vs. 0%). Serious adverse events were rare and were experienced by no participants in the phentermine/topiramate group, compared to one participant in the placebo group. Over twice many participants in the intervention arm discontinued due to adverse events (9.1%) compared to participants in the intervention arm (4.4%). See Table D20 for detailed harms results.

Bupropion/Naltrexone versus Placebo

In CVOT Light, over twice as many participants in the bupropion/naltrexone arm experienced any adverse events (36%) compared to participants in the placebo arm (15%).^{138,139} Rates of serious adverse events were similar and relatively low across the two arms (9-10%) (Table D20). More participants in the bupropion/naltrexone arm discontinued due to adverse events (28%) than in the placebo arm (9%). The most common adverse events that led to discontinuation of the drug in both the treatment arm and the placebo arm included gastrointestinal adverse reactions (14% and 2%, respectively), which included nausea, constipation, and vomiting, and central nervous system reactions (5% and 1%, respectively), which including tremor, dizziness, and headache. Psychiatric disorders, such as insomnia, anxiety, and depression, leading to discontinuation were infrequently observed in both arms (3% vs. 1%, respectively).

In the Ignite trial, rates of any adverse events up to 26 weeks, before patients in usual care were switched to open-label bupropion/naltrexone treatment, were 18% in the bupropion/naltrexone arm and 0% in the placebo arm (Table D20).^{140,142} Serious adverse events during the controlled treatment period (through 78 weeks) were low, with one participant in the intervention arm versus zero in the placebo arm experiencing a serious adverse reaction.

At 26 weeks, in the Ignite trial, discontinuations due to adverse events occurred at a higher rate in the bupropion/naltrexone arm (23%) than in the placebo arm (1.1%).^{140,142} Throughout the entire study period (78 weeks), adverse events that led to discontinuation were observed in 24% of patients who were randomized to and continued open-label bupropion/naltrexone treatment, and in 16% of patients who were initially in placebo, but switched to open-label treatment. The most frequent adverse reactions leading to discontinuation of the treatment for both groups included nausea (7%), anxiety (2.1%), headache (1.7%), dizziness (1.2%), and insomnia (1.2%). Rates of serious adverse events leading to discontinuation at this timepoint were low in both arms, with discontinuations occurring in two patients who continued on bupropion/naltrexone and zero patients in the placebo arm who switched to the treatment. These two serious adverse events were considered to be unrelated to the study drug. See Table D20 for detailed harms results.

Table D20. Harms in Other Trials of Phentermine/Topiramate and Bupropion/Naltrexone for the Management of Obesity and Obesity with Diabetes Mellitus¹³⁷⁻¹⁴²

	OB-204		CVOT Light		Ignite*	
Study Arms	PBO	P/T (high)	PBO	B/N	PBO	B/N
N	23	22	4450	4455	89	153
Any AE, n (%)	18 (78.2)	20 (90.9)	668 (15)	1620 (36.4)	0	27 (17.6)
SAE, n (%)	1 (4.4)	0	386 (8.7)	463 (10.4)	0	1 (0.7)
AE Leading to Disc., n (%)	1 (4.4)	2 (9.1)	388 (8.7)	1253 (28.1)	1 (1.1)	35 (22.9)
Gastrointestinal Disorders	NR	NR	84 (1.9) [†]	(2) [†]	NR	NR
Nausea	1 (4.4)	2 (9.1)	21 (0.5) [†]	333 (7.5) [†]	16 (10.5)	0
Dry Mouth	0	11 (50)	2 (0.04)	21 (0.5)	NR	NR
Nervous System Disorders	NR	NR	52 (1.2) [†]	226 (5.1) [†]	NR	NR
Headache	NR	NR	14 (0.3) [†]	51 (1.1) [†]	2 (1.3)	0
Dizziness	0	1 (4.6)	7 (0.2) [†]	62 (1.4) [†]	1 (0.7)	0
Dysgeusia	0	6 (27)	0	16 (0.4)	NR	NR
Infection	NR	NR	NR	NR	NR	NR
Sinusitis	0	5 (23)	0	1 (0.02)	NR	NR
Psychiatric Disorders	NR	NR	39 (0.9) [†]	136 (3.1) [†]	NR	NR
Anxiety	NR	NR	8 (0.2) [†]	26 (0.6) [†]	5 (3.3)	0
Insomnia	NR	NR	16 (0.4) [†]	35 (0.8) [†]	2 (1.3)	0

AE: adverse event, B/N: bupropion/naltrexone, disc.: discontinuation, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SAE: serious adverse event

*Timepoint up to 26 weeks.

[†]Rates of AEs leading to discontinuation

D3. Evidence Tables

Table D21. USPSTF Study Quality

Trial	USPSTF Rating									
	Comparable Groups	Non-Differential Follow-Up	Patient/ Investigator Blinding	Clear Definition of Intervention	Clear Definitions of Outcomes	Selective Outcome Reporting	Measurements Valid	ITT Analysis	Approach to Missing Data	USPSTF Overall Rating
Semaglutide										
STEP 1	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
STEP 2	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
STEP 3	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
STEP 4	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
STEP 5*	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unknown	Good
STEP 6	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
STEP 8	Yes	Yes	No†	Yes	Yes	No	Yes	Yes	MI	Fair
Liraglutide										
SCALE (Maintenance)	Yes	No	Yes	Yes	Yes	No	Yes	Yes	LOCF	Fair
SCALE (Sleep Apnea)	Yes	No	Yes	Yes	Yes	No	Yes	Yes	LOCF	Fair
SCALE (T2DM)	Yes	No	Yes	Yes	Yes	No	Yes	Yes (mITT)	MI	Fair
SCALE (Obesity & Pre-Diabetes)	Yes	No	Yes	Yes	Yes	No	Yes	Yes	LOCF	Fair
SCALE (IBT)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
SCALE (Insulin)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
LOSEIT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NRI	Good
Phentermine/Topiramate										
EQUATE	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes, mITT	LOCF	Good
EQUIP	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	LOCF	Good
CONQUER	Yes	Yes	Yes	Yes	Yes	Yes, BMI CFB	Yes	Yes	MI	Good
OB-204	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
Bupropion/Naltrexone										
COR-I	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes (mITT)	LOCF	Good
COR-II	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes (mITT)	LOCF	Good
COR BMOD	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes (mITT)	LOCF	Good
COR Diabetes	Yes	Yes	Yes	Yes	Yes	Yes, rescue medication	Yes	Yes (mITT)	LOCF	Good
CVOT Light	Yes	Yes	Yes	Yes	Yes	Yes, BMI CFB	Yes	Yes	No imp.	Good
Ignite	Yes	Yes	No†	Yes	Yes	Yes, PROs (QoL, binge eating, sexual function)	Yes	Yes, mITT	No imp.	Fair

BMI: body mass index, CFB: change from baseline, IBT: intensive behavioral therapy, ITT: intention to treat, PRO: patient-reported outcome, QoL: quality of life, T2DM: type 2 diabetes mellitus, USPSTF: United States Preventive Services Task Force

*No publication; the sources for this trial are a conference presentation and ClinicalTrials.gov.

†This was an open-label randomized trial.

Table D22. Study Design

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
Semaglutide						
STEP 1 ^{27,30,32} Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=655)	Counseling sessions every 4 wks; reduced-calorie diet and increase physical activity; daily diary to record diet and exercise	Adults with BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with at least 1 weight-related comorbid condition	DM; uncontrolled thyroid disease; CVD; treatment with GLP-1; 5 kg weight loss within 90 days	129 sites in 16 countries in Asia, Europe, and N/S America	Week 68: % Δ in body weight, absolute weight loss, body weight reduction of 5%, 10%, 15%; waist circ., SBP, LDL, A1C, fasting FBG, hsCRP, SF-36, IWQOL
	SC SEM 2.4 mg + LI (n=1306)					
STEP 2 ²⁸ Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=403)	Counseling sessions every 4 wks; reduced-calorie diet and increase physical activity; daily diary to record diet and exercise	Adults with BMI of ≥ 27 kg/m ² , HbA1C of 7-10%, and diagnosed with type 2 DM	Uncontrolled thyroid disease; treatment with GLP-1; previous/planned treatment with surgery; 5 kg weight loss within 90 days	149 sites in 12 countries in Europe, N/S America, Middle East, Africa, and Asia	Week 68: % Δ in body weight, absolute weight loss; body weight reduction of 5%, 10%, 15%, waist circ., SBP, LDL, A1C, fasting FBG, hsCRP, SF-36, IWQOL, Δ in DM medication
	SC SEM 1.0 mg + LI (n=403)					
	SC SEM 2.4 mg + LI (n=404)					
STEP 3 ^{29,33,37} Phase III, MC, PBO-controlled monotherapy	PBO + IBT (n=204)	Low-calorie meal replacement diet [Nutrisystem] for 8 wks and IBT during 68 wks. IBT: reduced calorie diet + physical activity (100	Adults with BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with at least 1 weight-related comorbid condition	DM; prior weight loss surgery; 5 kg weight loss within 90 days	41 sites in US	Week 68: % Δ in body weight; absolute weight loss; body weight reduction of 5%, 10%, 15%; waist circ.; SF-36 (68 weeks)

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
	SC SEM 2.4 mg + IBT (n=407)	min/wk increased by 25 min every 4 wks to reach 200 min/wk) + 30 IBT visits				
STEP 4 ^{37,133,134} Phase III, MC, PBO-controlled monotherapy	(Wks 0-20) Run-in period (n=803)	Monthly counseling, reduced-calorie diet (500 kcal/d deficit), increased physical activity (150 min/wk), recorded daily by participants and reviewed during counseling visits	Adults with BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with at least 1 weight-related comorbid condition	HbA1C $\geq 6.5\%$; 5 kg weight loss within 90 days	73 sites in 10 countries in Europe, North America (US), Middle East (Israel), Africa (South Africa)	Weeks 20-68: % Δ in body weight; waist circ., SBP, SF-36
	(Wks 20-68) From run-in with SEM \rightarrow PBO + LI (n=268)					
	(Wks 20-68) From run-in with SEM \rightarrow SC SEM 2.4 mg + LI (n=535)					
STEP 5 ³⁴⁻³⁶ Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=152)	Reduced calorie diet and increased physical activity	Adults with BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with at least 1 weight-related comorbid condition	HbA1C $\geq 6.5\%$; 5 kg weight loss within 90 days	41 sites in 5 countries (North America, Europe)	Weeks 52 and 104: % Δ from baseline in body weight; body weight reduction of 10%, 15%; waist circ.; SBP
	SC SEM 2.4 mg + LI (n=152)					
STEP 6 ¹³⁵ Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=101)	Counseling every 4 wks; reduced caloric intake (500 kcal/d); physical activity ≥ 150 min/wk	Adults (≥ 18 in South Korea, ≥ 20 in Japan) with BMI ≥ 35 kg/m ² with at least 1 weight-related comorbid condition OR BMI ≥ 27 kg/m ² with 2 or more weight-related comorbid conditions	5 kg weight loss within 90 days; previous obesity treatment with surgery or taking any medication for indication of obesity	22 sites in Japan and 6 sites in South Korea	Week 68: % Δ from baseline to week 68 in body weight; body weight reduction of 10%, 15%; waist circ.; SBP; A1c
	SC SEM 1.7 mg + LI (n=101)					
	SC SEM 2.4 mg + LI (n=199)					

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
Semaglutide vs. Liraglutide						
STEP 8 ³¹ Phase III, MC, open-label, PBO-controlled monotherapy	PBO +LI (n=85)	Counseling sessions every 4-6 wks; diet of 500 kcal/d deficit relative to baseline; physical activity ≥150 mins/wk	Adults with BMI ≥30 kg/m ² or ≥27 kg/m ² with at least 1 weight-related comorbid condition	DM, HbA1C ≥6.5%, 5 kg weight loss in last 90 days	19 sites in the US	Week 68: % Δ in body weight; body weight reduction of 10%, 15%, 20%
	SC SEM 2.4 mg + LI (n=126)					
	SC LIR 3.0 mg + LI (n=127)					
Liraglutide						
SCALE (Maintenance) ^{38,47} Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=210)	Low-calorie diet run-in with weekly counseling (4-12 wks) then counseling weekly during drug escalation, then every 4 wks; 500 kcal/day deficit relative to baseline; 150+ min/wk	Lost ≥5% initial bodyweight during run-in diet (4-12 wks); adults with BMI ≥30 kg/m ² or ≥27 kg/m ² with comorbidities of treated/untreated dyslipidemia or HTN	Diagnosis, type 1/2 DM; treatment with GLP-1 or medications causing significant weight loss/gain; bariatric surgery; history of pancreatitis	36 sites in the US and Canada	Week 56: % Δ body weight; weight reduction 5%, 10%; waist circ.; BMI; SBP; LDL; HbA1C; FPG
	SC LIR 3.0 mg + LI (n=212)					
SCALE (Sleep Apnea) ^{39,48} Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=179)	Counseling sessions every 4 wks; 500 kcal/day deficit relative to baseline; 150+ min/wk	Adults 18-64 years; BMI ≥30 kg/m ² ; moderate-severe OSA and unable/unwilling to use CPAP	>5% Δ in body weight during previous 3 months; central sleep apnea; T1/2 DM	40 sites in North America	Week 32: Δ in AHI; Δ in body weight; Δ in FPG; Δ in HbA1C; FOSQ; ESS
	SC LIR 3.0 mg + LI (n=180)					
SCALE (Type 2 Diabetes) ^{40,50} Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=212)	500 kcal/day deficit relative to baseline; 150+ min/wk	Adults ≥18; overweight or obese (BMI ≥27 kg/m ²); T2DM treated w/ diet and exercise alone or 1-	≥5 kg weight loss in last 90 days; previous surgical treatment; treatment with GLP-1 or DDP-4 or insulin within last 3 months	126 sites in 9 countries (France, Germany, Israel, South Africa, Spain,	Weeks 56: % Δ body weight; weight reduction 5%, 10%; HbA1C; waist circ.
	1.8mg SC LIR + LI (n=211)					

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
	SC LIR 3.0 mg + LI (n=423)		3 OHA (metformin, TZD, sulfonylurea)		Sweden, Turkey, UK)	Week 68: 68 weeks: % Δ body weight; waist circ. Weeks 56-68: % Δ body weight; waist circ.
SCALE (Obesity & Pre-Diabetes) ^{41,46} Phase III, MC, PBO-controlled monotherapy	PBO + LI (n=1244)	Monthly counseling; 500 kcal/day deficit relative to baseline; 150+ min/wk	Adults ≥ 18 ; BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with untreated dyslipidemia/HTN	T1/2 DM; history of pancreatitis; previous bariatric surgery	191 sites in 27 countries (Europe, N/S America, Asia, Africa, Australia)	Week 56: Weight Δ ; weight reduction 5%, 10%; Δ in BMI, waist circ., glycemic control variables
	SC LIR 3.0 mg + LI (n=2487)					
SCALE (IBT) ^{42,49} Phase III, MC, PBO-controlled monotherapy	PBO + IBT (n=140)	IBT, comprising behavioral counseling, hypocaloric diet, physical activity (100-250 min/wk)	Adults ≥ 18 ; BMI ≥ 30 kg/m ²	≥ 5 kg weight loss in last 90 days; T1/2 DM; use of medications known to induce weight loss/gain; history CVD	17 sites in US	Week 56: Δ in % body weight; weight reduction 5%, 10%, 15%; Δ in waist circ., LDL, SBP, HbA1C;
	SC LIR 3.0 mg + IBT (n=142)					
SCALE (Insulin) ⁴³ Phase III, MC, PBO-controlled monotherapy	PBO + IBT (n=198)	Hypocaloric diet, increased physical activity, behavioral therapy delivered in frequent counseling sessions	Adults ≥ 18 ; BMI ≥ 27 kg/m ² ; T2DM; receiving stable treatment with any basal insulin and ≤ 2 OADs	T1DM; ≥ 5 kg weight loss in last 90 days; treatment with GLP-1 or DDP-4 or insulin within last 3 months; use of medications known to induce significant weight change in last 90 days	53 sites globally	Week 56: % Δ in body weight; weight reduction 5%, 10%; Δ in waist circ., FPG, SBP
	SC LIR 3.0 mg + IBT (n=198)					

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
LOSEIT (KOA) ¹³⁶ Phase III, single-center, PBO-controlled monotherapy	PBO + LI (n= 76)	8 wk lead-in low-calorie diet (800-1,000 kcal/day) with meal bars/powders and wkly dietician consults; 1,200 kcal/day wks 0-8 and 1,500 kcal/day wks 8-52; dietary group sessions every 2 wks in first 8 wks	Adults aged 18-74; BMI ≥27 kg/m ² ; symptomatic KOA; stable body weight	Current use weight loss/gain medications; recent/ongoing participation in organized weight loss program; end-stage KOA on radiography	1 site in the US	Week 52: Δ in body weight; HrQoL; weight reduction 5%, 10%; Δ in BMI, waist circ.
	SC LIR 3.0 mg + LI (n= 80)					
Phentermine/Topiramate						
EQUIP ^{53,55} Phase III, MC, PBO-controlled combination therapy	PBO +LI (n=514)	Provided with standardized lifestyle counseling, (LEARN Manual), advised to follow 500-kcal diet deficit, increase water consumption, increase physical activity	Adults 18-70 years, BMI ≥35 kg/m ² , triglycerides ≤200 mg/dl with treatment of 0-1 lipid lowering med, BP ≤140/90 mm Hg with treatment of 0-2 anti-HTN medications, and fasting serum FBG level ≤110	Weight gain/loss >5 kg in 3 months; eating disorders, bariatric surgery, glaucoma, and nephrolithiasis; thyroid dysfunction; current substantial depression, stroke, MI, HF, DM	91 sites in the U.S.	Week 56: %/kg Δ in body weight; body weight reduction of 5%, 10%, 15%; waist circ.; blood pressure, heart rate, FBG, triglycerides, HDL, LDL, depression
	PT 3.75 mg/23 mg + LI (n=241)					
	PT 15 mg/92 mg + LI (n=512)					
EQUATE ^{52,54} Phase III, MC, PBO-controlled combination therapy	PBO +LI (n=109)	LEARN Manual (Lifestyle, Exercise, Attitude, Relationships, Nutrition,	Adults 18-70 years and BMI 30-45 kg/m ²	Use of phentermine or topiramate within past 3 months, weight gain/loss of >5 kg, use of a very low calorie	34 sites in US	Week 28: %/kg Δ in body weight; body weight reduction of 5%, 10%; waist circ.; blood pressure, heart
	Phentermine 7.5 mg +LI (n=109)					

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
	Topiramate 46 mg +LI (n=108) PT 7.5 mg/46 mg + LI (n=107) Phentermine 15 mg + LI (n=108) Topiramate 92 mg +LI (n=107) PT 15 mg/92 mg + LI (n=108)	counseling to reduce energy intake by 500 kcal/day, food diary, increase physical activity; brief monthly visits to discuss progress		diet, use of pharmacotherapy for weight loss, DM, stroke, participation in formal weight loss program within past 3 months, surgery		rate, FBG, HbA1C, insulin, inflammatory biomarkers, concomitant med use, RBANS, depression (PHQ-9 & C-SSRS)
CONQUER^{51,56} Phase III, MC, PBO-controlled combination therapy	PBO +LI (n=994) PT 7.5 mg/46 mg + LI (n=498)	Provided with LEARN manual, advised to implement lifestyle changes, and instructions to reduce caloric diet by 500 kcal/day, monthly check-in with study staff on progress	Adults (18-70 years) with overweight/obesity, BMI 27-45 kg/m ² and 2+ comorbidities: SBP 140-160 mm Hg, DBP 90-100 mm Hg (no BMI limit and diff SBP/DBP criteria for diabetic), 2+ anti-HTN drugs; concentration of	Blood pressure >160/100 mm Hg, concentration fasting FBG >13.32 mmol/L or triglycerides >4.52 mmol/L, T1DM, antidiabetic drugs besides metformin, nephrolithiasis, and current depressive symptoms (PHQ 21 total score ≥10), surgery	93 sites in US	Week 56: %/kg Δ in body weight; body weight reduction of 5%, 10%; waist circ.; BMI, blood pressure, triglycerides, LDL, HDL, FBG, insulin, biomarkers, concomitant drugs, progression to DM (for non-diabetic), body composition

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
	PT 15 mg/92 mg + LI (n=995)		triglycerides 2.26-4.52 mmol/L or 2+ lipid-lowering drugs; concentration FBG >5.55 mmol/L, blood FBG >7.77 mmol/L at 2hr, T2DM; waist circ. ≥102 cm for men or ≥88 cm for women			
OB-204 (Winslow 2012) ^{137,141} Phase I/II, single-center PBO-controlled combination therapy	PBO + LI (n=23)	Lifestyle modification counseling (LEARN behavioral weight loss and management program)	Adults 30-65 years, BMI between 30-40 kg/m², diagnosis of moderate to severe OSA syndrome, and AHI ≥15	Other sleep disorder, limb movement arousal index >10, uncontrolled blood pressure, unstable angina, surgery, cardiac arrhythmia, HF, valvulopathy, MI	1 site in US	Week 28: Δ in AHI, OSA parameters (apnea index, respiratory disturbance, oxygen saturation index), PSQI, ESS, SF-36, change in blood pressure, heart rate, lipid profile, glycemic variables, % Δ weight loss, body weight reduction of 5%, 10%
	PT 15 mg/92 mg + LI (n=22)					
Bupropion/Naltrexone						
COR-I ^{59,60} Phase III, MC, PBO-controlled combination therapy	PBO + LI (n=581)	Hypocaloric diet (500 kcal deficit/day), dietary counseling and weight management booklets, advice	Adults aged 18-65 years with had BMI 30–45 kg/m² and uncomplicated obesity, or BMI 27-45 kg/m² and controlled HTN or	DM; vascular, hepatic, or renal disease; surgical/device for obesity; or loss/gain >4 kg within 3 months, additional weight loss drugs	34 sites in US	Week 56: % Δ in body weight; body weight reduction of 5%, 10%, 15%; waist circ.; triglycerides, LDL, HDL, FBG, insulin, HOMA-IR; and hsCRP; COEQ; IW-
	BN 360 mg/16 mg + LI (n=578)					

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
	BN 360 mg/32 mg + LI (n=583)	on lifestyle modification (instructions, increase physical activity)	dyslipidemia, or both			QOL-Lite; FCI; SBP; DBP; IDS-SR
COR-II ^{61,62} Phase III, MC, PBO-controlled combination therapy	PBO + LI (n=495)	Instructions to follow hypocaloric diet (500 kcal deficit/day), increase physical activity, and behavioral modification	Adults aged 18-65 years with had BMI 30-45 kg/m ² and uncomplicated obesity, or BMI 27-45 kg/m ² and controlled HTN or dyslipidemia, or both	DM; vascular, hepatic, or renal disease; surgical/device for obesity; or loss/gain >4 kg within 3 months, additional weight loss drugs	36 sites in US	Week 56: %/kg Δ in body weight; body weight reduction of 5%, 10%, 15%; waist circ.; triglycerides, LDL, HDL, FBG, insulin, HOMA-IR; and hsCRP; COEQ; IW-QOL-Lite; SBP; DBP; IDS-SR
	BN 360 mg/32 mg + LI (n=1001)					
COR-BMOD ^{63,64} Phase III, MC, PBO-controlled combination therapy	PBO + BMOD (n=202)	Intensive behavioral group modification: group counseling (wks 1-16: wkly, wks 16-28: biweekly, after wk 28: monthly), deficit diet (varies depending on weight), exercise gradually increased to 180 min/wk, diary entry	Adults 18-65 years of age, with a BMI of 30–45 kg/m ² , or a BMI of 27-45 kg/m ² in presence of controlled HTN and/or dyslipidemia	DM; sig. cerebrovascular, CV, hepatic, or renal disease; treatment with bupropion/ naltrexone, surgical/device intervention; >4 kg loss/gain within 3 months	9 sites in US	Week 56: % Δ in body weight; body weight reduction of 5%, 10%, 15%; waist circ.; triglycerides, LDL, HDL, FBG, insulin, and hsCRP; IWQOL-Lite; FCI; SBP; DBP; IDS-SR
	BN 360 mg/32 mg + BMOD (n=591)					

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
COR Diabetes ^{57,58} Phase III, MC, PBO-controlled combination therapy	PBO + LI (n=159)	Hypocaloric diet (500 kcal deficit/day), dietary counseling and weight management booklets, advice on behavioral modification (instructions, increase physical activity [walking at least 30 min most days])	Adults aged 18-70 years, with T2DM, BMI ≥ 27 and $I \geq 45$ kg/m ² , HbA1C 7-10% (53-86 mmol/mol), and FBG 270 mg/dL	T1DM or “brittle-DM” or hospitalization/ER visit due to poor diabetic control, DM secondary to pancreatitis or pancreatectomy, loss/gain >5 kg within 3 months, surgical/device for obesity, tx with bupropion or naltrexone, weight loss program within 1 month, pregnant/breastfeeding	53 sites in US	Week 56: % Δ in body weight; body weight reduction of 5%, 10%; waist circ.; triglycerides, LDL, HDL, FBG, insulin, SBP; DBP; HOMA-IR, hsCRP; HbA1C; OADs; HbA1C <7% and <6.5%; rescue med use for DM; d/c due to poor glycemic control; IDS-SR
	BN 360 mg/32 mg + LI (n=265)					
CVOT (Light Study) ^{138,139} Phase IIb, MC, PBO-controlled combination therapy	PBO + LI (n=4450)	Internet-based weight management program (resources on healthy eating, exercise, behavioral modifications, weekly lessons/emails), access to personal weight loss coach, program to track weight, meals, physical activity, and low-fat, low-calorie meal plan	>50 years (women) or >45 years (men), BMI between 27-50 kg/m ² , waist circ. of >88 cm (women) or >102 cm (men), and have characteristics associated with an increased risk of adverse CV outcomes; and/or T2DM and at least 2 comorbidities (HTN, etc.)	MI, angina pectoris, NYHA class III or IV, HF, history of stroke, blood pressure >145/95 mm Hg, weight gain/loss of >3% within 3 months, bariatric or cardiac surgery	266 sites in US	Week 52: Time from randomization to first occurrence of a MACE, time to first occurrence of a MACE/hospitalization for unstable angina, stroke, or MI, Δ in body weight, BMI, waist circ., SBP, DBP, heart rate
	BN 360 mg/32 mg + LI (n=4455)					

Study Name & Type	Intervention(s)	Lifestyle Intervention Description	Inclusions	Exclusions	Study Location	Outcomes Available and Timepoint
Ignite^{140,142} Phase IIIb, MC, controlled combination therapy	Usual care (including LI) (n=89)	-CLI: Phone/ internet-based progressive nutrition and exercise program with dietician/coach with individualized goal setting and tracking tools -Usual care: Site-based LI program, exercise and hypocaloric diet (500 kcal deficit), nutrition tracker, pedometer, literature	Adults age 18-60 years, with either obesity (BMI 30-45 kg/m ²) or overweight (BMI 27-45 kg/m ²) with dyslipidemia and/or controlled HTN	DM; MI within 6 months; angina pectoris grade III/IV; clinical history of strokes, seizures, cranial trauma, bulimia, anorexia nervosa	15 sites in US	Weeks 26* and 78: %/kg Δ in body weight; body weight reduction of 5%, 10%, 15%; waist circ.; triglycerides, LDL, HDL, FBG, insulin, heart rate; HOMA-IR; ASEX, BES Total Score; IWQOL-Lite; SBP; DBP
	BN 360 mg/32 mg + CLI (n=153)					

AHI: apnea-hypopnea index, A1c: glycated hemoglobin, ASEX: Arizona Sexual Experience Scale, BES: Binge Eating Scale, BMI: body-mass index, BMOD: behavioral modification, BN: bupropion/naltrexone, BP: blood pressure, cm: centimeter, CLI: comprehensive lifestyle intervention, COEQ: Control of Eating Questionnaire, CPAP: continuous positive airway pressure, hsCRP: C-reactive protein, C-SSRS: Columbia Suicide Severity Rating Scale, CVD: cardiovascular disease, d: day, DBP: diastolic blood pressure, dL: deciliter, DM: diabetes mellitus, ER: emergency room, ESS: Epworth Sleepiness Scale, FCI: Food Craving Inventory, FBG: fasting blood glucose, FOSQ: Functional Outcomes of Sleep Questionnaire, GLP-1: glucagon-like peptide-1, HbA1C: glycated hemoglobin, HDL: high-density lipoprotein, HOMA-IR: Homeostasis Model Assessment for Insulin Resistance, HRQoL: health-related quality of life, HTN: hypertension, IBT: intensive behavioral therapy, IDS-SR: Inventory of Depressive Symptomatology (Self-Report), IWQOL-Lite: Impact of Weight on Quality of Life-Lite, kcal: calorie, kg: kilogram, KOA: knee osteoarthritis, L: liter, LDL: low-density lipoprotein, LEARN: lifestyle, exercise, attitudes, relationships, and nutrition, LI: lifestyle intervention, LIR: liraglutide, m: meter, MACE: major adverse cardiovascular events, MC: multi-center, mg: milligram, min: minute, mmHg: milliliter of mercury, mmol: millimole, NYHA: New York Heart Association, OAD: oral antidiabetic drug, OHA: oral hypoglycemic agents, OSA: obstructive sleep apnea, PBO: placebo, PHQ-9: Patient Health Questionnaire, PSQI: Pittsburgh Sleep Quality Index, PT: phentermine/topiramate, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SBP: systolic blood pressure, SC: subcutaneous, SEM: semaglutide, SF-36: Short Form Health Survey, TZD: thiazolidinediones, U.K.: United Kingdom, U.S.: United States, vs.: versus

*We focus on the 26-week timepoint, during the randomized period of the trial.

Table D23. Baseline Characteristics ^{127-43,46-64,133-142}

Study Name	Intervention(s)	Age, Years		Female Sex, %	Race/Ethnicity, %	BMI, kg/m ²		Baseline Weight, kg	
		Mean	SD			Mean	SD	Mean	SD
Semaglutide									
STEP 1	PBO + LI (n=655)	47	12	76	76% White, 12% Asian, 6% Black, 6% other; 13% Latinx	38	6.5	105.2	21.5
	SC SEM 2.4 mg + LI (n=1306)	46	13	73.1	75% White, 14% Asian, 6% Black, 6% other; 12% Latinx	37.8	6.7	105.4	22.1
STEP 2	PBO + LI (n=403)	55	11	47.1	60% White, 27% Asian, 9% Black, 4% other; 12% Latinx	35.9	6.5	100.5	20.9
	SC SEM 1.0 mg + LI (n=403)	56	10	50.4	68% White, 24% Asian, 7% Black, 2% other; 15% Latinx	35.3	5.9	99	21.1
	SC SEM 2.4 mg + LI (n=404)	55	11	55.2	59% White, 28% Asian, 9% Black, 5% other; 12% Latinx	35.9	6.4	99.9	22.5
STEP 3	PBO + IBT (n=204)	46	13	88.2	78% White, 3% Asian, 18% Black, 2% other; 23% Latinx	37.8	6.9	103.7	22.9
	SC SEM 2.4 mg + IBT (n=407)	46	13	77.4	75% White, 1% Asian, 20% Black, 3% other; 18% Latinx	38.1	6.7	106.9	22.8
STEP 4	Run-in period (n=803)	46	12	79	84% White, 2% Asian, 13% Black, 1% Other; 8% LatinX	38.4	6.9	107.2	22.7
	From run-in with SEM→ PBO + LI (n=268)*	46	12	76.5	84% White, 2% Asian, 13% Black, 1% Other; 8% LatinX	34.1	7.1	95.4	22.7
	From run-in with SEM→ SC SEM 2.4 mg + LI (n=535)*	47	12	80.2	83% White, 3% Asian, 13% Black, <1% other; 8% LatinX	34.5	6.9	96.5	22.5
STEP 5	PBO + LI (n=152)	47	10	74.3	93% White, 0% Asian, 3% Black, 1% American Indian/Alaskan Native, 3% other; 14% Latinx	38.5	6.9	106	NR
	SC SEM 2.4 mg + LI (n=152)	47	12	80.9	93% White, 1% Asian, 5% Black, 0% other, 1% American Indian/Alaskan Native; 12% Latinx				
STEP 6	PBO + LI (n=101)	50	9	25.7	100% Asian	31.9	4.2	90.2	15.1
	SC SEM 1.7 mg + LI (n=101)	51	10	36.6	100% Asian	31.6	3.7	86.1	11.9
	SC SEM 2.4 mg + LI (n=199)	52	12	42.7	100% Asian	32	4.6	86.9	16.5
Semaglutide vs. Liraglutide									
STEP 8	PBO + LI (n=85)	51	12	77.6	71% White, 4% Asian, 22% Black, 4% other; 8% Latinx	38.8	6.5	108.8	23.1

Study Name	Intervention(s)	Age, Years		Female Sex, %	Race/Ethnicity, %	BMI, kg/m ²		Baseline Weight, kg	
		Mean	SD			Mean	SD	Mean	SD
	SC SEM 2.4 mg + LI (n=126)	48	14	81	75% White, 3% Asian, 20% Black, 2% other; 12% Latinx	37	7.4	102.5	25.3
	SC LIR 3.0 mg + LI (n=127)	49	13	76.4	75% White, 5% Asian, 16% Black, 5% other; 13% Latinx	37.2	6.4	103.7	22.5
Liraglutide									
SCALE (Maintenance)	PBO + LI (n=210)	46.5	11	79	88% White, 11% Black, 0% Asian, 0% Native Hawaiian/Pacific Islander	35.2	5.9	98.7	21.2
	SC LIR 3.0 mg + LI (n=212)	45.9	11.9	84	80% White, 15% Black, 1% Asian, 1% Native Hawaiian/Pacific Islander	36	5.9	100.4	20.8
SCALE (Sleep Apnea)	PBO + LI (n=179)	48.4	9.5	27.9	75% White, 2% Asian, 20% Black, 1% Native Hawaiian/Pacific Islander, 2% other; 13% Latinx	39.4	7.4	118.7	25.4
	SC LIR 3.0 mg + LI (n=180)	48.6	9.9	28.3	72% White, 7% Asian, 18% Black, 1% Native Hawaiian/Pacific Islander, 2% other; 11% Latinx	38.9	6.4	116.5	23
SCALE (Type 2 Diabetes)	PBO + LI (n=212)	54.7	9.8	54.2	83% White, 2% Asian, 13% Black, 2% other; 11% Latinx	37.4	7.1	106.5	21.3
	1.8 mg SC LIR + LI (n=211)	54.9	10.7	48.8	84% White, 2% Asian, 13% Black, 1% other; 8% Latinx	37	6.9	105.8	21
	SC LIR 3.0 mg + LI (n=423)	55	10.8	48	84% White, 3% Asian, 10% Black, 3% other; 11% Latinx	37.1	6.5	105.7	21.9
SCALE (Obesity & Pre-Diabetes)	PBO + LI (n=1244)	45	12	78.1	85% White, 4% Asian, 9% Black, <1% American Indian/Alaska Native, <1% Native Hawaiian/Pacific Islander, 1% other; 11% Latinx	38.3	6.3	106.2	21.7
	SC LIR 3.0 mg + LI (n=2487)	45.2	12.1	78.7	85% White, 4% Asian, 10% Black, <1% American Indian/Alaska Native, <1% Native Hawaiian/Pacific Islander, 2% other; 10% Latinx	38.3	6.4	106.2	21.2
SCALE (IBT)	PBO + IBT (n=140)	49	11.2	82.9	82% White, 2% Asian, 16% Black; 6% Latinx	38.7	7.2	106.7	22
	SC LIR 3.0 mg + IBT (n=142)	45.4	11.6	83.8	79% White, 1% Asian, 19% Black; 17% Latinx	39.3	6.8	108.5	22.1
SCALE (Insulin)	PBO + IBT (n=198)	57.6	10.4	50	91% White, 3% Asian, 6% Black; 15% Latinx	35.3	5.8	98.9	19.9
	SC LIR 3.0 mg + IBT (n=198)	55.9	11.3	44.5	88% White, 2% Asian, 9% Black; 22% Latinx	35.9	6.5	100.6	20.8
LOSEIT (KOA)	PBO + LI (n=76)	59.3	9.7	64	NR	31.3	4	90.8	14.3
	SC LIR 3.0 mg + LI (n=80)	59.2	10.8	65	NR	32.8	5.5	96.3	18.2

Study Name	Intervention(s)	Age, Years		Female Sex, %	Race/Ethnicity, %	BMI, kg/m ²		Baseline Weight, kg	
		Mean	SD			Mean	SD	Mean	SD
Phentermine/Topiramate									
EQUIP	PBO + LI (n=514)	43	11.8	82.7	80% White, 18% Black, 1% American Indian/Alaskan Native, <1% Asian, <1% Native Hawaiian/Pacific Islander, <1% other	42	6.2	115.8	21.5
	P/T 3.75 mg/23 mg + LI (n=241)	43	11	83.4	80% White, 16% Black, <1% American Indian/Alaskan Native, <1% Asian, <1% Native Hawaiian/Pacific Islander, 2% other	42.6	6.5	118.5	21.9
	P/T 15 mg/92 mg + LI (n=512)	41.9	12.2	82.8	80% White, 18% Black, 1% American Indian/Alaskan Native, <1% Asian, <1% Native Hawaiian/Pacific Islander, 1% other	41.9	6	115.2	20.7
EQUATE	PBO + LI (n=109)	45	11.4	78.9	76% White, 23% Black, 0% Asian, 1% other	36.2	3.9	100	13
	Phentermine 7.5 mg + LI (n=109)	46.4	11.6	78.9	74% White, 24% Black, 2% Asian, 2% other	36.3	4	101	15.1
	Topiramate 46 mg + LI (n=108)	46.9	12.6	79.6	88% White, 10% Black, 2% Asian, 2% other	36.1	4.1	100.7	16.3
	P/T 7.5 mg/46 mg + LI (n=107)	44.6	11.1	79.4	75% White, 24% Black, 0% Asian, 1% other	36.6	3.9	102.2	16.5
	Phentermine 15 mg + LI (n=108)	45.7	12.4	79.6	83% White, 13% Black, 1% Asian, 3% other	36.2	4.2	101.4	16.4
	Topiramate 92 mg +LI (n=107)	45.8	11.2	79.4	77% White, 21% Black, 2% Asian, 2% other	37	4.3	104.5	15.6
	P/T 15 mg/92 mg + LI (n=108)	44.6	12.8	78.7	82% White, 15% Black, 2% Asian, 3% other	35.9	3.9	99.3	15.6
CONQUER (Diabetes subgroup)	PBO +LI (n=157)	52.6	9.8	71.3	85% White, 12% Black, 2% Asian, 2% other 29% Hispanic/Latinx, 71% not Hispanic/Latinx	36.2	5.2	99.3	18.6
	P/T 7.5 mg/46 mg + LI (n=67)	52.5	9.3	65.6	94% White, 5% Black, 0% Asian, 2% other 31% Hispanic/Latinx, 69% not Hispanic/Latinx	35.3	4.3	97.2	16.1
	P/T 15 mg/92 mg + LI (n=164)	52.1	10.1	62.1	83% White, 14% Black, 2% Asian, 3% other 31% Hispanic/Latinx, 69% not Hispanic/Latinx	37.1	5.2	103.2	20.1
OB-204 (Winslow 2012)	PBO + LI (n=23)	51.4	5.7	34.8	91% White, 9% Black, 4% Hispanic/Latinx, 96% not Hispanic/Latinx	35.3	3.1	106.9	16.7
	P/T 15 mg/92 mg + LI (n=22)	53.4	7	59.1	91% White, 9% Black, 0% Hispanic/Latinx, 100% not Hispanic/Latinx	36	3.1	103.7	14.6

Study Name	Intervention(s)	Age, Years		Female Sex, %	Race/Ethnicity, %	BMI, kg/m²		Baseline Weight, kg	
		Mean	SD			Mean	SD	Mean	SD
Bupropion/Naltrexone									
COR-I	PBO + LI (n=581)	43.7	11.1	85	76% White, 19% Black, 5% other	36.2	4	99.5	14.3
	B/N 360 mg/16 mg + LI (n=578)	44.4	11.3	85	74% White, 21% Black, 5% other	36.2	4.3	99.5	14.8
	B/N 360 mg/32 mg + LI (n=583)	44.4	11.1	85	75% White, 18% Black, 6% other	36.1	4.4	99.7	15.9
COR-II	PBO + LI (n=495)	44.4	11.4	84.8	84% White, 15% Black, 2% other	36.1	4.3	99.2	15.9
	B/N 360 mg/32 mg + LI (n=1001)	44.3	11.2	84.6	83% White, 13% Black, 3% other	36.2	4.5	100.3	16.6
COR-BMOD	PBO + BMOD (n=202)	45.6	11.4	91.6	74% White, 22% African American, 5% other	37	4.2	101.9	15
	B/N 360 mg/32 mg + BMOD (n=591)	45.9	10.4	89.3	69% White, 25% African American, 7% other	36.3	4.2	100.2	15.4
COR Diabetes	PBO + LI (n=159)	53.8	9.7	52.8	83% White, 11% Black, 6% other	36.3	4.5	105	17.1
	B/N 360 mg/32 mg + LI (n=265)	53.9	9.2	54.3	78% White, 19% Black, 3% other	36.7	4.8	106.3	19.1
CVOT (Light Study)	PBO + LI (n=4450)	60.9	7.4	54.4	83% White, 15% Black/African American, <1% Asian, <1% American Indian/Alaskan Native, <1% Native Hawaiian/Pacific Islander 93% non-Hispanic/Latinx, 7% Hispanic/Latinx	37.4	5.4	106.3	19.2
	B/N 360 mg/32 mg + LI (n=4455)	61.1	7.3	54.7	84% White, 15% Black/African American, <1% Asian, <1% American Indian/Alaskan Native, <1% Native Hawaiian/Pacific Islander 94% non-Hispanic/Latinx, 6% Hispanic/Latinx	37.2	5.3	105.6	19.1
Ignite	Usual care (including LI) (n=89)	47	10	86.5	72% White, 27% Black/African American, 0% Asian, 1% American Indian/Alaskan Native 6% Hispanic/LatinX, 94% not Hispanic/Latinx	36.3	4.4	100.2	16.6
	B/N 360 mg/32 mg + CLI (n=153)	46.1	9.7	81.7	81% White, 18% Black/African American, 1% Asian, 0% American Indian/Alaskan Native 3% Hispanic/LatinX, 97% not Hispanic/Latinx	36.3	4.2	101.4	15.1

BMI: body-mass index, BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, IBT: intensive behavioral therapy, kg: kilogram, KOA: knee osteoarthritis, LI: lifestyle intervention, LIR: liraglutide, m: meter, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SC: subcutaneous, SD: standard deviation, SEM: semaglutide, vs.: versus

*Baseline data measured at week 20.

Table D24. Baseline Characteristics II^{27-43,46-64,133-142}

Study Name	Intervention(s)	Waist Circumference, cm		A1C, Mean %		Diabetes %	Pre-Diabetes, %	SBP, mm HG		LDL, mg/dL		Fasting Blood Glucose, mg/dL	
		Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD
Semaglutide													
STEP 1	PBO + LI (n=655)	114.8	14.4	5.7	0.3	0	40.2	127	14	112.5	29.8	94.7	10.5
	SC SEM 2.4 mg + LI (n=1306)	114.6	14.8	5.7	0.3	0	45.4	126	14	110.3	31.6	95.4	10.7
STEP 2	PBO + LI (n=403)	115.5	13.9	8.1	0.8	100	0	130	13	89*	NR	158.4*	41.4
	SC SEM 1.0 mg + LI (n=403)	113.9	14	8.1	0.8	100	0	130	14	89*	NR	154.8*	41.4
	SC SEM 2.4 mg + LI (n=404)	114.5	14.3	8.1	0.8	100	0	130	13	89*	NR	153*	41.4
STEP 3	PBO + IBT (n=204)	111.8	16.2	5.8	0.3	0	52.9	124	15	111.8*	31.2	94*	9.8
	SC SEM 2.4 mg + IBT (n=407)	113.6	15.1	5.7	0.3	0	48.2	124	15	107.7*	30.3	93.9*	9.4
STEP 4	Run-in period (n=803)	115.3	15.5	5.7	0.3	0	NR	127	14	116.6*	IQR: 97.3-138.6	97	10.7
	From run-in with SEM→ PBO + LI (n=268)§	104.7	16.9	5.4	0.3	0	42.5	121	13	112.5	IQR: 93.6-130.9	86.9	7.6
	From run-in with SEM→ SC SEM 2.4 mg + LI (n=535)§	105.5	15.9	5.4	0.3	0	49	121	13	110.4	IQR: 91.1-130.9	87.9	7.7
STEP 5	PBO + LI (n=152)	115.7	14.8	5.7	0.3	0	46.4	125.5	14.5	112.1	NR	95.4	10.8
	SC SEM 2.4 mg + LI (n=152)					0							
STEP 6	PBO + LI (n=101)	103.8	9.9	6.4	1.1	25	25	133	14	123.7	NR	113.5	28.8
	SC SEM 1.7 mg + LI (n=101)	101.4	8.8	6.4	1.1	25	21	135	13	119.9	NR	111.7	27
	SC SEM 2.4 mg + LI (n=199)	103.8	11.8	6.4	1.2	25	22	133	14	116	NR	111.7	27
Semaglutide vs. Liraglutide													
STEP 8	PBO + LI (n=85)	115.4	15.1	5.6	0.4	0	40	123	14	105.2	NR	97.6	12.2

Study Name	Intervention(s)	Waist Circumference, cm		A1C, Mean %		Diabetes %	Pre-Diabetes, %	SBP, mm HG		LDL, mg/dL		Fasting Blood Glucose, mg/dL	
		Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD
	SC SEM 2.4 mg + LI (n=126)	111.8	16.3	5.5	0.3	0	34.1	125	14	106.4	NR	96.1	10.2
	SC LIR 3.0 mg + LI (n=127)	113.5	15	5.5	0.3	0	35.4	126	16	108.1	NR	95.2	8.5
Liraglutide													
SCALE (Maintenance)	PBO + LI (n=210)	107.8	15.2	5.6	0.4	0	NR	117.8	10.8	104.4	30.9	99	10.8
	SC LIR 3.0 mg + LI (n=212)	109.4	15.3	5.6	0.4	0	NR	116.6	12.5	100.5	27.1	97.2	9
SCALE (Sleep Apnea)	PBO + LI (n=179)	122.7	14.9	5.6	0.4	0	62.6	127.1	12.3	111.4	26.8	97.2	16.2
	SC LIR 3.0 mg + LI (n=180)	122.3	14.5	5.7	0.4	0	63.9	125.8	11.5	111.6	28.9	97.2	10.8
SCALE (Type 2 Diabetes)	PBO + LI (n=212)	117.3	14	7.9	0.8	100	0	129.2	13.6	85.2	39.3	155.5	33
	1.8 mg SC LIR + LI (n=211)	117.5	14.7	8	0.8	100	0	130.5	14.5	91.5	38.5	160.4	35.1
	SC LIR 3.0 mg + LI (n=423)	118	14.4	7.9	0.8	100	0	128.9	13.6	86.4	35.5	158.4	32.8
SCALE (Obesity & Pre-Diabetes)	PBO + LI (n=1244)	114.5	14.3	5.6	0.4	0	60.9	123.2	12.8	112.2	27.6	95.5	9.8
	SC LIR 3.0 mg + LI (n=2,487)	115	14.4	5.6	0.4	0	61.4	123	12.9	111.6	27.9	95.9	10.6
SCALE (IBT)	PBO + IBT (n=140)	115	15.6	5.5	0.4	0	NR	127	14	119.9	34.8	97.2	10.5
	SC LIR 3.0 mg + IBT (n=142)	116	14.4	5.5	0.4	0	NR	125	15	112.1	30.9	97.2	9
SCALE (Insulin)	PBO + IBT (n=198)	114.2	13.2	8	1	100	0	132	16	94	29	164	46
	SC LIR 3.0 mg + IBT (n=198)	114.8	13.7	7.9	1.1	100	0	129	14	94	33	141	40
LOSEIT (KOA)	PBO + LI (n=76)	101.8	11.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC LIR 3.0 mg + LI (n=80)	105.5	13.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phentermine/Topiramate													
EQUIP	PBO +LI (n=514)	120.5	13.9	NR	NR	0	NR	121.8	11.5	121.3	32	93	8.7
	P/T 3.75 mg/23 mg + LI (n=241)	121.7	15.2	NR	NR	0	NR	122.5	11.1	122.5	33	93.8	9.11

Study Name	Intervention(s)	Waist Circumference, cm		A1C, Mean %		Diabetes %	Pre-Diabetes, %	SBP, mm HG		LDL, mg/dL		Fasting Blood Glucose, mg/dL	
		Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD
	P/T 15 mg/92 mg + LI (n=512)	120.1	14.6	NR	NR	0	NR	122	11.6	119.8	30.1	93	9.47
EQUATE	PBO + LI (n=109)	110.7	9.5	5.4*	0.41	0	NR	120.6	14.1	NR	NR	5.3*	0.59
	Phentermine 7.5 mg + LI (n=109)	111.7	10.8	5.5*	0.4	0	NR	122.3	12.9	NR	NR	5.2*	0.53
	Topiramate 46 mg + LI (n=108)	110.6	11.5	5.5*	0.43	0	NR	123.4	13.7	NR	NR	5.2*	0.55
	P/T 7.5 mg/46 mg + LI (n=107)	111.7	12.9	5.4*	0.42	0	NR	123.4	12.2	NR	NR	5.2*	0.55
	Phentermine 15 mg + LI (n=108)	111.2	11.3	5.4*	0.37	0	NR	120.5	13.4	NR	NR	5.2*	0.53
	Topiramate 92 mg + LI (n=107)	112.6	11.3	5.5*	0.38	0	NR	123.2	14.1	NR	NR	5.3*	0.5
	P/T 15 mg/92 mg + LI (n=108)	109.5	10.5	5.5*	0.43	0	NR	121.2	12.4	NR	NR	5.3*	0.55
CONQUER (Diabetes Subgroup)	PBO + LI (n=157)	112.7	12.5	6.9	1.3	100	NR	125.7	13.9	3	0.9	NR	NR
	P/T 7.5 mg/46 mg + LI (n=67)	111.4	10.8	6.8	1.2	100	NR	127	12.1	2.8	0.9	NR	NR
	P/T 15 mg/92 mg + LI (n=164)	114.1	12.8	6.8	1.1	100	NR	126	14	3	1	NR	NR
OB-204 (Winslow 2012)	PBO + LI (n=23)	NR	NR	NR	NR	NR	NR	138.4	13.5	121.5	36.2	109.2	46.6
	P/T 15 mg/92 mg + LI (n=22)	NR	NR	NR	NR	NR	NR	137.5	12.1	131.6	35.5	110.2	30.1
Bupropion/Naltrexone													
COR-I	PBO + LI (n=581)	110	12.2	NR	NR	0	NR	119	9.8	3.1	0.9	93.6	10.8
	B/N 360 mg/16 mg + LI (n=578)	109.8	11.2	NR	NR	0	NR	119.5	9.9	3.2	0.8	95.4	10.8
	B/N 360 mg/32 mg + LI (n=583)	108.8	11.3	NR	NR	0	NR	118.9	9.9	3.1	0.8	93.6	12.6
COR-II	PBO + LI (n=495)	108.9*	11.7	NR	NR	0	NR	118.2*	10.5	117.1*	32.6	94.2*	10.4
	B/N 360 mg/32 mg + LI (n=1,001)	109.3*	11.9	NR	NR	0	NR	118.1*	10	119.8*	30.2	94.8*	11.2
COR-BMOD	PBO + BMOD (n=202)	109	11.8	NR	NR	0	NR	116.7	10.9	109.2	27.3	94.1	20.1

Study Name	Intervention(s)	Waist Circumference, cm		A1C, Mean %		Diabetes %	Pre-Diabetes, %	SBP, mm HG		LDL, mg/dL		Fasting Blood Glucose, mg/dL	
		Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD
	B/N 360 mg/32 mg + BMOD (n=591)	109.3	11.4	NR	NR	0	NR	116.6	10.1	109.5	27.5	92.4	10.7
COR Diabetes	PBO + LI (n=159)	114.3	12.4	8	0.9	100	NR	124.5	9.6	101	33.9	163.9	44.5
	B/N 360 mg/32 mg + LI (n=265)	115.6	12.6	8	0.8	100	NR	125	11	100.2	34.2	160	41.3
CVOT (Light Study)	PBO + LI (n=4,450)	118.5†	IQR: 110-128	7.1‡	IQR: 6.4-8.2	85.5	NR	125.5	12.6	82†	IQR: 65-106	NR	NR
	B/N 360 mg/32 mg + LI (n=4,455)	118†	IQR: 110-128	7‡	IQR: 6.1-8.1	84.9	NR	125.9	12.5	82†	IQR: 64-105	NR	NR
Ignite	Usual care (including LI) (n=89)	111.9	11.9	NR	NR	0	NR	120.6	11.4	118*	26.2	92.4*	11.5
	B/N 360 mg/32 mg + CLI (n=153)	112.2	11.2	NR	NR	0	NR	123.7	9.5	115.5*	27.6	89.7*	10.6

A1C: glycated hemoglobin, BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, cm: centimeter, dL: deciliter, IBT: intensive behavioral therapy, IQR: interquartile range, KOA: knee osteoarthritis, LDL: low-density lipoprotein, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, mm Hg: millimeter of mercury, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SBP: systolic blood pressure, SC: subcutaneous, SD: standard deviation, SEM: semaglutide, vs.: versus

*The number of patients for this characteristic may differ from the randomized population.

†Median.

‡Measured only in patients who had diabetes mellitus.

§Baseline data measured at Week 20.

Table D25. Baseline Characteristics III^{27-33,37-41,43,46-48,50-64,133-135,138,139}

Study Name	Intervention(s)	Pre-Existing Conditions	Medications
Semaglutide			
STEP 1	PBO + LI (n=655)	Dyslipidemia (35%), HTN (36%), knee arthritis (16%), sleep apnea (11%), asthma/COPD (12%), NAFLD (10%), PCOS (7%), CAD (3%)	Antihypertensive; lipid lowering
	SC SEM 2.4 mg + LI (n=1306)	Dyslipidemia (38%), HTN (36%), knee arthritis (13%), sleep apnea (12%), asthma/COPD (11%), NAFLD (7%), PCOS (7%), CAD (3%)	
STEP 2	PBO + LI (n=403)	CAD (8%), Dyslipidemia (71%), HTN (71%), knee arthritis (17%), OSP (13%), NAFLD (23%), PCOS (5%), asthma/COPD (8%)	Biguanides (90%), Sulfonylureas (25%), SGLT2i (26%), TZDs (5%), DDP4i (<1%), GLP1 (<1%)
	SC SEM 1.0 mg + LI (n=403)	CAD (10%), Dyslipidemia (71%), HTN (71%), knee arthritis (14%), OSP (13%), NAFLD (20%), PCOS (4%), asthma/COPD (12%)	Biguanides (94%), Sulfonylureas (25%), SGLT2i (24%), TZDs (4%), DDP4i (<1%), GLP1 (<1%)
	SC SEM 2.4 mg + LI (n=404)	CAD (6%), Dyslipidemia (66%), HTN (68%), knee arthritis (18%), OSP (17%), NAFLD (21%), PCOS (3%), asthma/COPD (9%)	Biguanides (92%), Sulfonylureas (27%), SGLT2i (25%), TZDs (5%), DDP4i (<1%), GLP-1 (<1%)
STEP 3	PBO + IBT (n=204)	Dyslipidemia (33%), HTN (33%), knee arthritis (15%), asthma/COPD (12%), OSP (9%), NAFLD (6%), PCOS (6%), CAD (2%)	NR
	SC SEM 2.4 mg + IBT (n=407)	Dyslipidemia (36%), HTN (36%), knee arthritis (19%), asthma/COPD (17%), OSP (14%), NAFLD (6%), PCOS (5%), CAD (2%)	NR
STEP 4	Run-in period (n=803)	Dyslipidemia (36%), HTN (37%), knee arthritis (12%), OSA (12%), asthma/COPD (12%), NAFLD (7%), PCOS (4%), CAD (<1%)	NR
	From run-in with SEM→ PBO + LI (n=268)*	Dyslipidemia (37%), HTN (37%), knee arthritis (10%), OSA (12%), asthma/COPD (13%), NAFLD (7%), PCOS (5%), CAD (1%)	NR
	From run-in with SEM→ SC SEM 2.4 mg + LI (n=535)*	Dyslipidemia (35%), HTN (37%), knee arthritis (14%), OSA (11%), asthma/COPD (11%), NAFLD (7%), PCOS (4%), CAD (<1%)	NR
STEP 5	PBO + LI (n=152)	NR	NR
	SC SEM 2.4 mg + LI (n=152)	NR	NR

Study Name	Intervention(s)	Pre-Existing Conditions	Medications
STEP 6	PBO + LI (n=101)	Dyslipidemia (79%), HTN (72%), NAFLD (46%), kidney disease (13%), OSA (10%), knee arthritis (9%)	Biguanides (72%), SGLT2 inhibitors (52%), Sulfonylureas (32%), Thiazolidinediones (12%)
	SC SEM 1.7 mg + LI (n=101)	Dyslipidemia (87%), HTN (73%), NAFLD (40%), kidney disease (15%), OSP (13%), knee arthritis (9%)	Biguanides (60%), SGLT2 inhibitors (44%), Sulfonylureas (24%), Thiazolidinediones (16%)
	SC SEM 2.4 mg + LI (n=199)	Dyslipidemia (90%), HTN (76%), NAFLD (47%), kidney disease (14%), OSP (9%), knee arthritis (11%)	Biguanides (53%), SGLT2 inhibitors (41%), Sulfonylureas (14%), Thiazolidinediones (16%)
Semaglutide vs. Liraglutide			
STEP 8	PBO +LI (n=85)	Dyslipidemia (42%), HTN (46%), knee arthritis (26%), OSA (22%), asthma/copd (15%), NAFLD (8%), PCOS (2%), CAD (5%)	NR
	SC 2.4 mg + LI (n=126)	Dyslipidemia (48%), HTN (38%), knee arthritis (18%), OSA (19%), asthma/copd (14%), NAFLD (4%), PCOS (5%), CAD (3%)	NR
	SC LIR 3.0 mg + LI (n=127)	Dyslipidemia (51%), HTN (43%), knee arthritis (13%), OSA (14%), asthma/copd (14%), NAFLD (9%), PCOS (6%), CAD (2%)	NR
Liraglutide			
SCALE (Maintenance)	PBO + LI (n=210)	Dyslipidemia (31%), HTN (29%)	NR
	SC LIR 3.0 mg + LI (n=212)	Dyslipidemia (28%), HTN (33%)	NR
SCALE (Sleep Apnea)	PBO + LI (n=179)	Dyslipidemia (31%), HTN (43%)	
	SC LIR 3.0 mg + LI (n=180)	Dyslipidemia (36%), HTN (42%)	
SCALE (Type 2 Diabetes)	PBO + LI (n=212)	Dyslipidemia (59%), HTN (68%)	Metformin, glitazone, sulfonylurea
	1.8mg SC LIR + LI (n=211)	Dyslipidemia (68%), HTN (70%)	
	SC LIR 3.0 mg + LI (n=423)	Dyslipidemia (70%), HTN (69%)	
SCALE (Obesity & Pre-Diabetes)	PBO + LI (n=1244)	Dyslipidemia (29%), HTN (36%)	Anti-hypertensives (33%), lipid-lowering drugs (15%)
	SC LIR 3.0 mg + LI (n=2487)	Dyslipidemia (39%), HTN (34%)	Anti-hypertensives (31%), lipid-lowering drugs (16%)
SCALE (IBT)	PBO + IBT (n=140)	NR	NR
	SC LIR 3.0 mg + IBT (n=142)	NR	NR
SCALE (Insulin)	PBO + IBT (n=198)	NR	biguanides, sulfonylureas, SGLT2i, TZDs

Study Name	Intervention(s)	Pre-Existing Conditions	Medications
	SC LIR 3.0 mg + IBT (n=198)	NR	
LOSEIT (KOA)	PBO + LI (n=76)	NR	NR
	SC LIR 3.0 mg + LI (n=80)	NR	NR
EQUIP	PBO +LI (n=514)	Depression (16%)	Antidepressants (13%)
	P/T 3.75 mg/23 mg + LI (n=241)	Depression (20%)	Antidepressants (15%)
	P/T 15 mg/92 mg + LI (n=512)	Depression (15%)	Antidepressants (13%)
EQUATE	PBO + LI (n=109)	HTN (33%) & dyslipidemia (22%)	SSRIs (9%)
	Phentermine 7.5 mg + LI (n=109)	HTN (32%) & dyslipidemia (26%)	SSRIs (13%)
	Topiramate 46 mg + LI (n=108)	HTN (23%) & dyslipidemia (31%)	SSRIs (13%)
	P/T 7.5 mg/46 mg + LI (n=107)	HTN (24%) & dyslipidemia (17%)	SSRIs (12%)
	Phentermine 15 mg + LI (n=108)	HTN (34%) & dyslipidemia (35%)	SSRIs (13%)
	Topiramate 92 mg + LI (n=107)	HTN (27%) & dyslipidemia (27%)	SSRIs (10%)
	P/T 15 mg/92 mg + LI (n=108)	HTN (30%) & dyslipidemia (24%)	SSRIs (10%)
CONQUER (Diabetes Subgroup)	PBO +LI (n=157)	Dyslipidemia (32%) & HTN (52%)	NR
	P/T 7.5 mg/46 mg + LI (n=67)	Dyslipidemia (40%) & HTN (60%)	NR
	P/T 15 mg/92 mg + LI (n=164)	Dyslipidemia (32%) & HTN (55%)	NR
OB-204 (Winslow 2012)	PBO + LI (n=23)	NR	NR
	P/T 15 mg/92 mg + LI (n=22)	NR	NR
COR-I	PBO + LI (n=581)	HTN (19%) and dyslipidemia (50%)	NR
	B/N 360 mg/16 mg + LI (n=578)	HTN (20%) and dyslipidemia (50%)	NR
	B/N 360 mg/32 mg + LI (n=583)	HTN (22%) and dyslipidemia (49%)	NR

Study Name	Intervention(s)	Pre-Existing Conditions	Medications
COR-II	PBO + LI (n=495)	HTN (21%) and dyslipidemia (53%)	NR
	B/N 360 mg/32 mg + LI (n=1001)	HTN (21%) and dyslipidemia (56%)	NR
COR-BMOD	PBO + BMOD (n=202)	HTN (NR) and dyslipidemia (NR)	NR
	B/N 360 mg/32 mg + BMOD (n=591)		
COR Diabetes	PBO + LI (n=159)	Dyslipidemia (86%)	Sulfonylurea (49%), TZDs (31%), Metformin (77%)
	B/N 360 mg/32 mg + LI (n=265)	Dyslipidemia (83%)	Sulfonylurea (49%), TZDs (31%), Metformin (80%)
CVOT (Light Study)	PBO + LI (n=4450)	CVD (33%), diabetes (86%), CVD & diabetes (18%), HTN (93%), dyslipidemia (92%)	Statin (79%), Insulin (23%), Metformin (57%), B-Blocker (38%), Diuretic (32%), ACE inhibitor/ARB (77%), Calcium channel blocker (19%)
	B/N 360 mg/32 mg + LI (n=4455)	CVD (32%), diabetes (85%), CVD & diabetes (17%), HTN (93%), dyslipidemia (92%)	Statin (79%), Insulin (23%), Metformin (57%), B-Blocker (40%), Diuretic (33%), ACE inhibitor/ARB (77%), Calcium channel blocker (20%)
Ignite	Usual care (including LI) (n=89)	NR	NR
	B/N 360 mg/32 mg + CLI (n=153)	NR	NR

ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, BMOD: behavioral modification, B/N: bupropion/naltrexone, CAD: coronary artery disease, CLI: comprehensive lifestyle intervention, COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, DDP4i: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, HTN: hypertension, IBT: intensive behavioral therapy, KOA: knee osteoarthritis, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, NAFLD: nonalcoholic fatty liver disease, NR: not reported, OSP: oral sodium phosphate, PBO: placebo, PCOS: polycystic ovarian syndrome, P/T: phentermine/topiramate, SC: subcutaneous, SEM: semaglutide, SGLT2: sodium-glucose cotransporter-2, TZD: thiazolidinediones, vs.: versus

*Baseline data measured at Week 20.

Table D26. Efficacy: Weight Loss Outcomes | 27-36,38-43,46-65,133-142

Study Name	Arms	N	Change in Body Weight from Baseline, Mean kg			Weight Loss from Baseline to Six Months, Mean %			Weight Loss from Baseline to One Year, Mean %		
			N	Mean	SE	N	Mean	SE	N	Mean	SE
Semaglutide											
STEP 1	PBO + LI	655	577	-2.6	NR	592	-2.9	0.2	577	-2.8	0.3*
	SC SEM 2.4 mg + LI	1306	1212	-15.3	NR	1232	-11.7	0.2	1212	-15.6	0.3*
STEP 2	PBO + LI	403	376	-3.5	0.4	381	-2.7	0.2	376	-3.4	0.4
	SC SEM 1.0 mg + LI	403	380	-6.9	0.4	378	-6.6	0.3	380	-7	0.4
	SC SEM 2.4 mg + LI	404	388	-9.7	0.4	386	-8.7	0.3	388	-9.6	0.4
STEP 3	PBO + IBT	204	204	-6.2	NR	189	-7.9	0.5*	189	-5.8	0.4*
	SC SEM 2.4 mg + IBT	407	407	-16.8	NR	380	-15.4	0.3*	373	-16.5	0.5*
STEP 4	Run-in period†	803	803	-11.1	0.2*	803	-10.6	0.2*	NR	NR	NR
	From run-in with SEM→ PBO + LI‡	268	250	6.1	0.5*	265	-9.6	0.3*	268	6.9	0.5*
	From run-in with SEM→ SC SEM 2.4 mg + LI‡	535	520	-7.1	0.3*	531	-13.2	0.3*	535	-7.9	0.4*
STEP 5	PBO + LI	152	129	-3.5	0.7*	129	-2.6	NR	129	-3.3	0.6*
	SC SEM 2.4 mg + LI	152	149	-16.7	0.8*	149	-12	NR	149	-15.8	0.8*
STEP 6	PBO + LI	101	100	-1.7	0.7	100	-2.4	0.4	101	-2.1	0.8
	SC SEM 1.7 mg + LI	101	98	-8.2	0.7	99	-8.3	0.6	98	-9.6	0.8
	SC SEM 2.4 mg + LI	199	193	-11.3	0.5	197	-10.1	0.4	193	-13.2	0.5
Semaglutide vs. Liraglutide											
STEP 8	PBO + LI	85	78	-1.6	1.2*	NR	NR	NR	78	-1.9	1.1*
	SC SEM 2.4 mg + LI	126	126	-15.3	1.0*	76	-13.3	NR	117	-15.8	0.9*
	SC LIR 3.0 mg	127	127	-6.8	1.0*	66	-6.8	NR	117	-6.4	0.9*
Liraglutide											
SCALE (Maintenance)	PBO + LI	206	206	-0.1	0.5*	168	-1	0.5	144	-0.2	0.5*
	SC LIR 3.0 mg + LI	207	207	-6	0.5*	181	-7.7	0.5	156	-6.2	0.5*
SCALE (Sleep Apnea)§	PBO + LI	178	178	-1.9	0.4	178	-1.6	0.3	NR	NR	NR
	SC LIR 3.0 mg + LI	175	175	-6.7	0.5	175	-5.7	0.4	NR	NR	NR
SCALE (Type 2 Diabetes)	PBO + LI	211	116	-3.1	0.5*	137	-2.7	0.3*	211	-2	0.3*
	SC LIR 1.8 mg + LI	204	158	-5.2	0.5*	172	-4.9	0.3*	204	-4.6	0.4*
	SC LIR 3.0 mg + LI	412	317	-7	0.3*	337	-6	0.3*	412	-5.9	0.3*
	PBO + LI	1225	1225	-2.8	6.5	1225	-2.9	0.3	1220	-2.6	0.2*

Study Name	Arms	N	Change in Body Weight from Baseline, Mean kg			Weight Loss from Baseline to Six Months, Mean %			Weight Loss from Baseline to One Year, Mean %		
			N	Mean	SE	N	Mean	SE	N	Mean	SE
SCALE (Obesity & Pre-Diabetes)	SC LIR 3.0 mg + LI	2437	2437	-8.4	7.3	2437	-8.2	0.2	2432	-8	0.1*
SCALE (IBT)	PBO + IBT	140	NR	NR	NR	128	-5.4	0.5	130	-4	0.6*
	SC LIR 3.0 mg + IBT	142	NR	NR	NR	137	-8.4	0.6	141	-7.4	0.7*
SCALE (Insulin)	PBO + IBT	198	NR	NR	NR	183	-2.1	0.4	193	-1.5	0.4
	SC LIR 3.0 mg + IBT	198	NR	NR	NR	188	-6.4	0.4	191	-5.8	0.4
LOSEIT	PBO + LI	76	76	1.2	1.2*	NR	NR	NR	NR	NR	NR
	SC LIR 3.0 mg + LI	80	80	-2.8	1.3*	NR	NR	NR	NR	NR	NR
Phentermine/Topiramate											
EQUIP	PBO + LI	498	NR	NR	NR	NR	NR	NR	498	-1.6	0.4
	P/T 3.75 mg/23 mg + LI	234	NR	NR	NR	NR	NR	NR	234	-5.1	0.5
	P/T 15 mg/92 mg + LI	498	NR	NR	NR	NR	NR	NR	498	-10.9	0.4
EQUATE	PBO + LI	103	103	-1.5	NR	103	-1.7	0.6	NR	NR	NR
	Phentermine 7.5 mg + LI	104	104	-5.3	NR	104	-5.5	0.6	NR	NR	NR
	Topiramate 46 mg + LI	102	102	-4.7	NR	102	-5.1	0.6	NR	NR	NR
	P/T 7.5 mg/46 mg + LI	103	103	-8.3	NR	103	-8.5	0.6	NR	NR	NR
	Phentermine 15 mg + LI	106	106	-6	NR	106	-6.1	0.6	NR	NR	NR
	Topiramate 92 mg + LI	105	105	-6.4	NR	105	-6.4	0.6	NR	NR	NR
	P/T 15 mg/92 mg + LI	103	103	-9	NR	103	-9.2	0.6	NR	NR	NR
CONQUER (Diabetes Subgroup)	PBO + LI	157	NR	NR	NR	NR	NR	NR	157	-1.9	0.6*
	P/T 7.5 mg/46 mg + LI	67	NR	NR	NR	NR	NR	NR	67	-6.8	0.9*
	P/T 15 mg/92 mg + LI	164	NR	NR	NR	NR	NR	NR	164	-8.8	0.6*
OB-204 (Winslow 2012)	PBO + LI	23	23	-4.7	1.2	23	-4.2	1.2	NR	NR	NR
	P/T 15 mg/92 mg + LI	22	22	-11	1.2	22	-10.3	1.2	NR	NR	NR
Bupropion/Naltrexone											
COR-I	PBO + LI	511	511	-1.4	0.3	NR	NR	NR	511	-1.3	0.3
	B/N 360 mg/16 mg + LI	471	471	-4.9	0.3	NR	NR	NR	471	-5	0.3
	B/N 360 mg/32 mg + LI	471	471	-6.1	0.3	NR	NR	NR	471	-6.1	0.3
COR-II	PBO + LI	456	456	-1.3	0.3	456	-1.9	0.3	456	-1.2	0.3
	B/N 360 mg/32 mg + LI	702	702	-6.2	0.2	825	-6.5	0.2	702	-6.4	0.3
COR-BMOD	PBO + BMOD	202	NR	NR	NR	NR	-5.6	0.5	193	-5.1	0.6

Study Name	Arms	N	Change in Body Weight from Baseline, Mean kg			Weight Loss from Baseline to Six Months, Mean %			Weight Loss from Baseline to One Year, Mean %		
			N	Mean	SE	N	Mean	SE	N	Mean	SE
	B/N 360 mg/32 mg + BMOD	591	NR	NR	NR	NR	-9.4	0.4	482	-9.3	0.4
COR-Diabetes	PBO + LI	159	NR	NR	NR	NR	-2	0.4	159	-1.8	0.4
	B/N 360 mg/32 mg + LI	265	NR	NR	NR	NR	-5.1	0.3	265	-5	0.3
CVOT (Light Study)	PBO + LI	4450	2848	-1.9	0.1*	3297	-1.7	NR	2848	-1.8	NR
	B/N 360 mg/32 mg + LI	4455	2995	-4.9	0.1*	3404	-4.5	NR	2995	-4.6	NR
Ignite	Usual care (including LI)	82	82	-1	0.5	82	-0.9	0.5	NR	NR	NR
	B/N 360 mg/32 mg + CLI	71	71	-9.5	0.6	71	-9.5	0.5	NR	NR	NR

BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, IBT: intensive behavioral therapy, KOA: knee osteoarthritis, kg: kilogram, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SC: subcutaneous, SE: standard error, SEM: semaglutide, vs.: versus

*SE manually derived from standard deviation or 95% CIs.

†Timepoint for outcomes is at Week 20.

‡Timepoint for outcomes is Week 20-68.

§Timepoint for all outcomes is at Week 32.

Table D27. Efficacy: Weight Loss Outcomes II^{27-36,38-43,46-50,52-55,57-65,133-137,140-142}

Study Name	Arms	N	% Participants with 5% Body Weight Loss			% Participants with 10% Body Weight Loss			% Participants with 15% Body Weight Loss		
			%	n	N	%	n	N	%	n	N
Semaglutide											
STEP 1	PBO + LI	655	31.5	182	577	12	69	577	4.9	28	577
	SC SEM 2.4 mg + LI	1306	86.4	1047	1212	69.1	838	1212	50.5	612	1212
STEP 2	PBO + LI	403	28.5	107	376	8.2	31	376	3.2	12	376
	SC SEM 1.0 mg + LI	403	57.1	217	380	28.7	109	380	13.7	52	380
	SC SEM 2.4 mg + LI	404	68.8	267	388	45.6	177	388	25.8	100	388
STEP 3	PBO + IBT	204	47.6	90	189	27	51	189	13.2	25	189
	SC SEM 2.4 mg + IBT	407	86.6	323	373	75.3	281	373	55.8	208	373
STEP 4	Run-in period	803	NR	NR	NR	NR	NR	NR	NR	NR	NR
	From run-in with SEM→ PBO + LI*	268	47.4	119	250	20.1	50	250	8.7	22	250
	From run-in with SEM→ SC SEM 2.4 mg + LI*	535	88.6	461	520	78.8	410	520	63.8	332	520
STEP 5	PBO + LI	152	29.5	38	129	13.2	17	129	5.4	7	129
	SC SEM 2.4 mg + LI	152	88.6	132	149	68.5	102	149	52.3	78	149
STEP 6	PBO	101	21	21	100	5	5	100	3	3	100
	SC SEM 1.7 mg + LI	101	72	71	98	42	41	98	24	24	98
	SC SEM 2.4 mg + LI	199	83	160	193	61	117	193	41	79	193
Semaglutide vs. Liraglutide											
STEP 8	PBO +LI	85	29.5	23	78	15.4	12	78	6.4	5	78
	SC SEM 2.4 mg + LI	126	87.2	102	117	70.9	83	117	55.6	65	117
	SC LIR 3.0 mg	127	58.1	68	117	25.6	30	117	12	14	117
Liraglutide											
SCALE (Maintenance)	PBO + LI	206	21.8	41	188	6.3	12	188	NR	NR	NR
	SC LIR 3.0 mg + LI	207	50.5	98	194	26.1	51	194	NR	NR	NR
SCALE (Sleep Apnea)†	PBO + LI	178	18.5	33	178	1.7	3	178	NR	NR	NR
	SC LIR 3.0 mg + LI	175	46.3	81	175	23.4	41	175	NR	NR	NR
SCALE (Type 2 Diabetes)	PBO + LI	211	21.4	45	211	6.7	14	211	NR	NR	NR
	SC LIR 1.8 mg + LI	204	40.4	82	204	15.9	32	204	NR	NR	NR
	SC LIR 3.0 mg + LI	412	54.3	224	412	25.2	104	412	NR	NR	NR
	PBO + LI	1225	27.1	331	1220	10.6	129	1220	NR	NR	NR

Study Name	Arms	N	% Participants with 5% Body Weight Loss			% Participants with 10% Body Weight Loss			% Participants with 15% Body Weight Loss		
			%	n	N	%	n	N	%	n	N
SCALE (Obesity & Pre-Diabetes)	SC LIR 3.0 mg + LI	2437	63.2	1537	2432	33.1	805	2432	NR	NR	NR
SCALE (IBT)	PBO + IBT	140	38.8	50	130	19.8	26	130	8.9	12	130
	SC LIR 3.0 mg + IBT	142	61.5	87	141	30.5	43	141	18.1	26	141
SCALE (Insulin)	PBO + IBT	198	24	46	193	6.6	13	193	NR	NR	NR
	SC LIR 3.0 mg + IBT	198	51.8	100	191	22.8	44	191	NR	NR	NR
LOSEIT	PBO + LI	76	17.1	13	76	9.6	7	76	NR	NR	NR
	SC LIR 3.0 mg + LI	80	35	28	80	21.3	17	80	NR	NR	NR
Phentermine/Topiramate											
EQUIP	PBO + LI	498	17.3	86	498	7.4	37	498	3.4	17	498
	P/T 3.75 mg/23 mg + LI	234	44.9	105	234	18.8	44	234	7.3	17	234
	P/T 15 mg/92 mg + LI	498	66.7	332	498	47.2	235	498	32.3	161	498
EQUATE	PBO + LI	103	15.5	16	103	6.8	7	103	NR	NR	NR
	Phentermine 7.5 mg + LI	104	43.3	45	104	12.5	13	104	NR	NR	NR
	Topiramate 46 mg + LI	102	39.2	40	102	18.6	19	102	NR	NR	NR
	P/T 7.5 mg/46 mg + LI	103	62.1	64	103	38.8	40	103	NR	NR	NR
	Phentermine 15 mg + LI	106	46.2	49	106	20.8	22	106	NR	NR	NR
	Topiramate 92 mg + LI	105	48.6	51	105	23.8	25	105	NR	NR	NR
	P/T 15 mg/92 mg + LI	103	66	68	103	40.8	42	103	NR	NR	NR
CONQUER (Diabetes subgroup)	PBO + LI	157	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P/T 7.5 mg/46 mg + LI	67	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P/T 15 mg/92 mg + LI	164	NR	NR	NR	NR	NR	NR	NR	NR	NR
OB-204 (Winslow 2012)	PBO + LI	23	47.8	11	23	13	3	23	NR	NR	NR
	P/T 15 mg/92 mg + LI	22	72.7	16	22	54.5	12	22	NR	NR	NR
Bupropion/Naltrexone											
COR-I	PBO + LI	511	16	84	511	7	38	511	2	10	511
	B/N 360 mg/16 mg + LI	471	39	186	471	20	95	471	9	41	471
	B/N 360 mg/32 mg + LI	471	48	226	471	25	116	471	12	56	471
COR-II	PBO + LI	456	17.1	80	456	5.7	26	456	2.4	11	456
	B/N 360 mg/32 mg + LI	702	50.5	354	702	28.3	199	702	13.5	95	702
COR-BMOD	PBO + BMOD	202	42.5	82	193	20.2	39	193	10.9	21	193

Study Name	Arms	N	% Participants with 5% Body Weight Loss			% Participants with 10% Body Weight Loss			% Participants with 15% Body Weight Loss		
			%	n	N	%	n	N	%	n	N
	B/N 360 mg/32 mg + BMOD	591	66.4	320	482	41.5	200	482	29.1	140	482
COR-Diabetes	PBO + LI	159	18.9	30	159	5.7	9	159	NR	NR	NR
	B/N 360 mg/32 mg + LI	265	44.5	118	265	18.5	49	265	NR	NR	NR
CVOT (Light Study)	PBO + LI	4450	NR	NR	NR	NR	NR	NR	NR	NR	NR
	B/N 360 mg/32 mg + LI	4455	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ignite	Usual care (including LI)	82	12.2	10	82	3.7	3	82	0	0	82
	B/N 360 mg/32 mg + CLI	71	84.5	60	71	42.3	30	71	12.7	9	71

BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, IBT: intensive behavioral therapy, KOA: knee osteoarthritis, kg: kilogram, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SC: subcutaneous, SEM: semaglutide, vs.: versus

*Timepoint for outcomes is Weeks 0-68.

†Timepoint for all outcomes is at Week 32.

Table D28. Efficacy: Secondary Outcomes ^{27-36,38-43,46-65,133-142}

Study Name	Arms	N	Change in A1C from Baseline, Mean %			Change in SBP from Baseline, Mean mm Hg			Change in Waist Circumference from Baseline, cm	
			N	Mean	SE	N	Mean	SE	Mean	SE
Semaglutide										
STEP 1	PBO + LI	655	563	-0.15	0.01*	577	-1.1	0.5*	-4.1	NR
	SC SEM 2.4 mg + LI	1306	1197	-0.45	0.01*	1212	-6.2	0.4*	-13.5	NR
STEP 2	PBO + LI	403	374	-0.4	0.1	376	-0.5	0.8	-4.5	0.4
	SC SEM 1.0 mg + LI	403	376	-0.4	0.1	379	-2.9	0.9	-6.7	0.4
	SC SEM 2.4 mg + LI	404	381	-0.4	0.1	387	-3.9	0.7	-9.4	0.4
STEP 3	PBO + IBT	204	204	-0.27	0.01*	188	-1.6	1.1*	-6.3	NR
	SC SEM 2.4 mg + IBT	407	407	-0.51	0.02*	372	-5.6	0.7*	-14.6	NR
STEP 4	Run-in period†	803	803	-0.4	0.01*	803	-5.7	0.5*	-10.1	0.2*
	From run-in with SEM→ PBO + LI‡	268	246	0.1	0*	248	4.4	0.8*	3.3	0.5*
	From run-in with SEM→ SC SEM 2.4 mg + LI‡	535	515	-0.1	0.03*	518	0.5	0.6*	-6.4	0.4*
STEP 5	PBO + LI	152	129	-0.2	0.02*	129	-1	1.2*	-4.5	0.6*
	SC SEM 2.4 mg + LI	152	149	-0.5	0.03*	149	-7	1.1*	-14.3	0.8*
STEP 6	PBO + LI	101	100	-0.03	0.07	100	-5.3	1.2	-1.8	0.7
	SC SEM 1.7 mg + LI	101	98	-0.89	0.07	98	-10.8	1.3	-7.7	0.7
	SC SEM 2.4 mg + LI	199	193	-0.93	0.05	193	-10.8	0.9	-11.1	0.5
Semaglutide vs. Liraglutide										
STEP 8	PBO + LI	85	76	0.1	0.02*	77	3.2	1.5*	-2	1.1*
	SC SEM 2.4 mg + LI	126	113	-0.2	0.03*	114	-5.7	1.2*	-13.2	0.9*
	SC LIR 3.0 mg	127	107	-0.1	0.03*	112	-2.9	1.2*	-6.6	0.9*
Liraglutide										
SCALE (Maintenance)	PBO + LI	206	206	0.1	0.03*	206	2.8	0.7*	-1.2	0.4*
	SC LIR 3.0 mg + LI	207	207	-0.1	0.03*	207	0.2	0.8*	-4.7	0.5*
SCALE (Sleep Apnea)§	PBO + LI	178	171	-0.2	0*	179	0	1	-3.1	0.5
	SC LIR 3.0 mg + LI	175	174	-0.4	0	178	-3.4	0.9	-6.4	0.5
SCALE (Type 2 Diabetes)	PBO + LI	211	211	-0.3	0.06*	211	-0.4	0.9*	-2.7	0.4*
	SC LIR 1.8 mg + LI	204	204	-1.1	0.07*	204	-3.5	0.9*	-4.8	0.4*

Study Name	Arms	N	Change in A1C from Baseline, Mean %			Change in SBP from Baseline, Mean mm Hg			Change in Waist Circumference from Baseline, cm	
			N	Mean	SE	N	Mean	SE	Mean	SE
	SC LIR 3.0 mg + LI	412	411	-1.3	0.04*	411	-2.8	0.7*	-6.1	0.3*
SCALE (Obesity & Pre-Diabetes)	PBO + LI	1225	1225	-0.06	0.01*	1225	-1.5	0.4*	-3.9	0.2*
	SC LIR 3.0 mg + LI	2437	2437	-0.3	0.01*	2437	-4.2	0.3*	-8.2	0.1*
SCALE (IBT)	PBO + IBT	140	140	-0.06	0.02*	130	-0.6	NR	-6.7	NR
	SC LIR 3.0 mg + IBT	142	142	-0.16	0.03*	141	-2.8	NR	-9.4	NR
SCALE (Insulin)	PBO + IBT	198	188	-0.6	NR	198	-1.6	0.9	-2.6	NR
	SC LIR 3.0 mg + IBT	198	187	-1.1	NR	198	-5.6	0.9	-5.3	NR
LOSEIT	PBO + LI	76	NR	NR	NR	NR	NR	NR	0.9	1.1*
	SC LIR 3.0 mg + LI	80	NR	NR	NR	NR	NR	NR	-1.4	1.1*
Phentermine/Topiramate										
EQUIP	PBO + LI	498	NR	NR	NR	498	0.9	0.6*	-3.1	0.5*
	P/T 3.75 mg/23 mg + LI	234	NR	NR	NR	234	-1.8	0.8*	-5.6	0.6*
	P/T 15 mg/92 mg + LI	498	NR	NR	NR	498	-2.9	0.6*	-10.9	0.5*
EQUATE	PBO + LI	103	87	0.1	0.02	103	-1.8	NR	-3.3	0.7
	Phentermine 7.5 mg + LI	104	89	0.1	0.02	104	-3.3	NR	-6.4	0.7
	Topiramate 46 mg + LI	102	89	0.1	0.02	102	-6.8	NR	-5.4	0.7
	P/T 7.5 mg/46 mg + LI	103	91	0	0.02	102	-7	NR	-8.8#	0.7
	Phentermine 15 mg + LI	106	90	0.1	0.02	104	-3.5	NR	-6.6	0.7
	Topiramate 92 mg + LI	105	93	0	0.02	105	-6.4	NR	-6.2	0.7
	P/T 15 mg/92 mg + LI	103	95	0	0.02	103	-5.2	NR	-8.7	0.7
CONQUER (Diabetes subgroup)	PBO + LI	157	144	-0.1	0.05	157	-2.1	1.1	NR	NR
	P/T 7.5 mg/46 mg + LI	67	63	-0.4	1.5*	67	-2.9	1.6	NR	NR
	P/T 15 mg/92 mg + LI	164	150	-0.4	0.6*	153	-4.2	1	NR	NR
	PBO + LI	23	NR	NR	NR	23	-7.3	2.6	NR	NR

Study Name	Arms	N	Change in A1C from Baseline, Mean %			Change in SBP from Baseline, Mean mm Hg			Change in Waist Circumference from Baseline, cm	
			N	Mean	SE	N	Mean	SE	Mean	SE
OB-204 (Winslow 2012)	P/T 15 mg/92 mg + LI	22	NR	NR	NR	22	-15	2.6	NR	NR
Bupropion/Naltrexone										
COR-I	PBO + LI	511	NR	NR	NR	511	-1.9	0.4	-2.5	0.4
	B/N 360 mg/16 mg + LI	471	NR	NR	NR	471	0.3	0.4	-5	0.4
	B/N 360 mg/32 mg + LI	471	NR	NR	NR	471	-0.1	0.4	-6.2	0.4
COR-II	PBO + LI	456	NR	NR	NR	456	-0.5	0.4	-2.1	0.5
	B/N 360 mg/32 mg + LI	702	NR	NR	NR	702	0.6	0.3	-6.7	0.3
COR-BMOD	PBO + BMOD	202	NR	NR	NR	193	-3.9	0.7	-6.8	0.8*
	B/N 360 mg/32 mg + BMOD	591	NR	NR	NR	482	-1.3	0.5	-10	0.5*
COR-Diabetes	PBO + LI	159	137	-0.14	0.09	159	-1.1	0.9	-2.9	0.6
	B/N 360 mg/32 mg + LI	265	222	-0.63	0.07	265	0	0.7	-5	0.5
CVOT (Light Study)	PBO + LI	4450	NR	NR	NR	2850	1	0.3*	-0.8	0.1*
	B/N 360 mg/32 mg + LI	4455	NR	NR	NR	2997	1.2	0.3*	-2.1	0.2*
Ignite	Usual care (including LI)	82	NR	NR	NR	82	-2.8	1	-1.6	0.7
	B/N 360 mg/32 mg + CLI	71	NR	NR	NR	71	-4.8	1.1	-7	0.7

A1C: glycated hemoglobin, BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, cm: centimeter, IBT: intensive behavioral therapy, KOA: knee osteoarthritis, kg: kilogram, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SBP: systolic blood pressure, SC: subcutaneous, SE: standard error, SEM: semaglutide, vs.: versus

*SE manually derived from standard deviation or 95% CIs.

†Timepoint for outcomes is at Week 20.

‡Timepoint for outcomes is Week 20-68.

§Timepoint for all outcomes is at Week 32.

#The number of patients for this outcome may differ from the primary analysis population.

Table D29. Efficacy: Secondary Outcomes II^{27-36,38-43,46-65,133-142}

Study Name	Arms	N	Change in LDL from Baseline, mg/dL			Ratio of LDL from Baseline			Change in Blood Glucose, mg/dL		Change in BMI, kg/m2	
			N	Mean	SE	N	Mean	SE	Mean	SE	Mean	SE
Semaglutide												
STEP 1	PBO + LI	655	561	1.1	NR	561	1.01	NR	-0.5	NR	-0.9	NR
	SC SEM 2.4 mg + LI	1306	1194	-3.3	NR	1194	0.97	NR	-8.4	NR	-5.5	NR
STEP 2	PBO + LI	403	374	0	NR	374	1.00	NR	-0.1	1.8	-1.3	0.1
	SC SEM 1.0 mg + LI	403	376	-0.9	NR	376	0.99	NR	-1.8	1.8	-2.5	0.1
	SC SEM 2.4 mg + LI	404	382	0	NR	382	1.00	NR	-2.1	1.8	-3.5	0.1
STEP 3	PBO + IBT	204	204	2.6	NR	NR	NR	NR	-0.7	NR	-2.2	NR
	SC SEM 2.4 mg + IBT	407	407	-4.7	NR	NR	NR	NR	-6.7	NR	-6.0	NR
STEP 4	Run-in period†	803	NR	NR	NR	798	1	IQR: 0.8-1.1	-9.5	0.4*	-4.0	0.1*
	From run-in with SEM→ PBO + LI‡	268	245	8	1.3*	NR	NR	NR	6.7	0.9*	2.2	0.2*
	From run-in with SEM→ SC SEM 2.4 mg + LI‡	535	517	1	1.0*	NR	NR	NR	-0.8	0.5*	-2.6	0.1*
STEP 5	PBO + LI	152	129	-1.1	NR	129	0.99	NR	1.6*	NR	-1.3	0.2*
	SC SEM 2.4 mg + LI	152	149	-7.8	NR	149	0.93	NR	-7.6*	NR	-6	0.3*
STEP 6	PBO	101	NR	NR	NR	99	0.96	NR	2.2	1.6	-0.6	0.2
	SC SEM 1.7 mg+ LI	101	NR	NR	NR	98	0.90	NR	-17.8	1.8	-3.1	0.2
	SC SEM 2.4 mg+ LI	199	NR	NR	NR	193	0.85	NR	-19.6	1.3	-4.2	0.2
Semaglutide vs. Liraglutide												
STEP 8	PBO +LI	85	74	-1.1	5.6*	NR	NR	NR	3.3	1.4*	NR	NR
	SC SEM 2.4 mg + LI	126	112	-6.5	3.1*	NR	NR	NR	-8.3	1.1*	NR	NR
	SC LIR 3.0 mg	127	107	0.9	2.8*	NR	NR	NR	-4.3	1.2*	NR	NR
Liraglutide												
SCALE (Maintenance)	PBO + LI	206	206	11.6	1.6*	NR	NR	NR	-3.6	0.9*	0	0.2*
	SC LIR 3.0 mg + LI	207	207	7.7	1.6*	NR	NR	NR	-9.0	0.8*	-2.1	0.2*
SCALE (Sleep Apnea)§	PBO + LI	178	NR	NR	NR	NR	NR	NR	3.6	1.8	-0.6	0.1
	SC LIR 3.0 mg + LI	175	NR	NR	NR	NR	NR	NR	-3.6	1.8	-2.2	0.2
SCALE (Type 2 Diabetes)	PBO + LI	211	211	5	NR	NR	NR	NR	-0.2	2.6*	-0.8	0.1*
	SC LIR 1.8 mg + LI	204	204	-3.1	NR	NR	NR	NR	-26.8	3.5*	-1.7	0.1*
	SC LIR 3.0 mg + LI	412	411	0.6	NR	NR	NR	NR	-34.3	1.9*	-2.2	0.1*
	PBO + LI	1225	1225	-1	NR	NR	NR	NR	0.1	0.3*	-1.0	0.1*

Study Name	Arms	N	Change in LDL from Baseline, mg/dL			Ratio of LDL from Baseline			Change in Blood Glucose, mg/dL		Change in BMI, kg/m2	
			N	Mean	SE	N	Mean	SE	Mean	SE	Mean	SE
SCALE (Obesity & Pre-Diabetes)	SC LIR 3.0 mg + LI	2437	2437	-3	NR	NR	NR	NR	-7.1	0.2*	-3.0	0.1*
SCALE (IBT)	PBO + IBT	140	130	1.5	NR	NR	NR	NR	0.2	NR	NR	NR
	SC LIR 3.0 mg + IBT	142	141	-1.5	NR	NR	NR	NR	-4.1	NR	NR	NR
SCALE (Insulin)	PBO + IBT	198	190	0.9	NR	190	1.01	NR	-11.5	NR	NR	NR
	SC LIR 3.0 mg + IBT	198	186	-2.8	NR	186	0.97	NR	-18.4	NR	NR	NR
LOSEIT	PBO + LI	76	NR	NR	NR	NR	NR	NR	NR	NR	0.3	0.4*
	SC LIR 3.0 mg + LI	80	NR	NR	NR	NR	NR	NR	NR	NR	-1.0	0.4*
Phentermine/Topiramate												
EQUIP	PBO +LI	498	478	-5.5 \bar{x}	0.9*	NR	NR	NR	1.9	0.5*	NR	NR
	P/T 3.75 mg/23 mg + LI	234	230	-7.7 \bar{x}	1.3*	NR	NR	NR	0.8	0.7*	NR	NR
	P/T 15 mg/92 mg + LI	498	486	-8.4 \bar{x}	0.9*	NR	NR	NR	-0.6	0.5*	NR	NR
EQUATE	PBO + LI	103	NR	NR	NR	NR	NR	NR	-0.1**	0.1	NR	NR
	Phentermine 7.5 mg + LI	104	NR	NR	NR	NR	NR	NR	0.0**	0.1	NR	NR
	Topiramate 46 mg + LI	102	NR	NR	NR	NR	NR	NR	0.0**	0.1	NR	NR
	P/T 7.5 mg/46 mg + LI	103	NR	NR	NR	NR	NR	NR	0.0**	0.1	NR	NR
	Phentermine 15 mg + LI	106	NR	NR	NR	NR	NR	NR	-0.1**	0.1	NR	NR
	Topiramate 92 mg + LI	105	NR	NR	NR	NR	NR	NR	0.0**	0.1	NR	NR
	P/T 15 mg/92 mg + LI	103	NR	NR	NR	NR	NR	NR	-0.1**	0.1	NR	NR
	PBO + LI	157	152	-2.3	2.1	NR	NR	NR	-5.4	1.8*	NR	NR
CONQUER (Diabetes Subgroup)	P/T 7.5 mg/46 mg + LI	67	65	-3.6	3.2	NR	NR	NR	-9	3.6*	NR	NR
	P/T 15 mg/92 mg + LI	164	158	-2.8	2	NR	NR	NR	-12.6	1.8*	NR	NR
	PBO + LI	23	22	-1.6	5.6	NR	NR	NR	-5.6	5.9	NR	NR
OB-204 (Winslow 2012)	P/T 15 mg/92 mg + LI	22	21	-11	6	NR	NR	NR	-8.9	6.1	NR	NR
	PBO + LI	23	22	-1.6	5.6	NR	NR	NR	-5.6	5.9	NR	NR
Bupropion/Naltrexone												
COR-I	PBO + LI	511	345	-3.3	1.2	NR	NR	NR	-1.3	0.6	NR	NR

Study Name	Arms	N	Change in LDL from Baseline, mg/dL			Ratio of LDL from Baseline			Change in Blood Glucose, mg/dL		Change in BMI, kg/m2	
			N	Mean	SE	N	Mean	SE	Mean	SE	Mean	SE
	B/N 360 mg/16 mg + LI	471	332	-3.7	1.2	NR	NR	NR	-2.4	0.6	NR	NR
	B/N 360 mg/32 mg + LI	471	358	-4.4	1.2	NR	NR	NR	-3.2	0.6	NR	NR
COR-II	PBO + LI	456	456	-2.1	1.3	NR	NR	NR	-1.3	0.6	NR	NR
	B/N 360 mg/32 mg + LI	702	702	-6.2	0.9	NR	NR	NR	-2.8	0.5	NR	NR
COR-BMOD	PBO + BMOD	202	143	8.1	2.1	NR	NR	NR	-1.1	1.0	NR	NR
	B/N 360 mg/32 mg + BMOD	591	392	5.4	1.4	NR	NR	NR	-2.4	0.6	NR	NR
COR-Diabetes	PBO + LI	159	134	0	2.4	NR	NR	NR	-4	3.4	NR	NR
	B/N 360 mg/32 mg + LI	265	220	-1.4	1.9	NR	NR	NR	-11.9	2.7	NR	NR
CVOT (Light Study)	PBO + LI	4450	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	B/N 360 mg/32 mg + LI	4455	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ignite	Usual care (including LI)	82	82	-1.9	2.1	NR	NR	NR	1.6	1.0	NR	NR
	B/N 360 mg/32 mg + CLI	71	71	-2	2.2	NR	NR	NR	-2.9	1.0	NR	NR

BMI: body-mass index, BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, IBT: intensive behavioral therapy, IQR: interquartile range, kg: kilogram, KOA: knee osteoarthritis, kg: kilogram, LDL: low-density lipoprotein, LI: lifestyle intervention, LIR: liraglutide, m: meter, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SC: subcutaneous, SE: standard error, SEM: semaglutide, vs.: versus

*SE manually derived from standard deviation or 95% CIs.

†Timepoint for outcomes is at Week 20.

‡Timepoint for outcomes is Week 20-68.

§Timepoint for all outcomes is at Week 32.

#Timepoint for this outcome is at Week 104.

⌘Percent change.

**The number of patients for this outcome may differ from the primary analysis population.

Table D30. Patient-Reported Outcomes^{27-30,32,33,39-43,46,48-50,52-55,57-65,133-135,137,140-142}

Study Name	Arms	N	SF-36, Change from Baseline						IWQOL-Lite-CT, Change from Baseline				Depression Score, Change from Baseline	
			Physical Functioning Score		Physical Component Score		Mental Component Score		Physical Function Score		Total Score			
			Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Semaglutide														
STEP 1	PBO + LI	655	0.4	NR	0.2*	0.3†	-2.1*	0.3†	5.3	NR	NR	NR	NR	NR
	SC SEM 2.4 mg + LI	1306	2.2	NR	2.4*	0.2†	-1.5*	0.2†	14.7	NR	NR	NR	NR	NR
STEP 2	PBO + LI	403	1*	0.4	NR	NR	NR	NR	5.3	1.1	NR	NR	NR	NR
	SC SEM 2.4 mg + LI	404	2.5*	0.4	NR	NR	NR	NR	10.1	1	NR	NR	NR	NR
STEP 3	PBO + IBT	204	1.6	NR	2.3	NR	-2.9	NR	NR	NR	NR	NR	NR	NR
	SC SEM 2.4 mg + IBT	407	2.4	NR	3	NR	-0.8	NR	NR	NR	NR	NR	NR	NR
STEP 4	Run-in period#	803	2.2	5.1†	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	From run-in with SEM→ PBO + LIα	268	-1.5	0.4†	-0.9	0.5†	-3.4	0.5†	NR	NR	NR	NR	NR	NR
	From run-in with SEM→ SC SEM 2.4 mg + LIα	535	1	0.2†	0.8	0.3†	0.1	0.3†	NR	NR	NR	NR	NR	NR
STEP 5	PBO + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC SEM 2.4 mg + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
STEP 6	PBO + LI	101	-0.3	0.4	NR	NR	NR	NR	0.8	1.4	NR	NR	NR	NR
	SC SEM 1.7 mg + LI	101	-0.1	0.5	NR	NR	NR	NR	2.8	1.5	NR	NR	NR	NR
	SC SEM 2.4 mg + LI	199	0.8	0.3	NR	NR	NR	NR	4.2	1.1	NR	NR	NR	NR
Semaglutide vs. Liraglutide														
STEP 8	PBO + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC SEM 2.4 mg + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC LIR 3.0 mg	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Liraglutide														
SCALE (Maintenance)	PBO + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC LIR 3.0 mg + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
SCALE (Sleep Apnea)**	PBO + LI	171	NR	NR	1.9	0.5	0.9	0.6	NR	NR	NR	NR	NR	NR
	SC LIR 3.0 mg + LI	174	NR	NR	3	0.6	1.4	0.6	NR	NR	NR	NR	NR	NR
SCALE (Type 2 Diabetes)	PBO + LI	211	NR	NR	NR	NR	NR	NR	8.9	1.1†	7.6	0.9†	NR	NR
	SC LIR 1.8 mg + LI	204	NR	NR	NR	NR	NR	NR	12.5	1.2†	9.1	1.0†	NR	NR

Study Name	Arms	N	SF-36, Change from Baseline						IWQOL-Lite-CT, Change from Baseline				Depression Score, Change from Baseline	
			Physical Functioning Score		Physical Component Score		Mental Component Score		Physical Function Score		Total Score			
			Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
	SC LIR 3.0 mg + LI	411	NR	NR	NR	NR	NR	NR	15.2	0.9†	11.7	0.7†	NR	NR
SCALE (Obesity & Pre-Diabetes)	PBO + LI	1225	NR	NR	2.1	0.2†	-0.9	0.3†	NR	NR	7.7	0.4†	NR	NR
	SC LIR 3.0 mg + LI	2437	NR	NR	3.6	0.1†	0.2	0.2†	NR	NR	10.6	0.3†	NR	NR
SCALE (IBT)	PBO + IBT	140	3.8	NR	3.8	0.6†	-2.2	0.7†	14.1†	NR	12.8	1.7†	NR	NR
	SC LIR 3.0 mg + IBT	142	4	NR	3.4	0.6†	-1.2	0.7†	14.9†	NR	13.2	1.6†	NR	NR
SCALE (Insulin)	PBO + IBT	198	2.6	0.5†	2.2	0.5†	-1.7	0.5†	5.7†	NR	4.8	1.2†	NR	NR
	SC LIR 3.0 mg + IBT	198	2.5	0.6†	2.7	0.5†	-1.9	0.6†	8.2†	NR	5.7	1.3†	NR	NR
LOSEIT	PBO + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC LIR 3.0 mg + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phentermine/Topiramate														
EQUIP	PBO + LI	498	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.3*‡	0.2†
	P/T 3.75 mg/23 mg + LI	234	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.2*‡	0.2†
	P/T 15 mg/92 mg + LI	498	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.5*‡	0.1†
EQUATE	PBO + LI	101	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-0.5*‡	0.4†
	Phentermine 7.5 mg + LI	103	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.1*‡	0.3†
	Topiramate 46 mg + LI	102	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.1*‡	0.3†
	P/T 7.5 mg/46 mg + LI	95	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.3*‡	0.2†
	Phentermine 15 mg + LI	104	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.4*‡	0.4†
	Topiramate 92 mg + LI	103	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.7*‡	0.3†
	P/T 15 mg/92 mg + LI	103	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-1.1*‡	0.4†
CONQUER (Diabetes Subgroup)	PBO + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P/T 7.5 mg/46 mg + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P/T 15 mg/92 mg + LI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
OB-204 (Winslow 2012)	PBO + LI	22	4.5	2.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P/T 15 mg/92 mg + LI	21	9.2	2.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bupropion/Naltrexone														
COR-I	PBO + LI	511	NR	NR	NR	NR	NR	NR	NR	NR	8.6*	0.5	-0.7*§	0.2
	B/N 360 mg/16 mg + LI	471	NR	NR	NR	NR	NR	NR	NR	NR	11.7*	0.5	0*§	0.2
	B/N 360 mg/32 mg + LI	471	NR	NR	NR	NR	NR	NR	NR	NR	12.7*	0.5	-0.3*§	0.2
COR-II	PBO + LI	456	NR	NR	NR	NR	NR	NR	8.2	0.8	6.4	0.6	-0.5*§	0.3

Study Name	Arms	N	SF-36, Change from Baseline						IWQOL-Lite-CT, Change from Baseline				Depression Score, Change from Baseline	
			Physical Functioning Score		Physical Component Score		Mental Component Score		Physical Function Score		Total Score			
			Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
	B/N 360 mg/32 mg + LI	702	NR	NR	NR	NR	NR	NR	14.1	0.6	10.9	0.5	-0.3*§	0.2
COR-BMOD	PBO + BMOD	202	NR	NR	NR	NR	NR	NR	12	0.8	10.3*	0.9	0*§	0.4
	B/N 360 mg/32 mg + BMOD	591	NR	NR	NR	NR	NR	NR	16.5	0.5	13.4*	0.6	0.1*§	0.2
COR-Diabetes	PBO + LI	159	NR	NR	NR	NR	NR	NR	NR	NR	7.9*	0.9	-1.6*§	0.4
	B/N 360 mg/32 mg + LI	265	NR	NR	NR	NR	NR	NR	NR	NR	9.3*	0.7	0*§	0.3
CVOT (Light Study)	PBO + LI	4450	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	B/N 360 mg/32 mg + LI	4455	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ignite	Usual care (including LI)	82	NR	NR	NR	NR	NR	NR	NR	NR	-1	1.4	NR	NR
	B/N 360 mg/32 mg + CLI	71	NR	NR	NR	NR	NR	NR	NR	NR	16.4	1.5	NR	NR

BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, IBT: intensive behavioral therapy, IWQOL-Lite: Impact of Weight on Quality of Life-Lite, KOA: knee osteoarthritis, kg: kilogram, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SC: subcutaneous, SE: standard error, SEM: semaglutide, SF-36: Short Form Health Survey, vs.: versus

*The number of patients for this outcome may differ from the primary analysis population.

†SE manually derived from standard deviation or 95% CIs.

‡Depression for this trial is measured by the PHQ-9.

§Depression for this trial is measured by the IDS-SR.

#Timepoint for outcomes is at Week 20.

⌘Timepoint for outcomes is Week 20-68.

**Timepoint for all outcomes is at Week 32.

Table D31. Patient-Reported Outcomes of Sleep Apnea Studies^{39,48,137,141}

Study Name	Arms	N	ESS		FOSQ		PSQI	
			Mean	SE	Mean	SE	Mean	SE
Liraglutide								
SCALE (Sleep Apnea)	PBO + LI	171	-2.3	0.3	1.1	0.1	NR	NR
	SC LIR 3.0 mg + LI	174	-2.5	0.3	1.3	0.2	NR	NR
Phentermine/Topiramate								
OB-204 (Winslow 2012)	PBO + LI	22	-1.8	0.8	NR	NR	-0.9	0.7
	P/T 15 mg/92 mg + LI	21	-1.9	0.8	NR	NR	-3.1	0.7

ESS: Epworth Sleepiness Scale, FOSQ: Functional Outcomes of Sleep Questionnaire, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, PSQI: Pittsburgh Sleep Quality Index, P/T: phentermine/topiramate, SC: subcutaneous, SE: standard error

Table D32. Safety^{27-36,38-43,46-64,133-142}

Study Name	Arms	N	Any Adverse Events		Serious Adverse Events		Adverse Events Leading to Discontinuation	
			n	%	n	%	n	%
Semaglutide								
STEP 1	PBO + LI	655	566	86.4	42	6.4	20	3.1
	SC SEM 2.4 mg + LI	1306	1171	89.7	128	9.8	92	7
STEP 2	PBO + LI	402	309	76.9	37	9.2	14	3.5
	SC SEM 2.4 mg + LI	403	353	87.6	40	9.9	25	6.2
STEP 3	PBO + IBT	204	196	96.1	6	2.9	6	2.9
	SC SEM 2.4 mg + IBT	407	390	95.8	37	9.1	24	5.9
STEP 4	Run-in period (Weeks 0-20)	902	760	84.3	21	2.3	48	5.3
	From run-in with SEM→ PBO + LI (Weeks 20-68)	268	201	75	15	5.6	6	2.2
	From run-in with SEM→ SC SEM 2.4 mg + LI (Weeks 20-68)	535	435	81.3	41	7.7	13	2.4
STEP 5	PBO + LI	152	136	89.5	18	11.8	7	4.6
	SC SEM 2.4 mg + LI	152	146	96.1	12	7.9	9	5.9
STEP 6	PBO + LI	101	80	79	7	7	1	1
	SC SEM 1.7 mg + LI	100	82	82	7	7	3	3
	SC SEM 2.4 mg + LI	199	171	86	10	5	5	3
Semaglutide vs. Liraglutide								
STEP 8	PBO + LI	85	81	95.3	6	7.1	3	3.5
	SC SEM 2.4 mg + LI	126	120	95.2	10	7.9	4	3.2
	SC LIR 3.0 mg	127	122	96.1	14	11	16	12.6
Liraglutide								
SCALE (Maintenance)	PBO + LI	210	186	88.6	5	2.4	18	8.6
	SC LIR 3.0 mg + LI	212	194	91.5	9	4.3	18	8.5
SCALE (Sleep Apnea)	PBO + LI	179	124	69.3	6	3.4	NR	NR
	SC LIR 3.0 mg + LI	176	141	80.1	6	3.4	NR	NR
SCALE (Type 2 Diabetes)	PBO + LI	212	182	85.8	21	9.9	7	3.3
	SC LIR 1.8 mg + LI	210	190	90.5	29	13.8	18	8.6
	SC LIR 3.0 mg + LI	422	392	92.9	52	12.3	39	9.2
	PBO + LI	1242	786	63.3	62	5	47	3.8

Study Name	Arms	N	Any Adverse Events		Serious Adverse Events		Adverse Events Leading to Discontinuation	
			n	%	n	%	n	%
SCALE (Obesity & Pre-Diabetes)	SC LIR 3.0 mg + LI	2481	1992	80.3	154	6.2	240*	9.7
SCALE (IBT)	PBO + IBT	140	124	88.6	2	1.4	6	4.3
	SC LIR 3.0 mg + IBT	142	136	95.8	6	4.2	12	8.5
SCALE (Insulin)	PBO + IBT	197	175	88.8	19	9.6	6	3
	SC LIR 3.0 mg + IBT	195	180	92.3	16	8.2	15	7.7
LOSEIT	PBO + LI	76	71	93	6	8	4	5.3
	SC LIR 3.0 mg + LI	80	77	96	7	9	10	12.5
Phentermine/Topiramate								
EQUIP	PBO + LI	513	374	72.9	13	2.5	43	8.4
	P/T 3.75 mg/23 mg + LI	240	192	80	6	2.5	27	11.3
	P/T 15 mg/92 mg + LI	511	432	84.5	13	2.5	82	16
EQUATE	PBO + LI	109	87	79.8	0	0	8	7.3
	Phentermine 7.5 mg + LI	109	87	79.8	2	1.8	10	9.2
	Topiramate 46 mg + LI	106	90	84.9	0	0	8	7.4
	P/T 7.5 mg/46 mg + LI	106	85	80.2	1	0.9	16	15.1
	Phentermine 15 mg + LI	108	89	82.4	1	0.9	11	10.2
	Topiramate 92 mg + LI	107	85	79.4	1	0.9	18	16.8
	P/T 15 mg/92 mg + LI	108	90	83.3	2	1.9	23	21.3
CONQUER (Diabetes subgroup)	PBO + LI	157	125	79.6	5	3.2	13	8.3
	P/T 7.5 mg/46 mg + LI	67	54	80.6	4	6	6	9
	P/T 15 mg/92 mg + LI	164	141	86	6	3.7	31	18.9
OB-204 (Winslow 2012)	PBO + LI	23	18	78.2	1	4.4	1	4.3
	P/T 15 mg/92 mg + LI	22	20	90.9	0	0	2	9.1
Bupropion/Naltrexone								
COR-I	PBO + LI	569	390	68.5	8	1.4	56	9.8
	B/N 360 mg/16 mg + LI	569	455	80	9	1.6	122	21.4
	B/N 360 mg/32 mg + LI	573	476	83.1	9	1.6	112	19.5
COR-II	PBO + LI	492	370	75.2	7	1.4	68	13.8
	B/N 360 mg/32 mg + LI	992	852	85.9	21	2.1	241	24.3
COR-BMOD	PBO + BMOD	200	133	66.5	1	0.5	25*	12.4
	B/N 360 mg/32 mg + BMOD	584	487	83.4	22	3.8	150*	25.4
COR-Diabetes	PBO + LI	169	144	85.2	13	4.7	26	15.4

Study Name	Arms	N	Any Adverse Events		Serious Adverse Events		Adverse Events Leading to Discontinuation	
			n	%	n	%	n	%
	B/N 360 mg/32 mg + LI	333	301	90.4	8	3.9	98	29.4
CVOT (Light Study)	PBO + LI	4450	668	15	386	8.7	388	8.7
	B/N 360 mg/32 mg + LI	4455	1620	36.4	463	10.4	1253	28.1
Ignite	Usual care (including LI)	89	0	0	0	0	1	1.1
	B/N 360 mg/32 mg + CLI	153	27	17.6	1	0.7	35	22.9

BMOD: behavioral modification, B/N: bupropion/naltrexone, CLI: comprehensive lifestyle intervention, IBT: intensive behavioral therapy, KOA: knee osteoarthritis, LI: lifestyle intervention, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, P/T: phentermine/topiramate, SC: subcutaneous, SEM: semaglutide, vs.: versus

*The number of patients for this outcome may differ from the safety analysis population.

Table D33. Safety Focus Areas for STEP Trials of Semaglutide^{27-29,31-36}

	STEP 1		STEP 2*		STEP 3		STEP 5		STEP 8		
Study Arms	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	LIR
N	655	1306	402	403	204	407	152	152	85	126	127
GI Disorders, n (%)	314 (47.9)	969 (74.2)	138 (34.3)	256 (63.5)	129 (63.2)	337 (82.8)	82 (53.9)	125 (82.2)	47 (55.3)	106 (84.1)	105 (82.7)
Gallbladder-Related Disorders, n (%)	8 (1.2)	34 (2.6)	3 (0.7)	1 (0.2)	24 (11.8)	60 (14.7)	2 (1.3)	4 (2.6)	1 (1.2)	1 (0.8)	4 (3.1)
Hepatic Disorders, n(%)	20 (3.1)	31 (2.4)	14 (3.5)	10 (2.5)	4 (2)	8 (2)	3 (2)	3 (2)	3 (3.5)	2 (1.6)	1 (0.8)
Acute Pancreatitis, n (%)	0 (0)	3 (0.2)	1 (0.2)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)
CV Disorders, n(%)	75 (11.5)	107 (8.2)	5 (1.2)	6 (1.5)	22 (10.8)	40 (9.8)	30 (19.7)	17 (11.2)	9 (10.6)	16 (12.7)	18 (14.2)
Psychiatric Disorders, n (%)	83 (12.7)	124 (9.5)	15 (3.7)	24 (6)	24 (11.8)	60 (14.7)	25 (16.4)	26 (17.1)	9 (10.6)	7 (5.6)	19 (15)
Acute Renal Failure, n (%)	2 (0.3)	3 (0.2)	2 (0.5)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.2)	1 (0.8)	0 (0)
Retinal Disorders, n (%)	NR (NR)	NR (NR)	17 (4.2)	28 (6.9)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

CV: cardiovascular, GI: gastrointestinal, LIR: liraglutide, NR: not reported, PBO: placebo

*Trial conducted in individuals with obesity and type 2 diabetes mellitus.

D4. Ongoing Studies

Table D34. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
Semaglutide					
Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) Novo Nordisk NCT03574597	Phase III MC, QB, PC, RCT N~17,500	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> Male or female, age ≥45 years BMI ≥27 kg/m² Have established CV disease with ≥1 of following: prior MI; prior stroke; or symptomatic PAD, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease <u>Exclusion Criteria</u> <ul style="list-style-type: none"> MI, stroke, hospitalization for unstable angina pectoris or transient ischemic attack within past 60 days HbA1C ≥ 48 mmol/mol (6.5%) History of T1DM or T2DM (history of gestational diabetes is allowed) 	<ul style="list-style-type: none"> Time to first occurrence of a composite endpoint consisting of: CV death, non-fatal MI, or non-fatal stroke [0-59 months] 	September 2023
Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity (STEP-HFpEF) Novo Nordisk NCT04788511	Phase III MC, DB, PC, RCT N~516	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> Male or female, age ≥18 years BMI ≥30.0 kg/m² NYHA Class II-IV LVEF ≥45% <u>Exclusion Criteria</u> <ul style="list-style-type: none"> Change in body weight >5 kg (11 lbs) within 90 days HbA1C ≥6.5% (48 mmol/mol) 	<ul style="list-style-type: none"> Change in KCCQ clinical summary score [week 0-52] Change in body weight [week 0-52] 	March 2023
Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes (STEP HFpEF DM)	Phase III MC, QB, PC, RCT N~610	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> Male or female, age ≥18 years BMI ≥30.0 kg/m² NYHA Class II-IV LVEF ≥45% Diagnosed with T2DM HbA1C ≤10% 	<ul style="list-style-type: none"> Change in KCCQ clinical summary score [week 0-52] Change in body weight [week 0-52] 	June 2023

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
Novo Nordisk NCT04916470			<u>Exclusion Criteria</u> <ul style="list-style-type: none"> Change in body weight >5 kg (11 lbs) within 90 days Uncontrolled and potentially unstable diabetic retinopathy or maculopathy 		
Research Study of How Well Semaglutide Works in People Living With Overweight or Obesity (STEP 7) Novo Nordisk NCT04251156	Phase III MC, QB, PC, RCT N~375	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> Male or female, age ≥18 years History of ≥1 unsuccessful dietary effort to lose body weight For subjects without T2DM: BMI ≥30 kg/m² or ≥27 kg/m² with the ≥1 weight-related comorbidity (treated or untreated): HTN, dyslipidemia, OSA, or CVD For subjects with T2DM: Treated with either diet and exercise alone OR stable treatment ≥60 days with up to 3 oral antidiabetic medications (metformin, α-glucosidase inhibitor, SU, glinides, SGLT2i or glitazone), HbA1C 7.0-10.0% (53-86 mmol/mol), BMI ≥27 kg/m² <u>Exclusion Criteria</u> <ul style="list-style-type: none"> Change in body weight >5 kg (11 lbs) within 90 days For subjects without T2DM at screening: HbA1C ≥6.5% (48 mmol/mol) For subjects with T2DM at screening: Renal impairment measured as eGFR <30 mL/min/1.73 m² (<60 mL/min/1.73 m² in subjects treated with SGLT2i) Uncontrolled and potentially unstable diabetic retinopathy or maculopathy 	<ul style="list-style-type: none"> Change in body weight [week 0-44] Subjects who achieve body weight reduction equal to or above 5% [week 0-44] 	August 2022
Research Study Looking at How Well Semaglutide Works in People Living With Obesity and Prediabetes (STEP 10) Novo Nordisk	Phase III MC, QB, PC, RCT N~201	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> Male or female aged ≥18 years BMI ≥30.0 kg/m² Prediabetes defined as at least one of following: HbA1C 6-6.4% (42-47 mmol/mol) or FBG 5.5-6.9 mmol/L (99-125 mg/dL) <u>Exclusion Criteria</u> <ul style="list-style-type: none"> History of T1 or T2DM 	<ul style="list-style-type: none"> Change in body weight [week 0-52] Change to normoglycemia (normoglycemia defined as having both 	January 2023

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
NCT05040971			<ul style="list-style-type: none"> Treatment with glucose-lowering agent(s) within 90 days HbA1C $\geq 6.5\%$ (≥ 48 mmol/mol) FPG ≥ 7.0 mmol/L (126 mg/dL) Change in body weight > 5 kg (11 lbs) within 90 days Treatment with any obesity medication within 90 days 	HbA1C $< 6.0\%$ (< 42 mmol/mol) and FPG < 5.5 mmol/L (< 99 mg/dL) [week 0-52]	
Research Study Investigating How Well Semaglutide Works in People From Thailand and South Korea Living With Obesity Novo Nordisk NCT04998136	Phase III MC, QB, PC, RCT N~150	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria:</u> <ul style="list-style-type: none"> Male or female aged ≥ 18 years BMI ≥ 25 kg/m² Both parents of Asian descent History of at least 1 unsuccessful dietary effort to lose body weight <u>Exclusion Criteria</u> <ul style="list-style-type: none"> HbA1C at least 48 mmol/mol (6.5%) History of T1 or T2DM Change in body weight > 5 kg (11 lbs) within 90 days Renal impairment with estimated eGFR < 15 mL/min/1.73 m² at screening 	<ul style="list-style-type: none"> Change in body weight [week 0-44] At least 5% body weight reduction (yes/no) [week 0-44] 	April 2023
Research Study Looking at How Well Semaglutide Works in People Suffering From Obesity and Knee Osteoarthritis Novo Nordisk NCT05064735	Phase III MC, TB, PC, RCT N~375	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> Male or female, age ≥ 18 years BMI ≥ 30.0 kg/m² Clinical diagnosis of knee OA with moderate radiographic changes KL grades 2 or 3 as per central reading) in target (most symptomatic) knee Pain due to knee OA <u>Exclusion Criteria</u> <ul style="list-style-type: none"> Joint replacement in target knee Arthroscopy or injections into target knee within last 3 months prior to enrolment Any other joint disease in target knee 	<ul style="list-style-type: none"> Change in body weight [week 0-68] Change in WOMAC pain score [week 0-68] 	April 2023
Latino Semaglutide Study (LSS)	Phase III single-center, TB, PC, RCT	Semaglutide 2.4 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> Self-identify as being of Hispanic/Latino ethnicity BMI > 30 kg/m² Age 18-75 years old 	<ul style="list-style-type: none"> Change from baseline in weight loss [week 0-final] 	August 2023

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
Loma Linda University & Novo Nordisk NCT05087342	N~375		<u>Exclusion Criteria</u> <ul style="list-style-type: none"> • Current cancer treatment • Diabetes, T1 or T2 • Eating disorders • Medication use targeting GPL-1 system • In last 30 days, attempted to lose weight by LSM alone or with use of anti-obesity medications resulting in >5 lbs weight loss • History of bariatric surgery • Use of obesogenic medications (including but not limited to steroids, haloperidol, clozapine, risperidone, olanzapine, amitriptyline, imipramine, paroxetine, and lithium), which cannot be substituted or stopped • Pregnant or planning to become pregnant in next 8 months • Any contraindication to semaglutide 2.4 mg including personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, hypersensitivity to semaglutide 2.4 mg or any product components 	study visit and 7 months post baseline]	
Liraglutide					
The Efficacy and Safety of Liraglutide on Body Weight Loss in Obese and Overweight Patients Shanghai Zhongshan Hospital NCT04605861	Phase III single-center, DB, PC, RCT N=414	Liraglutide 3 mg Placebo	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> • Aged 18-70 years old • Failed to control body weight in previous diet therapy • Stable body weight (patient reported body weight change <5 kg) in last 3 months • BMI ≥ 30 kg/m² (obesity) or BMI ≥ 27 kg/m² (overweight) with ≥ 1 related metabolic abnormality (HTN, dyslipidemia, T2DM) • Those with T2DM: Receiving diet and exercise therapy alone, or receiving metformin, sulfonylureas, glycosidase inhibitors and glinides alone or in combination on basis of diet and exercise therapy, with their treatment remaining 	<ul style="list-style-type: none"> • % of body weight loss [week 0-32] • Proportion of body weight loss $\geq 5\%$ [week 0-32] 	July 2022

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
			<p>stable, HbA1C 7.0-10.0%, and FBG <13.3 mmol/L (240 mg/dL)</p> <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> • T1DM or secondary DM, acute metabolic complications; 2 or more severe hypoglycemia events, binge-eating disorder, hyperthyroidism, pancreatic cancer, acute gallbladder disease, psychological disorders, CV and cerebrovascular diseases, MTC, AIDS, syphilis, proliferative retinopathy or maculopathy, malignancy • Receiving GLP-1, DPP-4 inhibitors, SGLT-2 inhibitor, insulin therapy, OTC weight-loss drugs or appetite inhibitors, prescription weight-loss drugs, lipid dissolving infections • Obesity caused by endocrine diseases • Taking drugs that can significantly increase weight in the 3 months • Previous or planned surgery for obesity • History of heart valve replacement • SBP ≥160 mmHg or DBP ≥100 mmHg • AST or ALT >3.0-fold ULN, or total bilirubin >2.0-fold ULN • eGFR <60 mL/min/1.73 m² • History of drug abuse • Pregnant or breastfeeding 		
Liraglutide, Phentermine/Topiramate, and Bupropion/Naltrexone					
<p>Individualized Obesity Pharmacotherapy</p> <p>Mayo Clinic NCT03374956</p>	<p>Phase III TB, parallel assignment, RCT</p> <p>N=200</p>	<p>Phenotype-guided therapy (intervention):</p> <ul style="list-style-type: none"> • Phen. 7.5mg/top. 46 mg • Liraglutide 3 mg • Bup. 360 mg/nalt. 32 mg <p>Randomly assigned therapy (control):</p>	<p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> • Adults with obesity (BMI >30 kg/m²) • No unstable psychiatric disease and controlled comorbidities or other diseases • Men or women of childbearing potential with negative pregnancy tests <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> • Abdominal bariatric surgery • Positive history of chronic GI diseases, or systemic disease that could affect GI motility, or use of 	Total body weight loss [12 weeks]	July 2022

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
		<ul style="list-style-type: none"> Phen. 7.5 mg/top. 46 mg Liraglutide 3 mg Bup. 360 mg/nalt. 32 mg Phen. 15-37.5 mg 	<ul style="list-style-type: none"> medications that may alter GI motility, appetite, or absorption Significant untreated psychiatric dysfunction based on Hospital Anxiety and Depression Inventory, and the Questionnaire on Eating and Weight Patterns (binge eating disorders and bulimia), with anxiety or depression score >11 		

AIDS: acquired immunodeficiency syndrome, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, CV: cardiovascular, CVD: cardiovascular disease, DM: diabetes mellitus, DBP: diastolic blood pressure, dL: deciliter, eGFR: estimated glomerular filtration rate, FBG: fasting blood glucose, GLP-1: glucagon-like peptide 1, HbA1C: glycated hemoglobin, HTN: hypertension, KCCQ: Kansas City Cardiomyopathy Questionnaire, kg: kilogram, KL: Kellgren and Lawrence, lb: pound, LSM: lifestyle modification, LVEF: left ventricular ejection fraction, m: meter, MC: multicenter, mg: milligram, MI: myocardial infarction, min: minute, mmol/mol: millimeters per mole, mmol/L: liters per mole, mL: milliliter, MTC: medullary thyroid cancer, N: number, NYHA: New York Heart Association, OA: osteoarthritis, OSA: obstructive sleep apnea, OTC: over the counter, PAD: peripheral artery disease, PC: placebo controlled, QB: quadruple blind, RCT: randomized controlled trial, SBP: systolic blood pressure, ULN: upper limits of normal, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies).

D5. Previous Systematic Reviews and Technology Assessments

We identified 15 systematic literature reviews or meta-analyses evaluating therapies for weight-loss treatment in adults with overweight or obesity, two of which are summarized below.

Shi, Q., et al. (2022). “Pharmacotherapy for Adults with Overweight and Obesity: A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials”⁸⁹

This systematic review and network meta-analysis evaluated the comparative efficacy and safety of several medications for adults with overweight and obesity who were seeking weight-loss management. The interventions assessed included semaglutide, liraglutide, phentermine/topiramate, bupropion/naltrexone, metformin, orlistat, exenatide, pramlintide, dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, ipragliflozin/metformin/pioglitazone, and sibutramine/levocarnitine. Inclusion criteria included randomized controlled trials evaluating a candidate weight-lowering drug in comparison to placebo, lifestyle modification, or an alternative drug. Studies were excluded if their outcomes did not focus on weight loss or quality of life measures and if they recruited patients with psychological disorders and eating disorders. Search terms for PubMed, Embase, and Cochrane Library searches included “weight loss,” “weight-loss drugs,” and “RCTs.” By March 2021, investigators identified 143 randomized controlled trials (N=49,810) for inclusion. Median age was 47, the proportion of females was 75%, median BMI was 35.3, and median duration of follow-up was 24 weeks. Data on the GLP-1 receptor agonists (semaglutide, liraglutide, and exenatide) were presented together.

Phentermine/topiramate (MD: -7.97; 95% CI: -9.28 to -6.66) and the GLP-1 receptor agonists (MD: 5.76; 95% CI: -6.30 to -5.21) were the most effective at helping participants achieve percentage and absolute body weight change from baseline, and all drugs except levocarnitine were associated with a reduction in body weight. For the categorical outcome of weight loss of at least 5% or 10% body weight, phentermine/topiramate, GLP-1 receptor agonists, and bupropion/naltrexone were the most effective at helping participants achieve these categorical outcomes, and more than doubled the proportion of participants receiving these interventions losing at least 5% or 10% body weight compared to participants who were receiving lifestyle modification alone. In post-hoc analyses, semaglutide (separate from the other GLP-1 agonists) demonstrated the largest percent weight loss (MD: -11.41; 95% CI: -12.54 to -10.27) and had the highest likelihood of achieving target weight loss of at least 5% and 10%. In terms of subgroup effects, participants receiving GLP-1 receptor agonists achieved a greater amount of weight loss if they were non-diabetic, compared to participants who had diabetes. However, this has low credibility due to inconsistency across studies.

Quality-of-life outcomes were available in 15 trials that looked at health-related quality of life scores, and in seven trials that assessed depression, and included the drugs phentermine/topiramate, bupropion/naltrexone, GLP-1 receptor agonists, and orlistat. All drugs in this network except orlistat helped improve quality of life, improvements in depression scores from

baseline were not statistically significant. For secondary outcomes, GLP-1 receptor agonists significantly reduced HbA1C levels when compared to lifestyle modification alone, and orlistat significantly reduced LDL cholesterol compared to lifestyle modification. GLP-1 receptor agonists and phentermine/topiramate were associated with the largest reductions in systolic blood pressure.

With regards to safety, phentermine/topiramate, bupropion/naltrexone, GLP-1 receptor agonists, and orlistat were associated with an increased risk of participants discontinuing due to adverse events. Between the drugs, bupropion/naltrexone and phentermine/topiramate were found to have the most discontinuations due to adverse events.

Investigators concluded that phentermine/topiramate and GLP-1 receptor agonists were most effective for weight loss, with high to moderate certainty of evidence, and demonstrated small benefits on quality-of-life outcomes. Evidence on other secondary outcomes were of low to very low certainty. Limitations included the lack of individual patient data pooling, which prevented more precise subgroup analyses, and heterogeneity in participant baseline characteristics and duration of follow-up.

Arastu, N., et al. (2022). “Efficacy of Subcutaneous Semaglutide Compared to Placebo for Weight Loss in Obese, Non-Diabetic Adults: A Systematic Review & Meta-Analysis”¹⁴³

Investigators conducted a systematic review and meta-analysis evaluating the efficacy of subcutaneous semaglutide in treating obesity in adults with overweight or obesity without diabetes, compared to placebo. Randomized controlled trials of adult participants with a BMI ≥ 27 kg/m² were included, and studies that included participants who were under 18 years of age or had type 1 or type 2 diabetes mellitus were excluded. EBSCOhost (including CINAHL Complete, Academic search Premier, MEDLINE, and Cochrane Central Register of Controlled Trials) was used for the literature search and included search terms such as “semaglutide,” “Wegovy,” “obesity,” and “overweight.” By August 31, 2021, investigators identified four studies (N=2,882) that met eligibility criteria and were included in quantitative synthesis. The mean age was 46 years. All studies were determined to have low risks of bias.

For the primary outcome of mean body weight loss, the mean difference of weight loss in participants receiving semaglutide versus placebo was -11.62 kg (95% CI: -13.03 to -10.21; $p < 0.00001$), indicating that semaglutide demonstrated a statistically significant reduction in weight loss compared to placebo. Additionally, the proportion of participants receiving semaglutide, who achieved weight loss of at least 5% was higher in all trials compared to placebo ($p < 0.001$). Semaglutide was also associated with a statistically significant reduction in waist circumference (MD: -9.16 cm; 95% CI: -9.91 to -8.40; $p < 0.00001$), and BMI (MD: -4.33 kg/m²; 95% CI: -4.88 to -3.78; $p < 0.00001$). Subgroup analyses between the semaglutide 2.4 mg dose and the 0.4 mg dose indicated no significant differences between the treatment doses.

While semaglutide was shown to be superior to placebo in helping reduce body weight in participants with overweight or obesity, investigators identified several potential limitations, including the limited number of studies, variability in type of lifestyle modification, and lack of long-term data on semaglutide.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Methods

Rationale for Not Including Certain Health States in the Base Case

We did not include cancer, osteoarthritis, joint surgery, or sleep apnea as separate Markov states in our model because: 1) the causal association between weight reduction and decreasing the incidence of cancer or osteoarthritis is uncertain, 2) any benefits of modest weight loss on cancer and osteoarthritis are estimated to be small relative to the cardiovascular benefits being assessed, 3) the impact of any improvement on cardiovascular outcomes from improvements in sleep apnea associated with weight loss would be captured from the changes in weight loss- and blood pressure-related cardiovascular disease and mortality, 4) the cost of treating sleep apnea, such as a continuous positive airway pressure machine, would have a negligible impact on the incremental cost, and 5) the short-term impact of weight loss on quality of life due to sleep apnea is inherently included as a utility gain associated with weight loss, measured directly in clinical trials but not explicitly stated as resulting from changes to sleep apnea.

Impact Inventory

Consistent with the recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine, the impact inventory of what was included in the base case and scenario analyses from the health care sector and societal perspectives, respectively, is shown in Table E1.¹⁴⁴

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from [...] Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	HRQoL effects	X	X	
	Adverse events	<input type="checkbox"/>	<input type="checkbox"/>	Evaluated, but did not include AEs. Expected that AEs would lead to treatment disc. early in therapy and not to significant costs or disutility.
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	Possibly	Possibly	Sources used for cost estimates provided comprehensive descriptions for what medical costs were included, but did not include whether out-of-pocket costs were included in estimates.
	Future related medical costs	X	X	
	Future unrelated medical costs	<input type="checkbox"/>	<input type="checkbox"/>	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	N/A	<input type="checkbox"/>	
	Unpaid caregiver-time costs	N/A	<input type="checkbox"/>	
	Transportation costs	N/A	<input type="checkbox"/>	
Non-Health Care Sector				
Productivity	Labor market earnings lost	N/A	X	
	Cost of unpaid lost productivity due to illness	N/A	X	
	Cost of uncompensated household production	N/A	<input type="checkbox"/>	
Consumption	Future consumption unrelated to health	N/A	<input type="checkbox"/>	
Social Services	Cost of social services as part of intervention	N/A	<input type="checkbox"/>	
Legal/Criminal Justice	Number of crimes related to intervention	N/A	<input type="checkbox"/>	
	Cost of crimes related to intervention	N/A	<input type="checkbox"/>	
Education	Impact of intervention on educational achievement of population	N/A	<input type="checkbox"/>	
Housing	Cost of home improvements, remediation	N/A	<input type="checkbox"/>	
Environment	Production of toxic waste pollution by intervention	N/A	<input type="checkbox"/>	
Other	Other impacts (if relevant)	N/A	<input type="checkbox"/>	

AE: adverse event, N/A: not applicable

Adapted from Sanders et al.¹⁴⁴

Description of evLY Calculations

The evLY considers any extension of life at the same “weight” no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

- 1) First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.¹⁴⁵
- 2) We calculate the evLY for each model cycle.
- 3) Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (Δ LY gained) within the cycle.
- 4) The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
- 5) The total evLY for a cycle is calculated by summing steps 3 and 4.
- 6) The evLY for the comparator arm is equivalent to the QALY for each model cycle.
- 7) The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

Model inputs were chosen based upon patient characteristics in clinical trials. Patient age, BMI, gender, SBP, smoking status, and presence of hypertension and diabetes mellitus were required inputs for calculating mortality and cardiovascular risk. Consistent with clinical trials and real-world evidence on users of medications for weight management, patients were 80% female with average age of 45 years, BMI of 38 kg/m², SBP of 125 mmHg, and HbA1C of 5.5% at model entry.^{31,41,51,53,59,77} The base-case model cohort characteristics are shown in Table E2.

Table E2. Base-Case Model Cohort Characteristics

	Value	Primary Sources
Mean Age	45 years	CONQUER, EQUIP, COR-I, SCALE, STEP 1, STEP 8 ^{31,41,51,53,59,77}
Mean BMI	38 kg/m ²	
Female	80.0%	
Mean SBP	125 mmHg	
Diagnosis of Hypertension (Actively Treated)	35.0%	
Diagnosis of Diabetes Mellitus	0%	Assumption for base case
Smoking	12.5%	CDC ¹⁴⁶

CDC: Centers for Disease Control and Prevention, BMI: body mass index, kg: kilogram, m: meter, mmHg: millimeter of mercury, SBP: systolic blood pressure

Treatment Strategies

- Semaglutide
 - Titration: 0.25 mg administered subcutaneously once weekly for the first four weeks, with the dose increased every four weeks to reach the maintenance dose of 2.4 mg by week 16
 - Maintenance dose: 2.4 mg administered subcutaneously once a week
- Liraglutide
 - Titration: Starting at a dose of 0.6 mg with weekly 0.6-mg increments to 3.0 mg
 - Maintenance dose: 3.0 mg administered subcutaneously once daily
- Phentermine/topiramate extended-release
 - Loading dose: 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg ER) daily for 14 days; then increase to the maintenance dose 1 and 2. Maintenance dose 2 is the target regimen of our study.
 - Maintenance dose 1: 7.5 mg/46 mg daily
 - Maintenance dose 2: 15 mg/92 mg daily
- Bupropion/naltrexone ER
 - Titration: Starting at a dose of 8 mg/90 mg once a day for a week, with weekly increases in 8 mg/90 mg increments until dose of 16 mg/180 mg twice daily is achieved at week four
 - Maintenance dose: 16 mg/180 mg twice daily (32 mg/360 mg per day)

E2. Model Inputs and Assumptions

Key model assumptions and rationales are presented in Table 4.1 of the Report. Additional model assumptions/rationales are listed in Table E3.

Table E3. Model Assumptions

Assumption	Rationale
Proportion of smokers does not vary over time	Smoking behavior has not been convincingly shown to be influenced by FDA-approved anti-obesity interventions. However, we do acknowledge that despite it not being a comparator or intervention in the base-case analysis, bupropion alone (Zyban®, GlaxoSmithKline) is approved for smoking cessation. This assumption may therefore result in an underestimation of bupropion's effect on cardiovascular events.
Proportion of actively treated hypertension is a function of BMI without a significant influence on the incremental cost-effectiveness ratio	BMI significantly influences the proportion of patients in need of hypertension treatment. Assuming hypertension treatment effectively manages overall SBP, average SBP would be similar across the treatment strategies over the model time horizon. The cost of hypertension medication is small and is therefore unlikely to influence the incremental cost-effectiveness ratio.
Inclusion of adverse events in the model would add significant complexity without providing much improvement in cost-effectiveness estimation or face validity to the model	Adverse events reported with these four medications occur early, are generally not severe in nature, and would normally not lead to appreciable treatment discontinuation as compared to inadequate weight loss response. However, we adjusted the cost of treatment by the probability of discontinuation to estimate the impact of early treatment discontinuation due to adverse events or lack of effectiveness.
Once patients develop diabetes mellitus, their diabetes care and associated diabetes outcomes is similar between those who are on weight management and those who are not	Although liraglutide and semaglutide affect blood glucose, the treatment pathways for diabetes mellitus in those who will have access to liraglutide and semaglutide would also include access to these treatments for diabetes mellitus, albeit potentially at a different dose. We assumed that diabetes treatment outcomes would not differ in patients with treatments that affect HbA1C versus those that did not.
In patients with hypertension, blood pressure is equally well managed across all weight loss treatments.	Weight loss treatments may affect blood pressure differently. The impact of treatments on reducing the likelihood of needing treatment for hypertension was included in the model. For those who continued to require treatment for hypertension, we assumed that all patients would have similar outcomes related to hypertension treatment.

BMI: body mass index, FDA: Food and Drug Administration, SBP: systolic blood pressure

Model Inputs

Clinical Inputs

The key model inputs are listed in Table 4.2 of the Report. Those inputs, plus additional inputs, are listed in Table E4.

Table E4. Key Model Inputs

Parameter	Input	Source
Clinical Inputs		
Absolute Difference in % Weight Change, SEM vs. LSM	-13.7%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, SEM vs. LSM	-0.30	STEP 1 ⁷⁷
Absolute Difference in % Weight Change, LIR vs. LSM	-5.0%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, LIR vs. LSM	-0.20	SCALE (Maintenance) ⁷⁸
Absolute Difference in % Weight Change, P/T vs. LSM	-9.1%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, P/T vs. LSM	0.00	EQUIP ^{51,53}
Absolute Difference in % Weight Change, B/N vs. LSM	-4.6%	ICER NMA, Table 3.11
Absolute Difference in HbA1C Change, B/N vs. LSM	-0.13	STEP 1 and STEP 2 ^{28,77}
Baseline Risk of CV Event, Female Non-Smoker without Treated HTN	0.04	Framingham Risk Calculation Coefficient ⁸²
Baseline Risk of CV Event, Male Smoker with Treated HTN	0.23	
Multiplier for Probability of MI from CV Risk	0.22	
Multiplier for Probability of Stroke from CV Risk	0.23	
Multiplier for Probability of Other CVD from CV Risk	0.55	
HbA1C Effect on the Annual Incidence of DM	$8.49 \times 10^{-6} \exp(1.58 \times \text{HbA1C})$	Exponential regression from Edelman et al. ⁷⁹
BMI Effect on the Annual Incidence of DM	$1.97 \times 10^{-2} \exp(0.101 \times \text{BMI})$	
Probability of Mortality Following Acute MI	0.08	OECD Statistics ¹⁴⁷
Probability of Mortality Following Acute Stroke	0.08	
Relative Risk of Annual Mortality Post-MI	1.58	Majed 2015 ⁷⁶
Relative Risk of Annual Mortality Post-Stroke	3.13	
Relative Risk of Annual Mortality with Other CVD	1.9	Pande 2011 ⁷⁴
Relative Risk of Annual Mortality Post-HF	1.82	Ødegaard 2020 ⁷⁵
Relative Risk of Annual Mortality Post-DM	1.15	Tancredi 2015 ⁷³
Annual Probability of Recurrent MI in Male	0.0813	Peters 2021 ¹⁴⁸
Annual Probability of Recurrent MI in Female	0.0723	
Annual Probability of Recurrent Stroke	0.12	Kolmos 2021 ¹⁴⁹
Proportion of Male Patients with Hypertension, BMI <25	0.14	Wang 2004 ¹⁵⁰
Proportion of Female Patients with Hypertension, BMI <25	0.164	
Proportion of Male Patients with Hypertension, BMI ≥25 to 30	0.268	
Proportion of Female Patients with Hypertension, BMI ≥25 to 30	0.292	
Proportion of Male Patients with Hypertension, BMI ≥30	0.431	
Proportion of Female Patients with Hypertension, BMI ≥30	0.42	
Probability of Developing HF from Acute MI, Age 25-54	0.0994	Sulo 2016 ⁸⁸

Parameter	Input	Source
Probability of Developing HF from Acute MI, Age 55-74	0.1648	
Probability of Developing HF from Acute MI, Age 75-85	0.268	
Annual probability of Developing HF Post MI, Age 25-54	0.012	
Annual probability of Developing HF Post MI, Age 55-74	0.031	
Annual probability of Developing HF Post MI, Age 75-85	0.080	
Comorbidity Cost Inputs		
Cost Other CVD	\$14,279	Scully 2017 ⁹¹
Cost Acute Stroke	\$17,316	HCUP ⁹²
Cost Post Stroke	\$6,500	Kazi 2019 ⁹³
Cost Acute MI	\$26,034	HCUP ⁹²
Cost Post MI	\$3,117	Kazi 2016 ⁹⁴
Cost HF	\$15,605	Patel 2021 ⁹⁵
Cost DM	\$11,425	ADA 2018 ⁹⁶

BMI: body mass index, B/N: bupropion/naltrexone, CV: cardiovascular, CVD: cardiovascular disease, DM: diabetes mellitus, HbA1C: glycated hemoglobin, HF: heart failure, HTN: hypertension, ICER: Institute for Clinical and Economic Review, LIR: liraglutide, LSM: lifestyle modification, NMA: network meta-analysis, P/T: phentermine/topiramate, SEM: semaglutide

Clinical Probabilities/Response to Treatment

Response to treatment was determined from clinical trials evaluating drug treatments plus lifestyle modification versus lifestyle modification alone or compared with other treatments, where such studies existed.^{31,51,53,59,77,78} The primary outcome evaluated for this model was weight change relative to the comparator, evaluated using the NMA depicted in Table 3.11 of the Report. A secondary outcome, needed for determining the proportion of people developing diabetes mellitus each cycle, was mean reduction in HbA1C.

Mortality

For patients without pre-existing comorbidities, mortality was estimated from age- and gender-adjusted mortality rates in the general population, using all-cause mortality from the Human Mortality Database US-specific tables.⁹⁰ This mortality probability was multiplied by the relative risk for mortality for each post-event state, specifically post-myocardial infarction, post-stroke, other cardiovascular disease, and heart failure.⁷³⁻⁷⁶ In addition, mortality from the acute myocardial infarction and acute stroke events was also factored into the model.¹⁴⁷

Adverse Events

Adverse events were not considered in the model, as adverse events of weight loss medications were unlikely to generate measurable health care costs or health utility losses. The costs of treatment were adjusted in sensitivity analyses to estimate the impact of patient discontinuation for lack of effect on the cost of care.

Economic Inputs

Administration and Monitoring Costs

Administration costs were determined to be nominal for these injectable and oral products, which are administered at home. The injectable products, semaglutide and liraglutide, are dispensed as single-use subcutaneous injection pens. Monitoring costs were also determined to be nominal and were not included in the model. Table E5 presents the dose, frequency, and route of administration as well as monitoring and administration utilization of each intervention.

Table E5. Dose, Frequency of Administration, and Annual Monitoring and Administration Utilization

Intervention	Route	Dose	Frequency of Administration
Semaglutide	Subcutaneous	2.4 mg	Weekly
Liraglutide	Subcutaneous	3 mg	Daily
Phentermine/ Topiramate	Oral	15 mg/92 mg	Daily
Bupropion/ Naltrexone	Oral	32 mg/360 mg	Daily

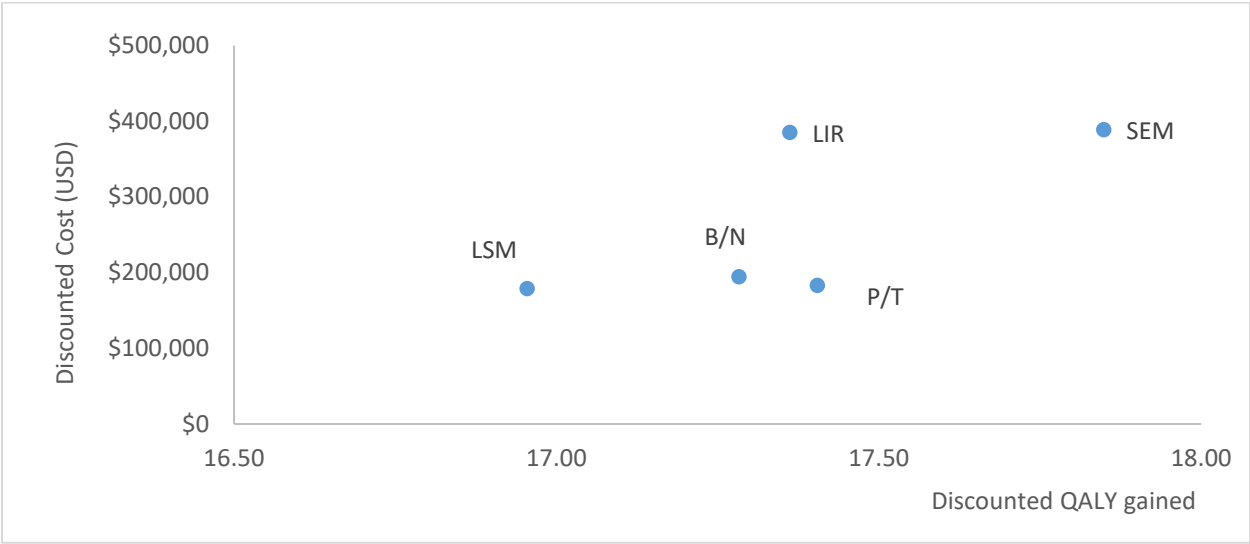
mg: milligram

E3. Results

Cost-Effectiveness Plane

Figure E1 presents the cost-effectiveness plane. The x-axis represents therapy benefit and the y-axis represents cost. Each point in the plane represents the estimated cost and effectiveness in the base-case result for a particular therapy option added to lifestyle modification.

Figure E1. Cost-Effectiveness Plane



B/N: bupropion/naltrexone, LIR: liraglutide, LSM: lifestyle management, P/T: phentermine/topiramate, QALY: quality-adjusted life year, SEM: semaglutide, USD: United States Dollar

Undiscounted Base-Case Results

Discounted base-case results and incremental results are presented in Report Tables 4.4 and 4.5. The undiscounted base case results are presented in Table E6. The undiscounted incremental results compared to lifestyle modification are shown in Table E7.

Table E6. Undiscounted Base-Case Results

Treatment	Drug Cost	Non-Drug Cost	Total Cost	Life Years	QALYs	evLYs
Semaglutide	\$458,600	\$212,900	\$671,500	34.14	28.73	28.76
Liraglutide	\$403,800	\$266,300	\$670,100	33.64	27.73	27.76
Phentermine/Topiramate	\$65,100	\$280,400	\$345,500	33.62	27.78	27.81
Bupropion/Naltrexone	\$83,000	\$280,600	\$363,600	33.54	27.56	27.58
Lifestyle Modification*	\$18,300	\$323,100	\$341,400	33.19	26.91	26.91

evLY: equal value life year, QALY: quality-adjusted life year

*Reference for evLY calculation for all active treatments.

Table E7. Undiscounted Incremental Results for the Base Case

Treatment	Incremental Values vs. Lifestyle Modification					
	Drug Cost	Non-Drug Cost	Total Cost	Life Years	QALYs	evLYs
Semaglutide	\$440,300	-\$110,200	\$330,100	0.95	1.82	1.85
Liraglutide	\$385,500	-\$56,800	\$328,700	0.45	0.82	0.85
Phentermine/Topiramate	\$46,800	-\$42,700	\$4,100	0.43	0.87	0.90
Bupropion/Naltrexone	\$64,700	-\$42,500	\$22,200	0.35	0.65	0.67
Lifestyle Modification*	--	--	--	--	--	--

evLY: equal value life year, QALY: quality-adjusted life year

*Reference for incremental calculation for all active treatments.

Key incremental cost per QALY ratios over the lifetime horizon are shown in Table 4.6 of the Report for each of the obesity treatment strategies. All calculated incremental ratios over the lifetime horizon between treatment options included in our model are shown in Table E8.

Table E8. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per Life Year Gained	Cost per QALY Gained	Cost per evLY Gained
Semaglutide	Lifestyle modification	\$615,000	\$234,000	\$231,000
Liraglutide	Lifestyle modification	\$1,262,000	\$506,000	\$496,000
Phentermine/Topiramate	Lifestyle modification	\$26,000	\$9,000	\$9,000
Bupropion/Naltrexone	Lifestyle modification	\$122,000	\$47,000	\$46,000
Semaglutide	Liraglutide	\$19,100	\$7,000	\$7,000
	Phentermine/topiramate	\$1,107,000	\$463,000	\$459,000
	Bupropion/naltrexone	\$909,000	\$343,000	\$341,000
Liraglutide	Phentermine/topiramate	\$24,803,000	P/T less costly, more effective	P/T less costly, more effective
	Bupropion/naltrexone	\$5,300,000	\$2,424,000	\$2,378,000
Phentermine/Topiramate	Bupropion/naltrexone	P/T less costly, more effective	P/T less costly, more effective	P/T less costly, more effective

evLY: equal value life year, PT: phentermine/topiramate, QALY: quality-adjusted life year

E4. Sensitivity Analyses

One-Way Sensitivity Analysis

The model was sensitive to several inputs, including the disutility per BMI change, baseline HbA1C, cost of diabetes mellitus management, baseline BMI, weight-lowering effect of treatment compared to lifestyle management, and change in HbA1c with treatment. The one-way sensitivity analysis results and tornado diagrams for each treatment option are presented in Table E9 on the following page.

Table E9. Tornado Diagram Inputs and Results for One-Way Sensitivity Analyses (by Incremental Cost-Effectiveness Ratio)†

SEM vs. LSM					
Input Variable	Lower Input	Higher Input	Lower Input ICER	Higher Input ICER	
Disutility per BMI change	-0.00555	-0.00111	\$194,000	\$297,000	
Baseline HbA1C	5.1	5.85	\$321,000	\$227,000	
Cost of DM	\$7,501	\$17,418	\$255,000	\$203,000	
Baseline BMI	35	40	\$268,000	\$219,000	
Difference in % Weight Change, SEM vs. LSM	-0.14974	-0.12466	\$218,000	\$254,000	
Difference in HbA1C between SEM and LSM	-0.33018	-0.26982	\$227,000	\$242,000	
Relative Risk of Mortality for Other CVD	1.3	2.8	\$240,000	\$228,000	
Relative Risk of Mortality for Stroke	1.98	4.92	\$240,000	\$229,000	
Age-Related Disutility	-0.0009	-0.0005	\$238,000	\$231,000	
Probability of Stroke Occurring in Those with CV	0.18793	0.274094	\$236,000	\$232,000	
Relative Risk of Mortality for MI	1.18	2.12	\$236,000	\$232,000	
SEM Treatment Discontinuation Rate	0.048	0.058	\$236,000	\$233,000	
Relative Risk of Mortality for DM	1.14	1.16	\$236,000	\$233,000	
Proportion Female	0.741	0.817504	\$232,000	\$235,000	
Cost of Other CVD	\$10,056	\$18,498	\$236,000	\$233,000	
Probability of Mortality for Acute MI	0.05274	0.098482	\$235,000	\$234,000	
Life-Course BMI Trajectory, Annual	0	0.004	\$234,000	\$236,000	
Probability of Mortality for Acute Stroke	0.05605	0.102826	\$235,000	\$234,000	
Proportion of CV events that are MIs	0.18032	0.265386	\$235,000	\$234,000	
Cost of HF	\$10,098	\$24,115	\$235,000	\$234,000	
LRG vs. LSM					
Input Variable	Lower Input	Higher Input	Lower Input ICER	Higher Input ICER	
Disutility per BMI change	-0.00555	-0.00111	\$437,000	\$601,000	
Difference in % Weight Change, LIR vs. LSM	-0.061	-0.039	\$442,000	\$591,000	
Baseline HbA1C	5.1	5.85	\$653,000	\$505,000	
Difference in HbA1C between LIR and LSM	-0.23018	-0.16982	\$473,000	\$544,000	
Baseline BMI	35	40	\$554,000	\$489,000	
Cost of DM	\$7,501	\$17,418	\$531,000	\$469,000	
Relative Risk of Mortality for Other CVD	1.3	2.8	\$521,000	\$491,000	
Relative Risk of Mortality for Stroke	1.98	4.92	\$520,000	\$494,000	
Age-Related Disutility	-0.0009	-0.0005	\$514,000	\$499,000	
Life-Course BMI Trajectory, Annual	0	0.004	\$506,000	\$521,000	
Probability of Stroke Occurring in Those with CV	0.18793	0.274094	\$511,000	\$502,000	
Relative Risk of Mortality for MI	1.18	2.12	\$511,000	\$501,000	
Relative Risk of Mortality for DM	1.14	1.16	\$510,000	\$502,000	
LIR Treatment Discontinuation Rate	0.02	0.03	\$509,000	\$503,000	
Proportion Female	0.741	0.817504	\$502,000	\$508,000	
Probability of Mortality for Acute MI	0.05274	0.098482	\$508,000	\$504,000	
Probability of Mortality for Acute Stroke	0.05605	0.102826	\$508,000	\$504,000	
Baseline Age	44.4246	45.57539	\$508,000	\$505,000	
Proportion of CV events that are MIs	0.18032	0.265386	\$508,000	\$505,000	
Cost of Other CVD	\$10,056	\$18,498	\$507,000	\$505,000	

P/T vs. LSM					
Input Variable	Lower Input	Higher Input	Lower Input ICER	Higher Input ICER	
Cost of DM	\$7,501	\$17,418	-\$15,000	\$25,000	
Difference in % Weight Change, P/T vs. LSM	-0.111	-0.0715	-\$2,000	\$26,000	
Baseline HbA1C	5.1	5.85	\$27,000	\$8,000	
Baseline BMI	35	40	\$17,000	\$5,000	
Disutility per BMI Change	-0.00555	-0.00111	\$7,000	\$12,000	
Cost of Other CVD	\$10,056	\$18,498	\$10,000	\$8,000	
Life-Course BMI Trajectory, Annual	0	0.004	\$9,000	\$11,000	
Cost of HF	\$10,098	\$24,115	\$9,000	\$8,000	
Relative Risk of Mortality for Other CVD	1.3	2.8	\$8,000	\$9,000	
P/T Treatment Discontinuation Rate	0.039	0.049	\$9,000	\$8,000	
Relative Risk of Mortality for Stroke	1.98	4.92	\$8,000	\$9,000	
Cost of Acute MI	\$16,462	\$41,171	\$9,000	\$8,000	
Cost of Acute Stroke	\$11,153	\$26,886	\$9,000	\$9,000	
Proportion of CV Events that are Strokes	0.188	0.274	\$9,000	\$9,000	
Cost of Post Stroke	\$5,418	\$7,801	\$9,000	\$9,000	
Proportion Female	0.741	0.818	\$9,000	\$9,000	
Relative Risk of Mortality for MI	1.18	2.12	\$9,000	\$9,000	
LSM Treatment Discontinuation Rate	0.017	0.027	\$9,000	\$9,000	
Age-Related Disutility	-0.0009	-0.0005	\$9,000	\$9,000	
Cost of Post MI	\$2,598	\$3,741	\$9,000	\$9,000	
B/N vs. LSM					
Input Variable	Lower Input	Higher Input	Lower Input ICER	Higher Input ICER	
Cost of DM	\$7,501	\$17,418	\$70,000	\$12,000	
Difference in % Weight Change, B/N vs. LSM	-0.0604	-0.0311	\$29,000	\$76,000	
Baseline HbA1C	5.1	5.85	\$82,000	\$47,000	
Disutility per BMI Change	-0.00555	-0.00111	\$40,000	\$58,000	
Baseline BMI	35	40	\$58,000	\$43,000	
Difference in HbA1C between B/N and LSM	-0.13872	-0.11128	\$42,000	\$53,000	
Life-Course BMI Trajectory, Annual	0	0.004	\$47,000	\$50,000	
Cost of Other CVD	\$10,056	\$18,498	\$48,000	\$46,000	
B/N Treatment Discontinuation Rate	0.063	0.073	\$48,000	\$46,000	
Relative Risk of Mortality for Other CVD	1.3	2.8	\$48,000	\$46,000	
Age-Related Disutility	-0.0009	-0.0005	\$48,000	\$47,000	
Relative Risk of Mortality for Stroke	1.98	4.92	\$48,000	\$47,000	
Cost of HF	\$10,098	\$24,115	\$48,000	\$47,000	
Cost of Acute MI	\$16,462	\$41,171	\$47,000	\$47,000	
Cost of Acute Stroke	\$11,153	\$26,886	\$47,000	\$47,000	
Proportion Female	0.741	0.818	\$47,000	\$47,000	
Relative Risk of Mortality for DM	1.14	1.16	\$47,000	\$47,000	
Relative Risk of Mortality for MI	1.18	2.12	\$47,000	\$47,000	
Cost of Post Stroke	\$5,418	\$7,801	\$47,000	\$47,000	
LSM Treatment Discontinuation Rate	0.017	0.027	\$47,000	\$47,000	

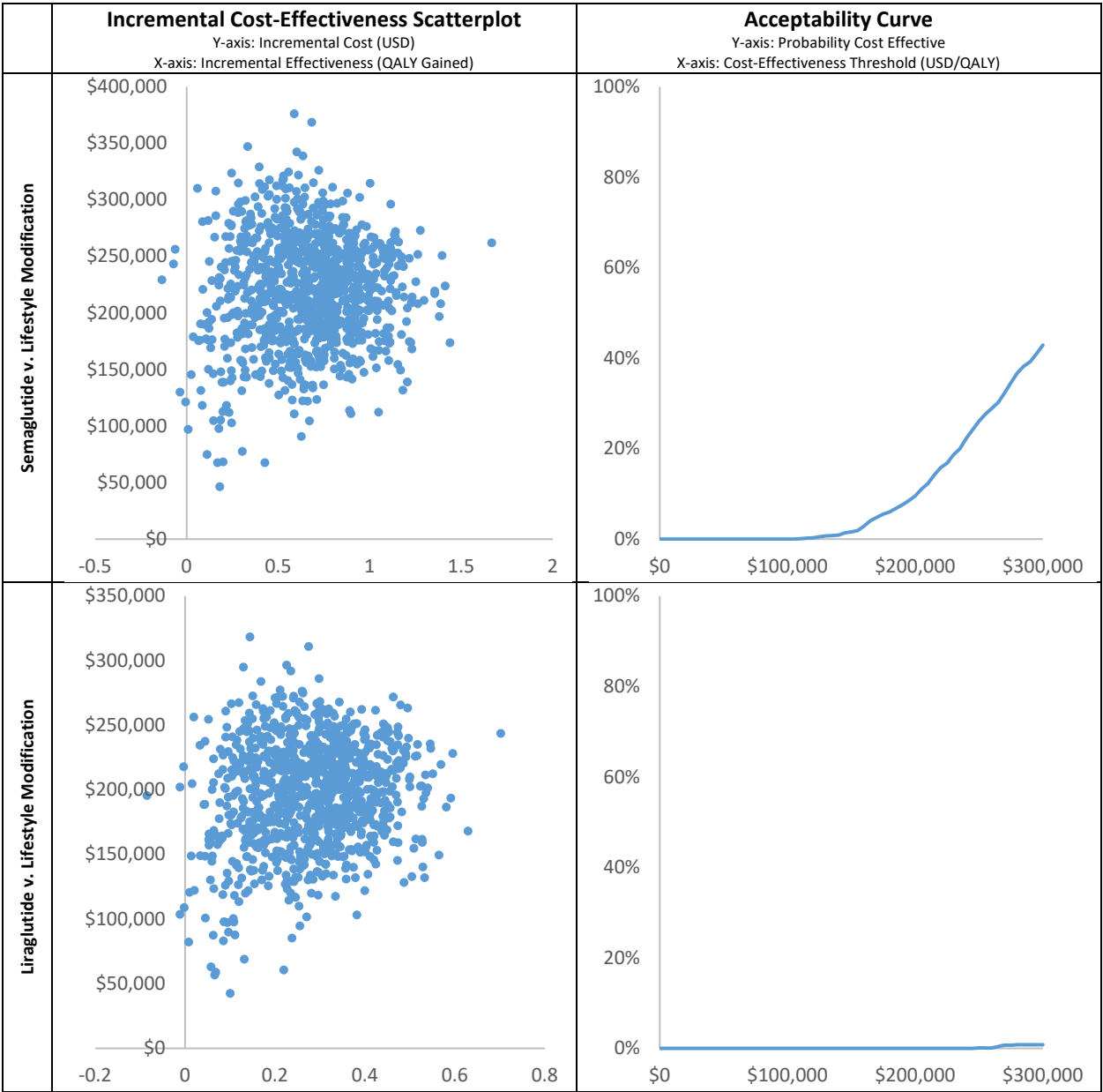
BMI: body mass index, B/N: bupropion/naltrexone, CV: cardiovascular, CVD: cardiovascular disease, DM: diabetes mellitus, Hb: hemoglobin, HF: heart failure, ICER: incremental cost-effectiveness ratio, LIR: liraglutide, LSM: lifestyle modification, MI: myocardial infarction, P/T: phentermine/topiramate, SEM: semaglutide

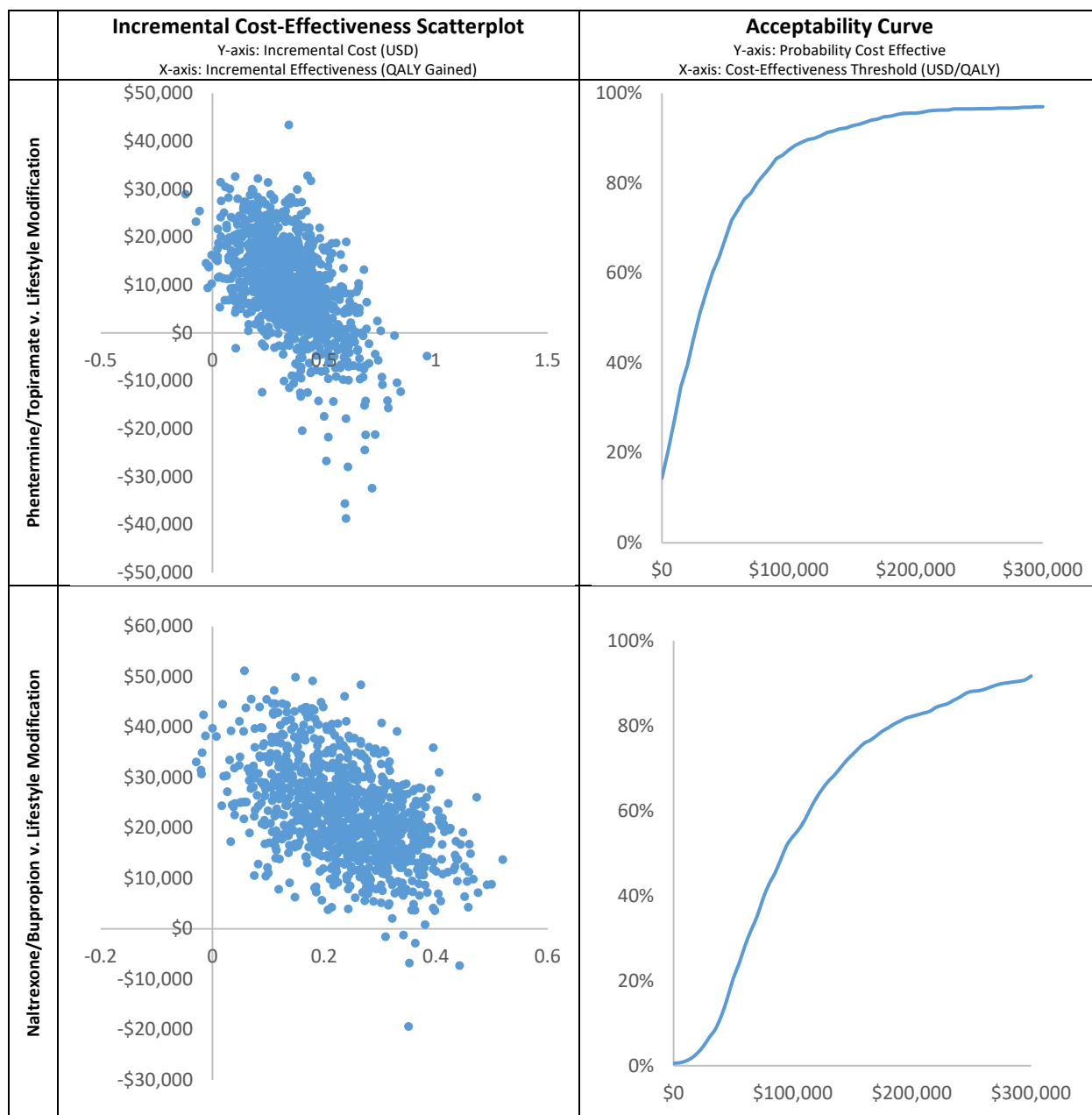
*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output. *In the tornado diagram, blue bars denote effects from low input estimates, while green bars denote effects from high input estimates.

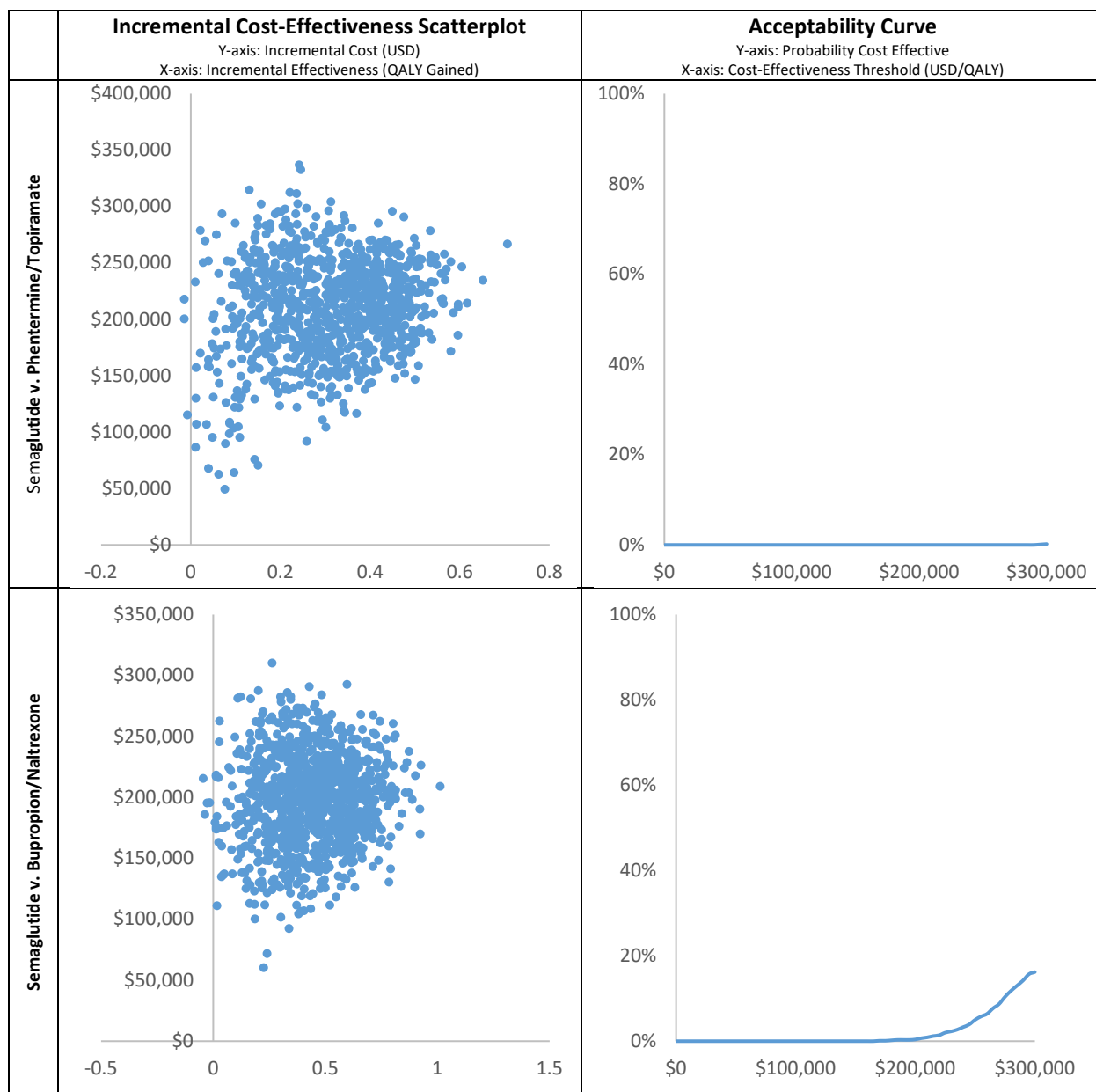
Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis results are presented in the Report. Additional results, including incremental cost-effectiveness scatterplots and acceptability curves are presented in Figure E2.

Figure E2. Results of Probabilistic Sensitivity Analysis, Incremental Cost-Effectiveness Scatterplots and Acceptability Curve







E5. Scenario Analyses

Key scenario analysis results are presented in the Report. Additional results for the societal perspective scenario analyses are presented by incremental cost per outcome gained in Table E10. Changes to inputs for Comorbidity X scenarios are presented in Table E11 whereas cost per life year, QALY, and evLY gained results of the Comorbidity X scenarios are presented in Tables E12, E13, and E14 respectively.

Table E10. Societal Perspective Incremental Cost-Effectiveness Ratios

Treatment	Comparator	Cost per Life Year Gained	Cost per QALY Gained	Cost per evLY Gained
Semaglutide	Lifestyle modification	\$559,000	\$213,000	\$210,000
Liraglutide	Lifestyle modification	\$1,204,000	\$482,000	\$472,000
Phentermine/Topiramate	Lifestyle modification	P/T less costly, more effective		
Bupropion/Naltrexone	Lifestyle modification	\$62,000	\$24,000	\$24,000
Semaglutide	Liraglutide	SEM less costly, more effective		
	Phentermine/topiramate	\$1,047,000	\$438,000	\$434,000
	Bupropion/naltrexone	\$855,000	\$323,000	\$320,000
Liraglutide	Phentermine/topiramate	\$24,557,000	P/T less costly, more effective	P/T less costly, more effective
	Bupropion/naltrexone	\$5,234,000	\$2,394,000	\$2,349,000
Phentermine/Topiramate	Bupropion/naltrexone	P/T less costly, more effective		

evLY: equal-value life year, P/T: phentermine/topiramate, QALY: quality-adjusted life year, SEM: semaglutide

Table E11. Inputs for Comorbidity X Scenarios

Parameter	Input	Source
Cancer Inputs		
Annual Incidence of Cancer for Ages 40-49 years	0.28%	White 2014 ¹⁵¹
Annual Incidence of Cancer for Ages 50-59 years	0.68%	
Annual Incidence of Cancer for Ages 60-69 years	1.39%	
Annual Incidence of Cancer for Ages 70-79 years	1.95%	
Annual Incidence of Cancer for Ages ≥ 80 years	1.83%	
Relative Risk of Cancer per One Unit Increase in BMI	1.04	Munsell 2014 ¹⁵²
Relative Risk of Death with Cancer	3.73	Kim 2022 ⁹⁸
Annual Cost of Cancer	\$15,756	
CKD Inputs		
Annual Incidence of CKD for BMI Range 25-30	0.32%	Mohammedi 2018 ¹⁵³
Annual Incidence of CKD for BMI Range 30-35	0.37%	
Annual Incidence of CKD for BMI Range 35-40	0.51%	
Annual Incidence of CKD for BMI Range 40-45	0.79%	
Relative Risk of Death with CKD	2.48	USRDS 2015 ¹⁵⁴
Annual Cost of CKD	\$12,497	USRDS 2021 ¹⁵⁵

BMI: body mass index, CKD: chronic kidney disease

Table E12. Comorbidity X Scenario Analysis (Cost per Life Year Gained)

Treatment	Comparator	Base-Case Results	BMI-Cancers	BMI-CKD
Semaglutide	Lifestyle modification	\$615,000	\$473,000	\$496,000
Liraglutide	Lifestyle modification	\$1,262,000	\$1,017,000	\$1,040,000
Phentermine/Topiramate	Lifestyle modification	\$26,000	\$16,000	\$11,000
Bupropion/Naltrexone	Lifestyle modification	\$122,000	\$95,000	\$92,000
Semaglutide	Liraglutide	\$19,000	\$16,000	\$13,000
	Phentermine/topiramate	\$1,107,000	\$950,000	\$1,037,000
	Bupropion/naltrexone	\$909,000	\$694,000	\$750,000
Liraglutide	Phentermine/topiramate	\$24,803,000	P/T less costly, more effective	P/T less costly, more effective
	Bupropion/naltrexone	\$5,300,000	\$4,937,000	\$5,341,000
Phentermine/Topiramate	Bupropion/naltrexone	P/T less costly, more effective		

BMI: body mass index, CKD: chronic kidney disease, P/T: phentermine/topiramate

Table E13. Comorbidity X Scenario Analysis (Cost per QALY Gained)

Treatment	Comparator	Base-Case Results	BMI-Cancers	BMI-CKD
Semaglutide	Lifestyle modification	\$234,000	\$212,000	\$209,000
Liraglutide	Lifestyle modification	\$506,000	\$466,000	\$457,000
Phentermine/Topiramate	Lifestyle modification	\$9,000	\$7,000	\$5,000
Bupropion/Naltrexone	Lifestyle modification	\$47,000	\$43,000	\$40,000
Semaglutide	Liraglutide	\$7,000	\$7,000	\$5,000
	Phentermine/topiramate	\$463,000	\$439,000	\$451,000
	Bupropion/naltrexone	\$343,000	\$309,000	\$311,000
Liraglutide	Phentermine/topiramate	P/T less costly, more effective		
	Bupropion/naltrexone	\$2,486,000	\$2,392,000	\$2,486,000
Phentermine/Topiramate	Bupropion/naltrexone	P/T less costly, more effective		

BMI: body mass index, CKD: chronic kidney disease, QALY: quality-adjusted life year

Table E14. Comorbidity X Scenario Analysis (Cost per evLY Gained)

Treatment	Comparator	Base Case Results	BMI-Cancers	BMI-CKD
Semaglutide	Lifestyle modification	\$231,000	\$207,000	\$206,000
Liraglutide	Lifestyle modification	\$496,000	\$452,000	\$445,000
Phentermine/Topiramate	Lifestyle modification	\$9,000	\$7,000	\$5,000
Bupropion/Naltrexone	Lifestyle modification	\$46,000	\$42,000	\$39,000
Semaglutide	Liraglutide	\$7,000	\$7,000	\$5,000
	Phentermine/topiramate	\$459,000	\$433,000	\$447,000
	Bupropion/naltrexone	\$341,000	\$304,000	\$307,000
Liraglutide	Phentermine/topiramate	P/T less costly, more effective		
	Bupropion/naltrexone	\$2,378,000	\$2,330,000	\$2,427,000
Phentermine/Topiramate	Bupropion/naltrexone	P/T less costly, more effective		

BMI: body mass index, CKD: chronic kidney disease, P/T: phentermine/topiramate

E6. Heterogeneity and Subgroups

There are patient-specific factors that may affect treatment response in patients with overweight or obesity. Our model was not specifically designed to test the cost effectiveness of weight-management in patients with diabetes mellitus. We continue to explore how the cost effectiveness is impacted by population characteristics including the average BMI prior to initiating treatment.

E7. Prior Economic Models

Our study adapted structurally-advanced prior economic models that focused on causal associations between BMI and cardiovascular comorbidities. Borisenko et al. developed a bariatric surgery Markov model in which the natural course of weight-related cardiovascular conditions was included as separate Markov states.^{84,85,156-158} A recently developed model linked BMI and glucose intolerance with the onset of diabetes mellitus and cardiovascular complications.¹⁵⁹ Similar to our model, both models incorporated the Framingham risk equation as a predictor of cardiovascular comorbidity onset. Due to ongoing uncertainty around the causal association between weight loss and non-cardiovascular comorbidities, the bariatric surgery Markov model excluded cancer, osteoarthritis, sleep apnea, and chronic kidney disease. In our model, we tested the potential influence of the non-cardiovascular conditions on the cost effectiveness using an add-on Comorbidity X state. This structural adaptation to the model, with the inclusion of conditions not evaluated in the base case, could be considered as an advanced method of scenario analysis in situations with limited evidence regarding exposure-outcome association.

Additionally, we critically evaluated economic models involving GLP-1 receptor agonists in the US health care setting. Lee et al. analyzed the cost effectiveness of medication-assisted weight loss options using treatment cost and BMI-dependent quality of life without including comorbid states in the model.¹⁶⁰ Similar to our findings, this study concluded that 1) phentermine/topiramate was

the most cost-effective strategy; 2) patients on semaglutide gained the largest clinical and QALY benefits; 3) liraglutide was dominated by phentermine/topiramate and semaglutide. These conclusions regarding semaglutide and liraglutide were supported by a recent analysis of four GLP-1 receptor agonists.¹⁶¹ A more detailed comparison of findings could not be made because the structure of the two previous models notably differed from our model.

Another recent publication analyzed the cost effectiveness of medication-assisted weight loss treatment strategies compared to lifestyle modification.⁹⁸ The study adapted a model to evaluate the cost effectiveness of semaglutide 2.4 mg for the treatment of adult patients with overweight or obesity. The Markov model examined semaglutide compared to no treatment, diet and exercise alone, and standard-of-care therapy options (liraglutide 3 mg, phentermine/topiramate, and bupropion/naltrexone) from the US third-party payer's perspective over a 30-year time horizon. Treatment duration with any therapy (aside from diet and exercise) did not exceed two years, after which a gradual weight regain to baseline was applied to address natural weight gain until the end of the time horizon. In the model, patients could transition between no comorbidity, single comorbidity, dual comorbidity, multi-comorbidity, and death. Comorbidities included in the model were post-myocardial infarction, type 2 diabetes mellitus, post-stroke, obstructive sleep apnea, and cancer. Patients could experience acute events of bariatric surgery, acute coronary syndrome, stroke/transient ischemic attack, and knee replacements. In this study, the base-case incremental cost-effectiveness ratios (cost per QALY) from this model for semaglutide 2.4 mg compared to liraglutide 3 mg, phentermine/topiramate, bupropion/naltrexone, diet and exercise, and no treatment were \$23,556, \$144,296, \$127,518, \$122,549, and \$27,113, respectively. Liraglutide 3 mg, phentermine/topiramate, and bupropion/naltrexone compared to diet and exercise resulted in incremental cost-effectiveness ratios of \$439,200, \$32,700, and \$86,500. In an exercise assessing how our model results compared with those of this published model, we edited our model to include a two-year treatment, 30-year time horizon, and used disutilities for cardiovascular events and diabetes mellitus reported in this study.⁹⁸ The resulting incremental cost-effectiveness ratio estimates for semaglutide compared with lifestyle modification from our model were approximately \$10,000 per QALY gained less than the same comparison reported by Kim N et al. This remaining difference is explained by structural differences, higher mortality leading to lower QALY gains, and other differences in inputs not modeled in our validation exercise. Due to concerns associated with attributing long-term benefits to a short-term (i.e., two-year) treatment and the likely poor performance of the ACC/AHA models in predicting cardiovascular risk after discontinuation of short-term treatment as well as the potential risks of weight cycling, we chose to focus solely on evaluating the cost effectiveness of lifetime treatment.^{162,163}

Additional differences noted between these two models included the incorporation of certain cancers, sleep apnea, and the acute events of bariatric surgery and knee replacements.⁹⁸ We evaluated the potential impact of cancers and chronic kidney disease in scenario analyses. In our Comorbidity X scenarios, we determined that conditions other than cardiovascular conditions likely

have a nominal impact on incremental cost-effectiveness ratios. Additionally, we were unable to assess differences in the application of risk equations to models. For example, Kim et al. utilized Framingham Recurring Coronary Heart Disease and United Kingdom Prospective Diabetes Study risk equations within their model structure, whereas we used the ACC/AHA risk equation model, which incorporates updated estimates from Framingham but not changes in cardiovascular risk due to HbA1C. Finally, treatment efficacy inputs were derived directly from clinical trials in this published analysis, whereas our analysis involved conducting an NMA to derive the primary effectiveness inputs.

F. Potential Budget Impact: Supplemental Information

Methods

The primary aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected semaglutide prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2022-2023, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately [\\$777 million per year](#) for a novel prescription drug therapy.

Potential budget impact was defined as the total differential cost of using semaglutide rather than relevant existing therapy (alone) for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs (for instance, due to offsets in major adverse cardiovascular events). All costs were undiscounted and estimated over one- and five-year-time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy. This longer-term budget impact horizon of five years is aligned with the durable treatment persistence assumption key to our underlying cost-effectiveness analytic approach.

To estimate the size of the potential candidate populations for treatment, we use the US adult population size and prevalence of obesity and overweight in conjunction specific weight-related comorbidities or biomarkers for such. Specifically, we utilize deidentified and merged patient records from the National Health and Nutrition Examination Survey (NHANES) over the 2017-2018 and 2019-March 2020 data collection cycles for estimates of prevalence. NHANES is a program combining interviews and physical examinations to assess health and nutritional status among US adults and children. To determine size of the salient cohort with overweight and with weight-related comorbidities specifically, we use the following patient-level data as captured within NHANES, where patient records must have evidence of one or more of the following in addition to reporting with overweight (defined as $27.0 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$): 1) Ever told you have high blood pressure, 2) Ever told you have high cholesterol, 3) Ever told you have prediabetes, 4) HbA1C $\geq 6.5\%$, 5) Ever told you have diabetes, 6) Insulin level ≥ 23 microunits/mL, and 7) Stop breathing three or more nights a week. Accordingly, we estimate a combined prevalence value for US adults with BMI ≥ 30 or $27.0 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$ with one or more weight-related comorbidities at 53.53% (41.96% with obesity, 11.57% with overweight and one or more weight-related comorbidities). Semaglutide captures market share proportionally from all modeled comparators (liraglutide, phentermine/topiramate, bupropion/naltrexone, lifestyle modification alone), with semaglutide

achieving 100% market share by year five. This is a key modeling assumption aimed at understanding the proportion of the total population that can be treated without crossing the annual budget impact threshold.

Results

Table F1 describes the per-patient budget impact calculations in more detail, based on WAC (\$17,597.48 per year), discounted WAC (\$13,618.22 per year), and the prices to reach \$150,000, \$100,000, and \$50,000 per QALY (\$9,800, \$7,600, and \$5,300 per year, respectively) compared lifestyle modification alone. Similarly, Figure F1 visualizes semaglutide’s cumulative net budget impact per treated patient per year at its calculated net price, assuming an incremental 20% uptake per year.

Table F1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	\$150,000/QALY	\$100,000/QALY	\$50,000/QALY
Semaglutide	\$12,900	\$9,100	\$5,600	\$3,400	\$1,300

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Figure F1. Cumulative Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

