Semaglutide and Tirzepatide for Obesity: Effectiveness and Value

Evidence Report
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Prepared for

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

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Grace Lin served as the lead author for the report. Shahariar Mohammed Fahim led the systematic review and authorship of the comparative effectiveness section of this report with assistance from Finn Raymond. Woojung Lee developed the cost-effectiveness model and authored corresponding sections of the report with support from Marina Richardson. Marie Phillips conducted the analysis for the budget impact model. David Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Becca Piltch, Anna Geiger, and Grace Ham for their contributions to this report.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2025/04/ICER_Obesity_Stakeholder-List_For-Publication_052925.pdf

Conflict of Interest Disclosures for the Report

Table 1. ICER Staff and External Collaborators Conflict of Interest Disclosures

ICER Staff and External Collaborators	Conflict of Interest
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Marie Phillips, BA, Health Economics Research Assistant, Institute for Clinical and Economic Review	No conflicts to disclose.
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Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures

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Michele Tedder, MSN, RN, Director of Chronic Disease, Black Women's Health Imperative	Michele Tedder is an Obesity Action Coalition board member.
Dan Touchette, PharmD, MA, Professor, University of Illinois, Chicago	No conflicts to disclose.
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List of Acronyms and Abbreviations Used in this Report

6MWT	6 minute walk test
ACE	American College of Endocrinology
AACE	American Association of Clinical Endocrinologists
AE	Adverse event
AGA	American Gastroenterology Association
AHI	Apnea-hypopnea index
AHRQ	Agency for Healthcare Research and Quality
AIAN	American Indian or Alaskan Native
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BMI	Body mass index
CE	Cost-effectiveness
CDR	Clinical trial Diversity Rating
CI	Confidence interval
CKD	Chronic kidney disease
CM	Centimeter
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CV	Cardiovascular
CV	Coefficient of variation
CVOT	Cardiovascular outcomes trial
DEXA	Dual energy X-ray absorptiometry
DGT	Dulaglutide
DM	Type 2 diabetes
DSU	Decision Support Unit
EDS	Excessive Daytime Sleepiness
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
EQ-5D-5L	EuroQol-5 Dimension-5 Level
ESKD	End-stage kidney disease
evLY	Equal-value life year
evLYG	Equal-value life year gained
G3-4	Grade 3-4
G	Gram
GERD	Gastroesophageal Reflux Disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GIP RA	Glucose-dependent insulinotropic polypeptide receptor agonist
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonists
HbA1C	Hemoglobin A1C
HDL	High-density lipoprotein
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HIDI	Health Improvement Distribution Index
HR	Hazard ratio
HRQoL	Health-related quality of life
hsCRP	high-sensitivity C-reactive protein

HTN	Hypertension
ICER MA	ICER's Meta Analysis
IQR	Interquartile range
ITT	Intention-to-treat
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	Kilogram
kg/m^2	Kilogram per square meter
LDL	Low-density lipoprotein
LSM	Lifestyle modification
LVEF	Left ventricular ejection fraction
M	Meter
MACE	Major adverse cardiovascular events
MASH	Metabolic Dysfunction-Associated Steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MCS	Mental component summary
Mg	Milligrams
Mg/dl	milligrams per deciliter
MI	Myocardial infarction
Min	Minute
Ml	Milliliter
mIU/liter	milli-international units per liter
mmHg	Millimeters of mercury
mmol/L	Millimoles per liter
NICE	National Institute for Health and Care Excellence
NA	Not applicable
NAS	Nonalcoholic fatty liver disease activity score
NC	Not calculated
NE	Not estimated
NHPI	Native Hawaiian or Pacific Islander
NMA	Network meta-analysis
No	Number
NR	Not reported
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OA	Osteoarthritis
OR	Odds ratio
OSA	Obstructive sleep apnea
PAD	Peripheral arterial disease
PBO	Placebo
PCS	Physical component summary
PDRR	Participant to Disease-prevalence Representation Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMIS	Patient-Reported Outcomes Measurement Information System
PSG	Polysomnography
QALY	Quality-adjusted life year
Qol	Quality of life
RCT	Randomized controlled trial
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SE	Standard error

SEM	Semaglutide
SF-36	Short Form 36 v2 Health Survey
STEP-HFpEF	STEP-Heart Failure with Preserved Ejection Fraction
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBD	To be determined
TOS	The Obesity Society
TZP	Tirzepatide
UACR	Urine albumin to creatinine ratio
US	United States
VLDL	very-low-density lipoprotein
WAC	Wholesale acquisition cost
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Executive Summary

Obesity is a complex, chronic, and costly disease that affects physical and mental health and can result in an increased risk for other conditions such as diabetes, hypertension, liver disease, sleep apnea, cancer, and cardiovascular disease. Around 40% of the US population is currently living with obesity; there are racial and ethnic differences in obesity prevalence, with Black and Hispanic adults having higher rates of obesity.[1] Adults living with obesity often have comorbidities – more than half have hypertension and nearly one-quarter have diabetes.[2] Thus, the consequences of obesity are costly to both patients and to the healthcare system.

Obesity can start in childhood and thus can have lifelong effects on an individual's education, work, and social interactions. People living with obesity face substantial social stigma from the disease, with discrimination in workplace, education, and healthcare settings resulting in high rates of depression and anxiety.[3] Additionally, individuals living with obesity shared that the healthcare system is ill-equipped to treat obesity, particularly as a lifelong, chronic disease. We heard that weight bias leads to delays in diagnosis and treatment and contributes to poorer health outcomes. Historically marginalized populations may have particular difficulty obtaining treatment for obesity and its complications. Finally, variable insurance coverage and high out-of-pocket costs substantially limit access to semaglutide and tirzepatide.

Comprehensive care for obesity includes lifestyle modifications (e.g., nutrition therapy, physical activity, behavioral modifications), medications, and bariatric surgery, alone or in combination. The emergence of GLP-1 receptor agonists (GLP-1 RA) like semaglutide and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) RA like tirzepatide have dramatically altered the landscape of obesity treatment. We evaluated the net health benefits of injectable semaglutide 2.4 mg, oral semaglutide 25 mg, and tirzepatide 15 mg in individuals with obesity and without diabetes. Treatment with all three drugs resulted in substantial weight loss compared with placebo, with a mean difference in weight loss compared with placebo of -17.8% with tirzepatide treatment, -13.1% with injectable semaglutide treatment, and -11.4% with oral semaglutide treatment. Greater weight loss with tirzepatide than injectable semaglutide was also seen in a head-to-head trial (-20.2% vs. -13.7%).

In patients with obesity and established cardiovascular (CV) disease, injectable semaglutide has been shown to reduce the risk of major cardiovascular events (MACE) (HR 0.80, 95% CI 0.72, 0.90) and all-cause mortality (HR 0.81, 95% CI 0.71, 0.93). Whether this CV risk reduction extends to oral semaglutide 25 mg is not clear, as this dose results in less weight loss than the injectable form, and a lower dose (14 mg) resulted in smaller CV risk reduction in a diabetes population. For tirzepatide, reported results from a CV outcomes trial in patients with diabetes showed an 8% reduction in MACE and a 16% reduction in all-cause mortality compared with dulaglutide, a GLP-1 RA, although full trial results have yet to be published.

All three drugs generally improved health-related quality of life, as well as metabolic risk factors such as blood pressure, blood glucose, and lipids. However, stopping semaglutide or tirzepatide appears to result in weight regain and regression of improvement in metabolic risk factors.

Treatment with injectable semaglutide and tirzepatide have also been associated with improvements in obesity-related complications. Injectable semaglutide has been shown to improve outcomes in knee osteoarthritis (OA), metabolic-associated steatohepatitis (MASH), and heart failure with preserved ejection fraction (HFpEF), as well as reduce the risk of diabetes and chronic kidney disease (CKD). Tirzepatide has been shown to reduce the risk of diabetes and improve symptoms of obstructive sleep apnea.

The most common harms of both semaglutide and tirzepatide are gastrointestinal (GI) side effects, with around three-quarters of participants taking either injectable or oral semaglutide reporting GI side effects. For tirzepatide, 20-40% of participants reported nausea, diarrhea, or constipation in clinical trials. However, serious adverse events were uncommon, occurring in 3-7% of participants in the semaglutide trials and 4-7% in the tirzepatide trials. Finally, discontinuation due to adverse events was also less than 10% for all three drugs.

Because treatment with all three drugs results in substantial weight loss and improvement in metabolic risk factors, we have high certainty that all three drugs have substantial net health benefit over lifestyle modifications alone (**A**) (Table ES1). There is less certainty about the relative effects of the drugs to each other, particularly for outcomes beyond weight loss (e.g., CV outcomes), and thus we have judged the comparison between tirzepatide and semaglutide as "promising but inconclusive" (**P/I**). Treatment with oral semaglutide results in slightly lower amounts of weight loss compared with injectable semaglutide, with uncertainty about the degree of CV benefit, and thus we judged oral semaglutide to be "comparable or worse" than injectable semaglutide (**C-**).

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Population: Adults with Obesity or Overweight with ≥1 Obesity-Related Comorbidity		
Injectable Semaglutide	Lifestyle modifications	A
Oral Semaglutide	Lifestyle modifications	A
Tirzepatide	Lifestyle modifications	A
Tirzepatide	Injectable semaglutide	P/I
Tirzepatide	Oral semaglutide	P/I
Oral Semaglutide	Injectable semaglutide	C-

In cost-effectiveness analyses, we used estimated net prices from SSR Health of $6,830 for injectable semaglutide and $7,973 for tirzepatide; we assumed the price of oral semaglutide was the same as injectable semaglutide. Treatment with injectable semaglutide, oral semaglutide, and

tirzepatide resulted in increased QALYs, evLYs and life-years and fewer CV events compared with treatment with lifestyle modifications alone, with tirzepatide treatment resulting in the greatest gains. The incremental cost-effectiveness ratios for each drug are listed in Table ES2. All drugs were cost-effective at the $100,000 per QALY and evLY gained thresholds.

Table ES2. Incremental Cost-Effectiveness Ratios

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained
Injectable Semaglutide	Lifestyle Modification	$66,355	$65,280
Oral Semaglutide*	Lifestyle Modification	$75,456	$74,143
Tirzepatide	Lifestyle Modification	$57,779	$57,188

*Using a placeholder price for oral semaglutide

Despite these therapies being highly cost-effective, their potential budget impact is large. We estimate that fewer than 1% of eligible patients could be treated at current and assumed net prices before crossing the ICER budget impact threshold of $880,000,000 annually. This raises serious concerns about affordability.

1. Background

Obesity is a complex, chronic disease that affects physical and mental health and can result in an increased risk for other conditions such as diabetes, hypertension, liver disease, sleep apnea, cancer, and cardiovascular disease. Severe obesity can shorten life expectancy by up to 14 years, similar to the effect of smoking.[4] The prevalence of obesity has been increasing: currently around 40% percent of the US population is living with obesity, with nearly 10% living with severe obesity.[2] Under some proposed definitions of obesity, the percentages may be much higher.[5] There are racial and ethnic differences in obesity prevalence, with Black and Hispanic adults having higher rates of obesity.[1] Adults living with obesity often have comorbidities – more than half have hypertension and nearly one-quarter have diabetes.[2] Obesity is costly to the healthcare system, with an estimated $172 billion in medical costs annually attributed to the disease.[6]

Obesity is typically defined using body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, although the units (kg/m^2) are frequently not included. An individual is considered overweight at a BMI ≥25; obesity is defined as a BMI ≥30, and individuals with a BMI ≥40 are considered to have severe obesity. Although BMI is a standard measure for obesity, it has limitations, as it does not distinguish between fat and lean body mass, nor does it take into consideration how differences in age, sex, race/ethnicity, and body fat distribution may affect the health risks associated with obesity.[7] For example, many Asian subgroups have higher rates of diabetes at lower BMI cut points.[8] Thus, other measures (e.g., waist circumference, waist to hip ratio, body fat composition) in addition to BMI are being used to better define the potential impact of obesity on an individual's health.

There are multiple factors that affect a person's risk of developing obesity, including variations in genes that affect metabolic processes, appetite regulation, body fat distribution, and environmental factors such as geography, food and physical activity environment, and socioeconomic status.[9,10] Obesity can start in childhood and thus can have lifelong effects on an individual's education, work, and social interactions. People living with obesity also face substantial social stigma from the disease, with discrimination in workplace, education, and health care settings resulting in high rates of depression and anxiety.[3] Weight bias – the view that individuals are to blame for their weight – in the health care setting can negatively affect provider-patient interactions and lead to both physical and psychological harm, including discouraging people from seeking care, causing delays in diagnosis and treatment, and contributing to poorer health outcomes.[3]

Comprehensive care for obesity includes nutrition therapy, physical activity, behavioral counseling, and pharmacotherapy.[11] There are multiple modalities for treating obesity including lifestyle modifications (e.g., diet, physical activity, and behavioral modifications), medications, and bariatric surgery, usually in combination. Weight loss can lead to improvement in metabolic markers (e.g., fasting glucose, cholesterol, blood pressure), depression, and quality of life, as well as a decreased risk of developing obesity-related complications (e.g., diabetes, hypertension, obstructive sleep apnea (OSA), hyperlipidemia, metabolic dysfunction-associated steatohepatitis (MASH)) and death.[12,13] Lifestyle modifications, typically in structured programs, generally result in five to ten percent loss of body weight, however many people do not achieve this level of weight loss and most are unable to sustain weight loss over time.[14,15] In adults living with obesity or overweight with weight-related complications who require additional weight loss after lifestyle modifications, clinical practice guidelines recommend adding pharmacotherapy.[16] Various medications are available, including oral agents such as phentermine-topiramate and naltrexone-bupropion and injectable drugs such as semaglutide targeting glucagon-like peptide-1 receptor agonists (GLP-1 RA). For most people, long-term use of such agents will likely be necessary to maintain weight loss. For those people living with severe obesity, bariatric surgery has been shown to result in durable and substantial weight loss and a lower incidence of Type 2 diabetes (T2D) and cardiovascular (CV) events.[17]

The availability of semaglutide, a GLP-1 RA, and tirzepatide, a dual GLP-1/glucose-dependent insulinotropic polypeptide receptor agonist (GLP-1/GIP RA), have dramatically altered the landscape of obesity treatment. Both drugs are available as weekly injections; a daily oral form of semaglutide is available for treatment of diabetes and is being evaluated by the US FDA, at a higher dose, for treatment of obesity. These therapies mediate weight loss through multiple mechanisms, as GLP-1 receptors are present in the central nervous system, pancreas, liver, and intestines. Through both central and peripheral pathways, GLP-1 RAs affect appetite regulation, hunger and satiety signaling, gut hormone regulation, gastric emptying, glucose metabolism, energy expenditure and lipid metabolism.[18] GIP RAs also modulate both insulin and lipid metabolism.[18] Thus, treatment with semaglutide and tirzepatide not only commonly results in substantial weight loss but can also result in improvements in obesity-related complications. For example, treatment with semaglutide has been shown to reduce CV events and decrease progression of chronic kidney disease (CKD);[19,20] treatment with tirzepatide has been shown to improve symptoms of OSA.[21]

The promise of semaglutide and tirzepatide for weight loss and to prevent or reverse obesity-related complications, coupled with the large eligible population for treatment and the cost of the drugs, has led to the need for an assessment of their value. Although ICER reviewed treatments for obesity in 2022,[22] additional data have since been published. This ICER report is focused on the comparative effectiveness and value of semaglutide (oral and injectable) and tirzepatide for the treatment of obesity.

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Semaglutide (Wegovy®)	GLP-1 receptor agonist	Subcutaneous injection	Maximum dose of 2.4 mg weekly
Semaglutide	GLP-1 receptor agonist	Oral	25 mg daily
Tirzepatide (Zepbound®)	GLP-1/GIP receptor agonist	Subcutaneous injection	Maximum dose of 15 mg weekly

GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulinotropic polypeptide; mg: milligrams

2. Patient and Other Stakeholder Input

During the course of this review, we sought input from diverse stakeholders, including patients and patient advocates, clinicians, researchers, payers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders, data from ICER's 2022 obesity report,[22] and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of obesity treatments.

2.1 Patient Community Insights

We heard from stakeholders that obesity is a lifelong disease, often starting in childhood, and both genetic and environmental factors lead to difficulty losing weight and maintaining weight loss over a lifetime. Individuals living with obesity described having difficulty managing "food noise", which was described as constant and sometimes intrusive thoughts about food and obsessing about calorie counts or food restrictions, as well as not feeling appropriate satiety signals. They also described the stigma and bias associated with obesity, which can affect individuals' mental health, self-esteem, and their willingness to engage with the healthcare system for treatment.

Individuals living with obesity shared that the healthcare system is not well equipped to treat obesity, particularly as a lifelong, chronic disease. They recounted situations where medical professionals did not treat them with dignity, were biased towards them based on their weight, and blamed them for their weight gain. They also stated that they often needed to advocate for themselves to get appropriate medical care, recounting instances where there were delays in diagnosing medical issues that were instead blamed on their weight and delays in obtaining routine care such as mammograms to screen for breast cancer. We also heard about a lack of comprehensive, compassionate care for obesity, with individuals we spoke with sharing difficulties finding primary care providers with the time and expertise to treat obesity as a disease, the lack of psychological support, and the lack of high-quality education and educational materials about managing obesity. Although seeing obesity medicine specialists might be ideal, these specialists are in short supply and very few individuals we talked with were able to access this resource or any kind of comprehensive care. Too often, individuals living with obesity reported the failure of providers to even broach the subject of obesity and treatment for obesity, resulting in delays in treatment with medications until after comorbidities had developed.

In terms of treatment for obesity, we heard that individuals living with obesity try multiple treatments throughout their lifetime, including lifestyle modifications, apps, weight loss programs like Weight Watchers, and medication. Success with weight loss interventions was varied, with most individuals having lost and gained weight multiple times over the years. Individuals shared several

challenges with treatment with weight loss medications, including finding providers who are knowledgeable about the treatment of obesity and who could offer comprehensive treatment rather than just write a prescription; trying to find a medication that works for them since the effectiveness of treatment varies from individual to individual, and having adequate support (e.g., information about side effects, nutritional and psychological support, etc.). Finally, those individuals who had been treated with semaglutide or tirzepatide described that the medication helped them manage "food noise" and their relationships with food more successfully. One participant described having feelings of satiety for the first time in their life after starting tirzepatide, describing the medication as "life-changing".

Individuals living with obesity, patient advocacy groups, and clinical experts all emphasized that the main limitation of access to semaglutide and tirzepatide is economic – namely, insurance coverage is variable and out-of-pocket costs are high for individuals without insurance coverage. Insurance coverage was easier to obtain for individuals who had a comorbidity that was included on the FDA label for a medication – e.g., obstructive sleep apnea or cardiovascular disease. Even with insurance coverage, the high cost of therapy also affects medication persistence, as some individuals were not able to afford to stay on the drugs long-term, which then led to regain of weight. Since individuals may respond better to one drug compared to another, changes in insurance coverage that would force a change to a medication that was not as effective was mentioned as a prominent concern.

2.2 Health Equity Considerations

We heard from individuals living with obesity that there are racial and ethnic disparities in medical treatment for obesity. For example, Black women, who are more likely to be living with obesity, are less likely to be offered comprehensive treatment for obesity, and less likely to be referred for surgery when appropriate. Individuals living with obesity also reported difficulty finding culturally appropriate care, particularly in the area of nutrition, where often patient education does not take into account cultural differences in diet. Finally, we heard that insurance coverage issues had the potential to widen inequities – for example, Medicare and state exchange insurance plans largely do not cover obesity medications, though some state Medicaid plans do. Without widespread coverage, and a lack of patient assistance programs, many individuals living with obesity are not able to afford treatment.

2.3 Comments from Other Stakeholders

We heard from clinical experts that there is variability in response to medications to treat obesity. There are individuals who are hyperresponders and lose large amounts of weight on low doses of semaglutide or tirzepatide; on the other hand, individuals with higher BMI at baseline may not have as robust a response to medication. There may also be differences in response based on sex, race,

and ethnicity, with women tending to respond better to medication and Black participants losing less weight relative to their White counterparts. Some individuals living with obesity may respond to older, cheaper medications; those are not as effective as semaglutide and tirzepatide and thus are mainly offered when these drugs are cost-prohibitive or not available. Finally, we heard that there is excitement about the use of semaglutide and tirzepatide for treatment of diseases other than obesity and T2D, including substance use disorder and Alzheimer's disease.

We spoke with a payer, who discussed the challenges to insurance coverage of obesity medications. We heard that because the eligible population is so large and the price of obesity medications is so high, that it is difficult for payers to cover the medication for all eligible individuals without substantial increases in premiums. We also heard that updated clinical practice guidelines are critical for coverage as the ability to use contemporary clinical guidelines decreases the need for appeals, which are expensive to health plans. Finally, we heard that Medicare price negotiations for semaglutide could have a large impact on the pricing and coverage.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Detailed methods for the systematic literature review assessing the evidence on semaglutide (injectable and oral) and tirzepatide for the treatment of obesity are detailed in Supplement Section D1.

Scope of Review

We reviewed the clinical effectiveness of semaglutide (injectable and oral) and tirzepatide, with or without lifestyle modifications, compared to either lifestyle modifications alone or no specific intervention for obesity. Where appropriate, we also compared the interventions to each other.

For all interventions, the population included adults with obesity or with overweight and at least one weight-related comorbid condition, who are actively seeking medical management for weight loss. Adults with established diabetes were excluded. We reviewed the maximum effective dose of a medication when multiple doses had been evaluated. Lifestyle modifications usually involved a reduced-calorie diet and increased physical activity, with some also incorporating behavioral counseling. We searched for evidence on patient-important outcomes including weight loss outcomes (e.g., % weight loss and categorical weight loss), CV outcomes, kidney outcomes, functional status, and health-related quality of life (HRQoL). Additional patient-important outcomes include changes in systolic blood pressure (SBP), glycated hemoglobin (HbA1C), waist circumference, weight regain, and gastrointestinal (GI) harms from these interventions. The initial literature search for the systematic review was conducted in June 2025 and later updated in September 2025; additional data were incorporated as they became available. The full scope of the review is available in Supplement Section D1.

Evidence Base

Injectable Semaglutide

The evidence base for efficacy for weight loss for injectable semaglutide primarily comes from the STEP 1, 3, 5, 8, and 10 trials. All five STEP trials were Phase III randomized, controlled trials (RCT) that evaluated injectable semaglutide 2.4 mg plus lifestyle intervention versus placebo plus lifestyle intervention; STEP 8 also included a liraglutide arm that was excluded from this review.[23-27] All trials had a standardized dose escalation period, where patients initiated once-weekly semaglutide or placebo at a dose of 0.25 mg and the dose was escalated to reach the maintenance dose of 2.4 mg by week 16. Follow-up was a total of 68 weeks for the STEP 1, STEP 3, and STEP 8 trials, 104 weeks for STEP 5 and 52 weeks for STEP 10.[23-27]

The key inclusion and exclusion criteria were identical across all five STEP trials included in this review. Participants were required to have a BMI $\geq$30 or $\geq$27 with the presence of at least one weight-related comorbidity (i.e., hypertension, dyslipidemia, OSA, or CV disease). Participants with a history of type 1 or type 2 diabetes (T1D or T2D) were excluded; STEP 10 exclusively enrolled participants with prediabetes.[23-27] Baseline characteristics for the five trials are listed in Supplement Table D2.5 The populations for all five STEP trials were mostly similar. The majority of participants in these STEP trials were White (71%-93%), female (68-88%), and comorbid conditions were common (>70%).[23-25,27] Participants in STEP 10 were slightly older, with a higher baseline BMI and mean systolic blood pressure.[26]

The SELECT trial evaluated CV outcomes by randomizing patients with obesity and known CV disease to injectable semaglutide 2.4 mg or placebo.[19] Patients with diabetes were excluded. The primary endpoint was the first occurrence of any component of a composite of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke, assessed in a time-to-event analysis. See Supplement Table D2.9.

The STEP 9 trial evaluated injectable semaglutide for weight loss and pain measures related to knee osteoarthritis (OA) in participants with obesity and a diagnosis of at least moderate knee OA.[28] The ESSENCE trial examined the impact of injectable semaglutide on liver fibrosis in participants with obesity and MASH.[29] The STEP-Heart Failure with Preserved Ejection Fraction (STEP-HFpEF) trial assessed CV outcomes in addition to weight loss in a population with existing HFpEF.[30] Details about the study design and baseline characteristics of these trials are presented in Supplemental Section D2.

The SURMOUNT 5 trial comparing semaglutide and tirzepatide is described below.

Our search identified six peer-reviewed, full-text, observational real-world evidence (RWE) studies that directly compared injectable semaglutide and tirzepatide.[31-35] We also identified four publications that assessed injectable semaglutide against no treatment,[36-39] and two publications that compared semaglutide with other obesity medications.[40,41] One single arm study evaluated injectable semaglutide alone.[42] Details about the key observational RWE studies are available in Supplement Section D2.

Oral Semaglutide

Evidence informing our review of oral semaglutide 25 mg for the treatment of obesity was derived from the OASIS 4 trial.[43]

OASIS 4 was a 64-week Phase III RCT that evaluated oral semaglutide 25 mg plus lifestyle intervention versus placebo plus lifestyle intervention. The trial design included a dose escalation period of 12 weeks, a maintenance period of 52 weeks, and an additional follow-up of 7 weeks off-treatment. Adult participants with obesity or with overweight plus at least one weight-related comorbidity (N=307) were randomized 2:1 to oral semaglutide or placebo. Key exclusion criteria included HbA1C ≥6.5% and self-reported change in body weight of ≥5 kg in the 90 days before screening.[43] Overall, the baseline characteristics of OASIS 4 appear to be similar to the STEP trials of injectable semaglutide. See Supplement Table D2.6.

We did not identify any RCTs assessing the CV outcomes of oral semaglutide 25 mg for the management of obesity with or without diabetes. PIONEER 6 and SOUL are two Phase III trials evaluating oral semaglutide 14 mg versus placebo in adults with T2D with established CV disease or at high risk for CV events.[44,45] They are described briefly in the section below discussing CV outcomes of oral semaglutide.

Tirzepatide

The evidence base for efficacy for weight loss for tirzepatide primarily comes from SURMOUNT 1 and SURMOUNT 3, both designed to compare tirzepatide 15 mg plus lifestyle intervention versus placebo plus lifestyle intervention.[46,47]

SURMOUNT 1 and 3 were multicenter, Phase III RCTs that included a 20-week dose escalation period, initiating with 2.5 mg and gradually reaching a 15 mg dose, and a 52-week maintenance period.[46,47] SURMOUNT 3 also allowed 10 mg as a maximum tolerated dose and had an additional 12-week pre-titration lead-in period featuring eight counseling sessions along with typical lifestyle interventions.[47] Participants were included in the trial if they had a BMI ≥30 or a BMI ≥27 with at least one weight-related comorbidity. Participants with T1D or T2D, prior or planned weight loss surgeries, or change in body weight of >5 kg in the three months prior to enrollment were excluded.[46,47] Supplement Table D2.7.

SURMOUNT 5 was an open-label trial that randomized 750 adults with overweight or obesity to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or injectable semaglutide (1.7 mg or 2.4 mg). The design of this trial, including inclusion and exclusion criteria, was otherwise identical to that of the other two SURMOUNT trials. The primary endpoint was the percent change from baseline in body weight at week 72.[48] See Supplement Table D2.8.

Our search did not reveal any clinical trials evaluating the CV effects of tirzepatide for the management of obesity without diabetes. The currently unpublished SURPASS CVOT trial randomized patients with T2D and known atherosclerotic cardiovascular disease (ASCVD) to tirzepatide 15 mg or dulaglutide 1.5 mg.[49] Data from this trial were drawn from a recent conference presentation.[50]

The SUMMIT trial examined the effect of tirzepatide on CV death or worsening heart failure in individuals with obesity and HFpEF.[51] The SURMOUNT-OSA trial examined the effect of tirzepatide on outcomes related to OSA.[21] Details about the study design and baseline characteristics of these trials are presented in the Supplemental Section D2.

We identified four additional single-arm observational RWE studies evaluating tirzepatide alone.[52-55] Observational data comparing tirzepatide and semaglutide are discussed above.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[56] All key trials assessing weight loss as a primary outcome achieved "fair" or "good" diversity for race and ethnicity. Trials rated as "fair" on race and ethnicity (STEP 1, STEP 4, STEP 5, STEP 10, SURMOUNT 1, and SURMOUNT 3) had inadequate representation of those who identify as Black, Asian, and/or Hispanic. STEP 1, STEP 10, and all SURMOUNT trials achieved a "fair" rating on sex, while others received a poor rating because of the underrepresentation of male patients. Of the trials that reported data on adults over 65, SURMOUNT 1 and SURMOUNT 5 both achieved a "poor" rating. See Supplement D1 for full details of CDR methods and results.

Table 3.1. Diversity Ratings for Key Trials Assessing Weight Loss Outcomes

Trial	Race and Ethnicity	Sex	Age (Older Adults)
STEP-1	Fair	Fair	NR
STEP-3	Good	Poor	NR
STEP-5	Fair	Poor	NR
STEP-8	Good	Poor	NR
STEP-10	Fair	Fair	NR
OASIS 4	Poor	Poor	NR
SURMOUNT-1	Fair	Fair	Poor
SURMOUNT-3	Fair	Fair	NR
SURMOUNT-5	Good	Fair	Poor

NR: not reported

The ratings presented above reflect representation based on estimates for the U.S. obesity population.

We also rated the trials for CV outcomes or trials for other obesity-related complications. Results of these trials are available in the Supplement Section D1.

3.2. Results

Clinical Benefits

Weight-Related Outcomes

Injectable Semaglutide

Participants in the STEP 1, 3, 5, 8, and 10 trials saw percentage weight loss from baseline to one year of -14.4 to -17.4 in the semaglutide arms and -1.6 to -5.8 in the placebo arms. We conducted a meta-analysis of the results from STEP 1, 3, 5, and 8. Percentage weight loss was greater with semaglutide than placebo (unadjusted -13.1%; 95% CI: -15 to -11.3; I^2 83% and adjusted -12%; 95% CI: -13.9 to -10.2; I^2 77%) at 68 weeks. Semaglutide also resulted in greater categorical weight loss at pre-specified cut points. See Table 3.1 and Supplement Table D2.14-15.

Table 3.2. Key Trial Results Related to Weight Loss Outcomes for Injectable Semaglutide

Trials Follow-Up	Arms	N	% Weight Loss from Baseline to One Year, Mean		≥5% Weight Loss, %	≥10% Weight Loss, %	≥15% Weight Loss, %	≥20% Weight Loss, %
			Unadjusted	Adjusted				
STEP 1 68 Weeks	SEM	1306	-15.6	-14.9	86%	69%	51%	32%
	PBO	655	-2.8	-2.4	32%	12%	5%	2%
STEP 3 68 Weeks	SEM	407	-16.5	-16	87%	75%	56%	36%
	PBO	204	-5.8	-5.7	48%	27%	13%	4%
STEP 5 104 Weeks	SEM	152	-17.4	-15.2	77%	62%	52%	36%
	PBO	152	-2.7	-2.6	34%	13%	7%	2%
STEP 8 68 Weeks	SEM	126	-16.4	-15.8	87%	71%	56%	39%
	PBO	85	-1.6	-1.9	30%	15%	6%	3%
STEP 10 52 Weeks	SEM	138	-14.4	-13.9	86%	74%	48%	25%
	PBO	69	-2.7	-2.7	26%	8%	2%	0%

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

Oral Semaglutide

In the OASIS 4 trial, participants receiving oral semaglutide showed an adjusted 13.6% reduction in percent change from baseline weight compared with a 2.2% reduction in the placebo group (mean difference -11.4; 95% CI: -13.9 to -9; p <0.0001) at week 64. Half of the participants lost ≥15% of their body weight and nearly one-third lost more than 20% of their body weight at week 64.[43] See Table 3.2 and Supplement Table D2.23.

Table 3.3. Key Trial Results Related to Weight Loss Outcomes for Oral Semaglutide

Trials Follow-Up	Arms	N	% Weight Loss from Baseline to One Year, Mean		≥5% Weight Loss, %	≥10% Weight Loss, %	≥15% Weight Loss, %	≥20% Weight Loss, %
			Unadjusted	Adjusted				
OASIS	SEM	205	-14.6	-13.6	79%	63%	50%	30%
64 Weeks	PBO	102	-2.6	-2.2	31%	14%	6%	3%

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

Tirzepatide

In both SURMOUNT-1 and SURMOUNT-3, treatment with tirzepatide resulted in a greater percentage reduction in weight compared with placebo at week 72 (adjusted mean difference vs. placebo in SURMOUNT-1 was -17.8%; 95% CI: -19.3 to -16.3; mean difference in SURMOUNT-3 was -20.8%; 95% CI: -23.2 to -18.5). Tirzepatide also resulted in greater categorical weight loss at pre-specified cut points. See Table 3.3 and Supplement Table D2.24.

SURMOUNT-5 was a head-to-head trial (N=751) comparing tirzepatide (10 mg or 15 mg) with injectable semaglutide (1.7 mg or 2.4 mg). At week 72, participants treated with tirzepatide lost almost 7% more weight than those treated with semaglutide (adjusted weight loss from baseline -20.2% vs -13.7%, mean treatment difference 6.5%; 95% CI: -8.1 to -4.9). Categorical weight loss was also greater with tirzepatide. See Table 3.3 and Supplement Table D2.26.

Table 3.4. Key Trial Results Related to Weight Loss Outcomes for Tirzepatide

Trials Follow-Up	Arms	N	% Weight Loss from Baseline to One Year, Mean		≥5% Weight Loss, %	≥10% Weight Loss, %	≥15% Weight Loss, %	≥20% Weight Loss, %	≥25% Weight Loss, %
			Unadjusted	Adjusted					
SURMOUNT 1	TZP	630	NR	-20.9	91%	84%	71%	57%	36%
72 Weeks	PBO	643	NR	-3.1	35%	19%	9%	3%	2%
SURMOUNT 3	TZP	287	NR	-18.4	88%	77%	65%	44%	29%
72 Weeks	PBO	292	NR	2.5	17%	9%	4%	2%	1%
SURMOUNT 5	TZP	374	-21.8	-20.2	NR	82%	65%	48%	32%
72 Weeks	SEM	376	-15.4	-13.7	NR	61%	40%	27%	16%

NR: not reported, PBO: placebo, TZP: tirzepatide

Cardiovascular Outcomes

Injectable Semaglutide

The SELECT trial assessed CV outcomes in participants treated with injectable semaglutide compared with placebo in a population of adults with obesity and pre-existing CV disease. The primary endpoint was a composite of major adverse CV events (MACE): death from CV causes, nonfatal MI, or nonfatal stroke. Over 48 months of follow-up, participants receiving semaglutide had a 20% risk reduction (HR 0.80; 95% CI: 0.72 to 0.90) in MACE compared to placebo. The risk reduction was primarily driven by the individual component of nonfatal MI (HR 0.72); there were no statistically significant reductions in death from CV causes or nonfatal stroke. Semaglutide also reduced all-cause mortality (HR 0.81; 95% CI: 0.71 to 0.93).[19] See Supplement Table D2.27.

Oral Semaglutide

There were no clinical trials assessing CV outcomes of oral semaglutide 25 mg for the management of obesity with or without diabetes. There were two oral semaglutide CV outcomes trials in the T2D population, using the 14 mg dose. PIONEER 6 randomized 3,183 patients with T2D at high CV risk to treatment with oral semaglutide 14 mg daily or placebo.[44] After a median follow-up of 15.9 months, there was a numerical reduction in a MACE (CV death, nonfatal MI, nonfatal stroke) with semaglutide (HR 0.79; 95% CI: 0.57 to 1.11), though this difference was not statistically significant. Similarly, the SOUL trial randomized 9,650 patients with T2D and known atherosclerotic CV disease, CKD, or both to treatment with oral semaglutide 14 mg daily or placebo.[45] After a median follow-up of 49.5 months, treatment with semaglutide resulted in a statistically significant 14% risk reduction in MACE (HR 0.86; 95% CI: 0.77 to 0.96). An ICER meta-analysis of these two trials using number of MACE events occurred in these trials as input and relative risk as output resulted in a similar risk reduction in MACE to the SOUL trial (RR 0.86; 95% CI: 0.78 to 0.95, I^2 0%).

Tirzepatide

We did not find any trials examining CV outcomes in patients with obesity and without diabetes treated with tirzepatide. The SURPASS-CVOT trial compared tirzepatide with dulaglutide in adults with T2D and ASCVD. The primary outcome was the incidence of least one component of MACE (death from CV causes, MI, or stroke).[49] Results presented at a recent conference showed that participants treated with tirzepatide had an 8% reduction in the risk of MACE compared to the dulaglutide group (HR 0.92). Participants treated with tirzepatide also had a reduced risk of all-cause death (HR 0.84; 95% CI: 0.75 to 0.94) compared with dulaglutide.[50] However, full trial results from SURPASS-CVOT have yet to be published in a peer-reviewed journal.

Health-Related Quality of Life (HRQoL)

Injectable Semaglutide

The STEP 1 and STEP 3 trials reported HRQoL outcomes, mostly assessed using at least one of these two instruments: Short Form 36v2 Health Survey (SF-36) and Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT). Although mean changes in the SF-36 scores all favored semaglutide compared with placebo, results varied both across components and across trials. For example, on the SF-36 physical functioning scale, participants treated with semaglutide had statistically significant improvements compared with placebo in STEP 1 but not in STEP 3 [23] [24] More participants in STEP 1 treated with semaglutide had clinically meaningful improvements than in the placebo group (40% vs 27%).[23] For the SF-36 PCS component, scores were higher in the semaglutide-treated group than the placebo group; this differences was statistically significant in the STEP 1 trial but not in STEP 3.[23,57] Mental component scores dropped from baseline in both trials, but less in the semaglutide group than with placebo. The mean difference was statistically significant in both trials.[24,57] Treatment with semaglutide also resulted in greater improvements in the IWQOL-Lite-CT physical function score in STEP 1, with 51% versus 33% achieving a clinically meaningful change.[23,58] See Supplement Table D2.22.

Oral Semaglutide

The OASIS 4 trial assessed mean change from baseline in IWQOL-Lite-CT physical function at week 64 as a confirmatory secondary endpoint. Approximately 55% of the participants treated with semaglutide achieved a clinically meaningful increase in IWQOL-Lite-CT physical function compared to only 35% treated with placebo.[43] See Supplement Table D2.23.

Tirzepatide

Participants treated with tirzepatide had statistically significant improvements in the SF-36 physical functioning score, PCS, MCS, and IWQOL-Lite-CT physical function score compared to placebo in both SURMOUNT-1 and SURMOUNT-3 trials.[59,60] Groups who lost more weight saw larger gains in HRQoL in SURMOUNT-1, and more patients in the tirzepatide treated group saw clinically meaningful improvements than in the placebo group across all HRQoL scales.[59] See Supplement Table D2.25.

Other Outcomes and Obesity-Related Complications

Injectable Semaglutide

ICER's meta-analyses of the STEP 1, 3, and 8 trials showed that semaglutide compared with placebo reduces systolic blood pressure by approximately 6 mmHg and HbA1C by approximately 0.3%.[23,24,27] See additional meta-analysis results of the STEP trials in Supplement Table D1.12. Lipids were also improved, and BMI decreased across all STEP trials.[23-27] Treatment with semaglutide decreased the risk of developing T2D (3.5% vs. 12%, HR 0.27) at week 156 and severe kidney disease (HR 0.78, 95% CI 0.63, 0.96) in the SELECT trial.[61] [20] See Supplement Table D2.27. Treatment with semaglutide also improved pain from knee OA compared with placebo (mean difference vs. placebo -14.1; minimal clinically important difference 10 points[62]) in the STEP 9 trial.[63] See Supplement Table D2.30.

In patients with MASH, two-thirds of the non-diabetic participants treated with semaglutide achieved resolution of steatohepatitis with no worsening of liver fibrosis after 72 weeks, compared to only 34% of the participants treated with placebo. Semaglutide also improved liver fibrosis with no worsening of steatohepatitis in 37% of the non-diabetic participants compared to 22% of the participants in the placebo group.[29] See Supplement Table D2.29.

Oral Semaglutide

In the OASIS-4 trial, participants treated with semaglutide saw improvements in HbA1C, waist circumference, and LDL cholesterol from baseline at week 64 in a prespecified analysis. A greater proportion of participants with prediabetes reverted to normoglycemia in the semaglutide group compared with placebo (71% vs 33%).[43] See Supplement Table D2.23.

Tirzepatide

Participants treated with tirzepatide in SURMOUNT 1 had greater reductions in SBP (mean difference -6.4 mmHg) and HbA1C (mean difference -0.44%) compared to placebo.[46] See Supplement Table D2.24.

In long-term follow-up of the SURMOUNT 1 trial, only ten (1%) participants in the pooled tirzepatide group (5 mg, 10 mg, or 15 mg) with prediabetes developed T2D compared to 36 (13%) participants in the placebo group (HR 0.07) at 176 weeks.[64]

In the two SURMOUNT OSA trials, the primary endpoint was the mean change in apnea-hypopnea index (i.e., the number of apneas and hypopneas during an hour of sleep). At week 52, there was a reduction in the number of AHI events from baseline in the groups treated with tirzepatide in both trials (Trial 1 treatment difference from placebo -20; Trial 2 treatment difference from placebo -23.8).[21] See Supplement Table D2.28.

Harms

Injectable Semaglutide

Although follow-up varied (52 weeks to 104 weeks), all STEP trials reported largely similar proportions of any adverse events across the arms. Serious adverse events were generally more common in the semaglutide arm (8-10%) than in the placebo arm (3-9%), except for STEP 5.[23,24,26,27] Across all trials, discontinuations due to adverse events were higher in the semaglutide (3-7%) than in the placebo arms (0-5%).[23,24,26,27] Gastrointestinal side effects are among the most common side effects for GLP-1 RAs. Participants treated with semaglutide experienced more GI side effects (74-84%) than those receiving placebo (48-63%). Similarly, severe GI side effects were more common in the semaglutide arms (3-5%) than placebo arms (0-4%). [23,24,26,27] See Table 3.4. and Supplement Table D2.32.

Table 3.5. Harms in Key Trials of Injectable Semaglutide versus Placebo

Trials	STEP 1		STEP 3		STEP 5		STEP 8		STEP 10	
Study Arms	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**
Sample Size	**1306**	**655**	**407**	**204**	**152**	**152**	**126**	**85**	**138**	**69**
Follow-Up	**68 Weeks**		**68 Weeks**		**68 Weeks**		**104 Weeks**		**52 Weeks**	
Any AE, n (%)	1171 (89.7)	566 (86.4)	390 (95.8)	196 (96.1)	146 (96.1)	136 (89.5)	120 (95.2)	81 (95.3)	NR	NR
SAE, n (%)	128 (9.8)	42 (6.4)	37 (9.1)	6 (2.9)	12 (7.9)	18 (11.8)	10 (7.9)	6 (7.1)	12 (9)	6 (9)
Death, n (%)	1 (0.1)	1 (0.2)	0	0	1 (0.7)	0	0	0	2 (1)	0
AEs leading to Discontinuation, n (%)	92 (7)	20 (3.1)	24 (5.9)	6 (2.9)	9 (5.9)	7 (4.6)	4 (3.2)	3 (3.5)	4 (3)	0
Discontinuations due to GI AEs, n (%)	59 (4.5)	5 (0.8)	14 (3.4)	0	6 (3.9)	1 (0.7)	NR	NR	NR	NR
Any GI AEs, n (%)	969 (74.2)	314 (47.9)	337 (82.8)	129 (63.2)	125 (82.2)	82 (53.9)	106 (84.1)	47 (55.3)	NR	NR
Severe GI AEs, n (%)	18 (1.4)	0	5%	1%	NR	NR	4 (3.2)	3 (3.5)	3 (2)	0
Gallbladder-related Disorders, n (%)	34 (2.6)	8 (1.2)	20 (4.9)	3 (1.5)	4 (2.6)	2 (1.3)	1 (0.8)	1 (1.2)	1 (1)*	0
Serious Hepatobiliary Disorders, n (%)	17 (1.3)	1 (0.2)	10 (2.5)	0	NR	NR	NR	NR	1 (1)	0
Cardiovascular Disorders, n (%)	107 (8.2)	75 (11.5)	40 (9.8)	22 (10.8)	17 (11.2)	32 (21.1)	16 (12.7)	9 (10.6)	4 (3)	3 (4)

Trials	STEP 1		STEP 3		STEP 5		STEP 8		STEP 10	
Study Arms	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**
Sample Size	**1306**	**655**	**407**	**204**	**152**	**152**	**126**	**85**	**138**	**69**
Follow-Up	**68 Weeks**		**68 Weeks**		**68 Weeks**		**104 Weeks**		**52 Weeks**	
Acute Pancreatitis, n (%)	3 (0.2)	0	0	0	0	0	0	0	2 (1)	0
Acute Renal Failure, n (%)	3 (0.2)	2 (0.3)	0	0	0	0	1 (0.8)	1 (1.2)	NR	NR

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

Note: Severe GI side effects data are coming from Qin et. al 2024

*acute gallbladder disease

Oral Semaglutide

Data related to harms of oral semaglutide 25 mg were drawn from OASIS 4. At 64 weeks, rates of any adverse events were higher in the semaglutide group (93%) compared to the placebo group (85%). Serious adverse events were more common in the placebo arm (9%) compared to the semaglutide arm (4%). Discontinuations due to adverse events were similar in the semaglutide arm (7%) and placebo arm (6%). There were no deaths reported.[43]

More participants in the semaglutide group experienced GI side effects compared with placebo (74% vs. 42%). Discontinuation due to GI side effects was higher in the semaglutide arm compared with the placebo arm (3.4% vs 2%). The most frequent GI side effects in the semaglutide arm were nausea (47%), vomiting (31%), and constipation (20%). Cardiac disorders were more common in the placebo arm (6%) than in the semaglutide arm (2%).[43] See Supplement Table D2.33.

Tirzepatide

In SURMOUNT 1 and SURMOUNT 3, adverse events and serious adverse events were reported at comparable rates across trials and arms during the 72-week follow-up period. More participants in the tirzepatide group discontinued due to adverse events compared to placebo (6.2% vs 2.6% in SURMOUNT 1; 10.5% vs 2.1% in SURMOUNT 3) (Table 3.5).[46,47]

Severe GI side effects were relatively higher in the tirzepatide group (3-6%) compared to placebo (1-2%) in both trials. Gallbladder-related disorders, CV disorders, acute pancreatitis, and serious renal events were rare events in all arms.[46,47] See Table 3.5 and Supplement Table D2.34.

Table 3.6. Harms in Key Trials of Tirzepatide versus Placebo

Trials	SURMOUNT 1		SURMOUNT 3	
Study Arms	TZP	PBO	TZP	PBO
Sample Size	630	643	287	292
Follow-Up	72 Weeks		72 Weeks	
Any AE, n (%)	497 (78.9)	463 (72)	250 (87.1)	224 (76.7)
SAE, n (%)	32 (5.1)	44 (6.8)	17 (5.9)	14 (4.8)
Death, n (%)	1 (0.2)	4 (0.6)	1 (0.3)	1 (0.3)
AEs Leading to Discontinuation, n (%)	39 (6.2)	17 (2.6)	30 (10.5)	6 (2.1)
Severe GI AEs, n (%)	21 (3.3)	7 (1.1)	16 (5.6)	5 (1.7)
Gallbladder-Related Disorders, n (%)	6 (1)	5 (0.8)	2 (0.7)	0
Cholelithiasis, n (%)	4 (0.6)	6 (0.9)	4 (1.4)	3 (1)
Acute Cholecystitis, n (%)	1 (0.2)	0	1 (0.3)	0
Chronic Cholecystitis, n (%)	3 (0.5)	3 (0.5)	0	1 (0.3)
Cardiovascular Disorders, n (%)	2 (0.3)	1 (0.2)	0	1 (0.3)
Acute Pancreatitis, n (%)	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Serious Renal Events, n (%)	0	0	1 (0.3)	0

AE: adverse events, GI: gastrointestinal, PBO: placebo, SAE: serious adverse events, TZP: tirzepatide

The majority of the SURMOUNT 5 trial participants (78%) experienced at least one treatment-emergent adverse event. Rates of serious adverse events were marginally higher in the tirzepatide group compared to the injectable semaglutide group. A higher proportion of the trial participants receiving semaglutide (8%) discontinued treatment due to adverse events compared to tirzepatide (6%). More participants receiving semaglutide (5.6%) discontinued treatment due to GI-related side effects than those receiving tirzepatide (2.7%). Serious GI-related side effects and serious gallbladder disease were infrequent and similar across arms. The most frequent adverse events, occurring at similar rates in both arms, were nausea (44%), constipation (28%), diarrhea (24%), COVID-19 (13%), and fatigue (11%).[48] See Supplement Table D2.35.

Adherence and Persistence

Data on adherence and persistence were obtained from four observational RWE studies, most of which were conducted during a time of considerable supply shortages. Gleason et al 2024 measured adherence and persistence at one year to GLP-1 agonists among non-diabetic patients with obesity. Among 419 commercially insured adults who used injectable semaglutide for weight loss, 36% remained on treatment without a 60-day gap at one year. The mean proportion of days covered (PDC) for injectable semaglutide users was 53% (SD 33) and approximately 32% of them had PDC ≥80%. A total of 285 patients used oral semaglutide (Rybelsus®) as an off-label indication for weight loss. Approximately one-quarter of those patients remained on treatment without a 60-day gap at 1 year. The mean PDC for oral semaglutide users was 45% (SD 31) and about 20% of them had PDC ≥80%.[41] Four real-world studies showed that 54-76% of patients initiating tirzepatide

persisted on the therapy for six months, defined as no 60-day gap in therapy.[52-55] Around 56% of the patients achieved a PDC of at least 80% at six months.[54]

Subgroup Analyses and Heterogeneity

We did not find evidence of major differences in the balance of benefits and risks for the following subgroups: age, sex at birth, race and ethnicity, BMI categories, use and intensity of lifestyle interventions, established CV disease, and prior bariatric surgery. Post-hoc analyses of STEP trials showed no statistically significant differences in the change in body weight from baseline regardless of age, sex, race or ethnicity, though Black, Asian, and Hispanic participants in the STEP 1 trial had numerically less weight loss than White participants.[25,65-67] Semaglutide maintained favorable effects on weight loss, glycemic status, and cardiometabolic risk factors across subgroups based on baseline BMI and the presence of comorbidities.[67,68] Tirzepatide also demonstrated consistent percent changes in body weight from baseline versus placebo in BMI-defined subgroups (BMI <30, BMI 30-35, BMI 35-40, and BMI >40).[69-71]

Uncertainty and Controversies

- Although current data from clinical trials demonstrate that treatment with both semaglutide and tirzepatide can result in substantial weight loss in adults living with obesity, for key CV outcomes, there are limitations to the evidence base. Injectable semaglutide reduces CV events in the population with obesity and known CV disease; whether this benefit extends to primary prevention is not known but is reasonable to assume given the improvements in CV risk factors (e.g., SBP, HbA1c, progression to diabetes). For oral semaglutide, data are limited to a trial in the T2D population with CV disease or CKD, using a lower dose (14 mg) than proposed dose obesity treatment. The magnitude of benefit treating people with obesity without T2D with a higher dose (25 mg) is not known. Tirzepatide reduces CV events in people with T2D and existing CV disease, but only limited results are currently available and the comparator was with another GLP-1 RA, dulaglutide, making comparisons with semaglutide more indirect.

- Obesity is a lifelong disease; however, there are a lack of long-term follow-up data for both benefits and harms. For example, there are few data from clinical trials on outcomes beyond 2-3 years, particularly for weight maintenance. One concern about long-term safety that has been raised is the loss of muscle mass (sarcopenia) with substantial weight loss, particularly in older adults. Sarcopenia has been associated with functional decline, an increased risk of falls and death, and reduced quality of life.[72] Longer-term data are needed to understand the magnitude of risk and whether those risks can be mitigated. Additionally, animal models and the mechanism of action of GLP-1s raise the concern of an increased risk of pancreatitis, as well as pancreatic and thyroid cancer. Although clinical trial and

observational data have not found increased risks thus far, longer-term follow-up from both clinical trials and observational data are needed to confirm the risks or lack thereof.

- Data continue to emerge about the impact of GLP-1 RA and GLP-1/GIP RA drugs on various obesity-related complications (e.g., OSA, HFpEF, knee OA, etc.). However, many of the trials were done in a diabetes population and thus efficacy in non-diabetic populations is often less clear. Additionally, some trials rely on surrogate markers rather than patient-important outcomes (e.g., liver histology rather than cirrhosis; eGFR rather than end-stage kidney disease) due to the infeasibility of measuring outcomes with a long lead time in a time-limited clinical trial. Some surrogate markers have strong associations with clinical outcomes (e.g., liver histology in MASH predicts progression to cirrhosis; decline in eGFR is associated with an increased risk of ESKD); for others, the correlation is less clear. For example, the WOMAC scale is generally used to assess joint pain and function after joint replacement surgery; correlation with preventing joint replacement surgery is not clear. Observational data may help close some gaps.

- Treatment with injectable semaglutide was associated with lower mental component scores than baseline on the SF-36. Although reasons for the lower MCS scores were not reported for the STEP 1 and 3 trials, data from patients with T2D suggests that the occurrence of GI adverse events, CV events, and weight loss below 5% may contribute to lower MCS scores.[73] Further elucidation of factors that may contribute to worsened mental health and ways to mitigate any decline with semaglutide treatment is needed.

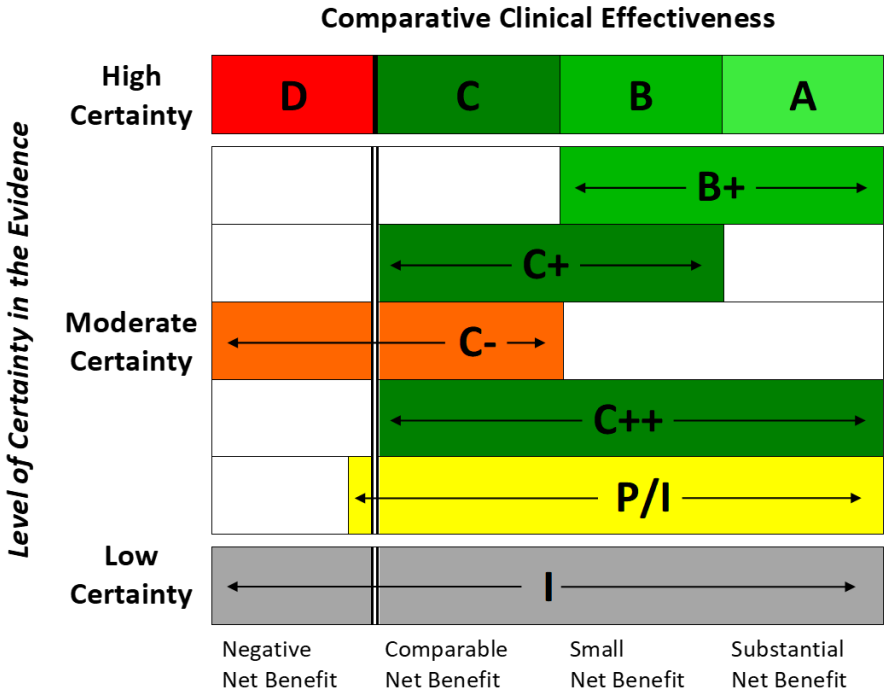
- Data suggest that stopping treatment with semaglutide or tirzepatide results in substantial weight regain and regression of improvement in metabolic markers (HbA1c, lipids, etc.). However, we do not yet have data on the impact of discontinuation on other outcomes (e.g., risk of CV events, progression of MASH or CKD, etc.) or data on whether re-treatment in the future conveys the same benefits as initial treatment. This information would be important for clinicians and patients to know when making decisions about potential discontinuation of therapy.

- Although subgroup analysis did not show statistically significant differences in weight loss by sex and race/ethnicity in post-hoc analyses of the STEP trials, Black, Hispanic, and Asian participants had numerically less weight loss than White participants. Clinical experts also noted that in their real-world experience, there appear to be differences in the efficacy of weight loss medications such as semaglutide and tirzepatide among subgroups. Given the underrepresentation of Black and Hispanic populations in the STEP and SURMOUNT trials, additional data are needed to ascertain if there may be differences in outcome by subgroup.

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



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

The evidence base for semaglutide and tirzepatide is constantly evolving, not only with clinical trials examining obesity-related outcomes, but real-world studies reporting comparative effectiveness data and adherence. Our assessments are based on the data currently available; these may change based on the emergence of more data.

Each of the drugs in our review is effective for weight loss. Treatment with tirzepatide results in greater weight loss than treatment with injectable or oral semaglutide. There continues to be uncertainty about long-term patient-important outcomes with regard to weight loss maintenance. Additionally, some potential long-term benefits of weight loss such as reduction in the need for joint replacement procedures and prevention of end-stage kidney disease and cirrhosis have not yet been demonstrated.

Injectable semaglutide has demonstrated clear improvements in secondary prevention of CV disease, and we feel this can be extrapolated to primary prevention. We are less certain about oral semaglutide as the doses apparently planned for treatment of obesity result in less weight loss than injectable semaglutide, making it uncertain how the benefits compare. Tirzepatide has demonstrated reductions in CV events in patients with diabetes in comparison with the GLP-1 RA dulaglutide at the same dose of tirzepatide used for weight loss. As such, we expect primary and secondary prevention CV benefits when tirzepatide is used for weight loss, although the magnitude of this benefit compared with semaglutide is uncertain.

Serious harms appear similar across drugs in randomized trials. However, we heard from clinicians and patients that, from a gastrointestinal standpoint, tirzepatide appears to be better tolerated than semaglutide. The relative frequency of rare, serious harms, such as pancreatitis, is uncertain. Additionally, there have been concerns raised about loss of muscle mass in patients treated with any of these agents, and relative effects among them are uncertain.

For **injectable semaglutide, oral semaglutide, and tirzepatide added on to lifestyle modifications compared with lifestyle modifications alone**, there is evidence of substantial weight loss, improvements in HRQoL, improvement of cardiometabolic risk factors, and reduction in major adverse CV events. Thus, we have high certainty of substantial net benefit from these treatments over lifestyle modification **(A)**.

For **tirzepatide compared with injectable semaglutide**, we have consistent evidence demonstrating greater weight loss with tirzepatide, and tirzepatide may have better GI tolerability. However, CV effects are extremely important in assessing this comparison, and we have substantial uncertainty about whether one treatment or the other has greater CV benefits. In the absence of greater certainty about relative CV effects, we consider treatment with tirzepatide compared with injectable semaglutide to be "Promising but Inconclusive" (**P/I**).

For **tirzepatide compared with oral semaglutide**, we again have consistent evidence demonstrating greater weight loss with tirzepatide. The magnitude of CV benefits with oral semaglutide are less clear. As with injectable semaglutide, in the absence of greater certainty about relative CV effects, we consider treatment with tirzepatide compared with oral semaglutide to be "Promising but Inconclusive" (**P/I**).

For **oral semaglutide compared with injectable semaglutide**, weight loss is slightly less at the 25 mg dose but with similar tolerability to the injectable form. In terms of CV benefit, there is evidence that the 14 mg dose of oral semaglutide confers CV risk in the T2D population but at a rate less than injectable semaglutide; the magnitude of that benefit with a higher dosage and in an obesity only population is not yet known. Thus, the net health benefit of oral semaglutide may be "comparable or worse" than injectable semaglutide **(C-)**.

Table 3.7. Evidence Ratings

Treatment	Comparator	Evidence Rating
Population: Adults with obesity or overweight with ≥1 Obesity-Related Comorbidity		
Injectable Semaglutide	Lifestyle modifications	A
Oral Semaglutide	Lifestyle modifications	A
Tirzepatide	Lifestyle modifications	A
Tirzepatide	Injectable semaglutide	P/I
Tirzepatide	Oral semaglutide	P/I
Oral Semaglutide	Injectable semaglutide	C-

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the cost-effectiveness of three weight-lowering medications over a lifetime horizon. We developed a *de novo* decision analytic Markov cohort model for this evaluation, informed by key clinical trials and prior relevant economic models, with primary reference to ICER's previously developed obesity model.[74] The model focused on an intention-to-treat (ITT) analysis, with a hypothetical cohort of patients living with obesity or with overweight and at least one obesity-related comorbidity, excluding those with already established type 2 diabetes (T2D), being treated with one of the three weight-lowering medications (injectable semaglutide, oral semaglutide, or tirzepatide) added on to lifestyle modification (e.g., caloric restriction and increased physical activity) or lifestyle modification alone. Model cycle length was one year, based on what was observed in prior published economic models and clinical data.

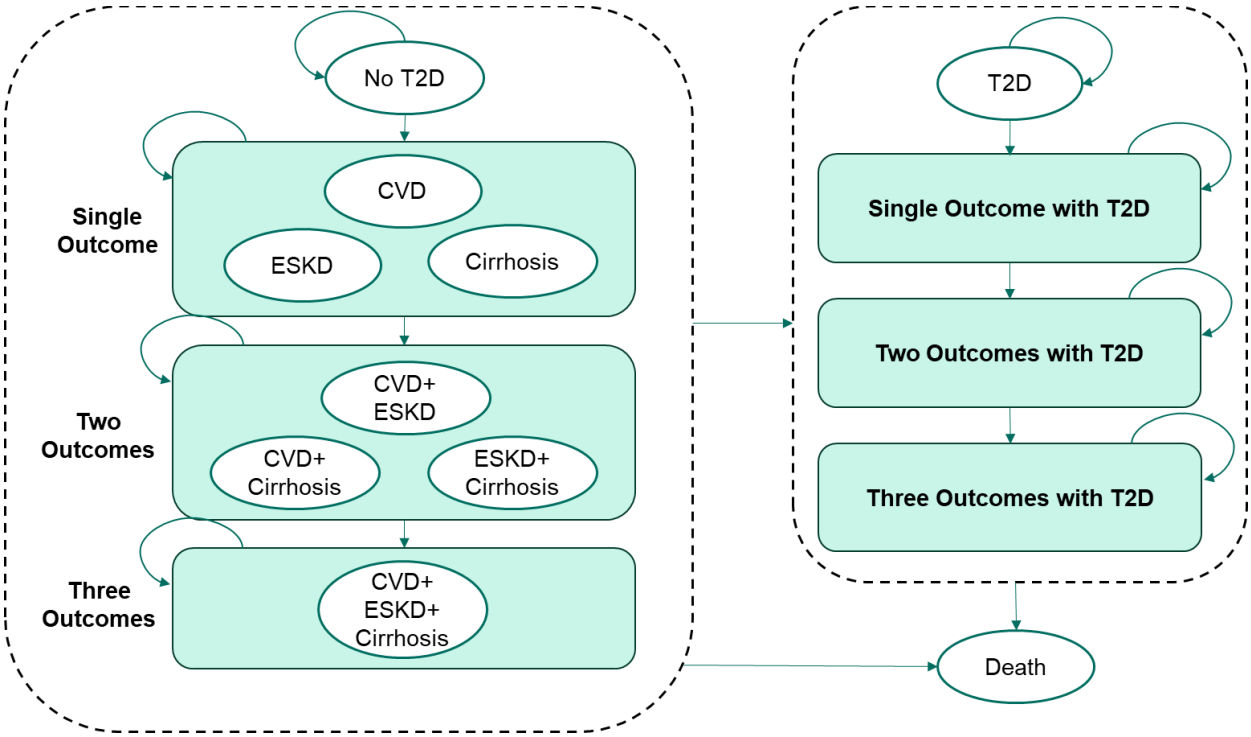
The model was primarily designed to simulate the treatment's impact on weight and on preventing the onset of key obesity-related outcomes. Based on clinical evidence, expert opinion, and public comments, the model focused on the following obesity-related outcomes: T2D, CV disease and events, end-stage kidney disease (ESKD), cirrhosis, hip or knee replacement, and OSA. Additionally, quality of life changes based on BMI, independent of the obesity-related outcomes included in the model, were applied to account for residual treatment benefits not fully represented in the model, such as effects on obesity-related outcomes not captured as health states or acute events, functional status, or mental health.

The model consisted of health states representing one or more combinations of obesity-related outcomes of interest (Figure 4.1). Patients enter the model in a non-diabetic health state and may, over time, develop obesity-related outcomes and transition to more advanced health states. Some patients may also develop diabetes and move to a corresponding diabetic health state. Multiple outcomes can develop within a single cycle, and patients may die from any health state. Each health state was associated with specific mortality risks, quality of life values, and costs. In any health state, patients may experience OSA or undergo knee or hip replacement, with the model tracking the proportions of patients with these conditions. Within the CV disease health state, patient distribution across specific subtypes was tracked over time, using the same categories as ICER's previous obesity model: post-MI, post-stroke, post-MI and post-stroke, heart failure (HF) post-MI, post-stroke and HF post-MI, and other CV disease (including other forms of HF, peripheral artery disease, angina, and transient ischemic attack).[74] To estimate the distribution of CV disease subtypes among patients with CVD over time, we used a simplified Markov tracker model with health states for CV disease subtypes and death, incorporating differing CV disease risks by diabetes

status. This approach avoided the need to model every possible combination of CV disease subtypes and other obesity-related outcomes in the main Markov model, which would have resulted in an unmanageable number of states. These subtype distributions were then applied to calculate weighted averages of mortality, utility, and costs within the CV disease health state, based on subtype-specific estimates, and to track individual CV disease events over time.

Analyses were conducted from the health sector perspective as a base case (i.e., focus on direct medical care costs only) and the modified societal perspective as a scenario analysis. Costs and outcomes are discounted at 3% per year. Our analysis follows the approach outlined in ICER's Reference Case, and additional details can be found in the Supplement. The model was developed in Microsoft Excel.

Figure 4.1. Model Structure



CVD: Cardiovascular disease; T2D: Type 2 diabetes; ESKD: End-stage kidney disease
The model tracked the proportion of patients with obstructive sleep apnea and knee or hip replacement across all health states. Within the CVD health state, patients were categorized as: post-myocardial infarction (MI), post-stroke, post-MI and post-stroke, heart failure (HF) post-MI, post-stroke and HF post-MI, and other CVD. Multiple outcomes can develop within a single cycle, and patients may die from any health state.

The following changes were made to the economic evaluation between the Draft Report and the revised Evidence Report:

- Based on public feedback, we adjusted the direct BMI impact on quality of life to address concerns about double-counting (revised from -0.007 to -0.006 per BMI unit). The concern was that the direct BMI effect may include some impacts on obesity-related conditions that are separately captured in the model, particularly OSA. We therefore calculated the OSA-attributable quality of life impact per BMI unit and excluded it from the direct BMI effect.

- Based on public feedback, the annual healthcare costs for the 'other CVD' health state were reduced from $10,718 to $8,253 to better align with the modeled population's mean age, as the previous estimate appeared elevated for this age group.

- Following publication of the OASIS 4 trial results, we updated the weight loss estimates for oral semaglutide based on the published data: the absolute difference in percent weight change for oral semaglutide plus lifestyle modification versus lifestyle modification alone was revised from -11.90% to -11.40% in year 1. Accordingly, the year 2 estimate, which is based on the year 1 estimate, was revised from -12.7% to -12.46%.

- Following internal discussion, we updated the direct CVD impact of oral semaglutide based on a meta-analysis of the SOUL and PIONEER 6 trials instead of the SOUL trial alone. The base-case estimate (HR=0.86) remained unchanged, but the 95% CI changed from 0.77-0.96 to 0.78-0.95.

4.2. Key Model Assumptions and Inputs

Our model includes several assumptions, as stated in Table 4.1.

Table 4.1. Model Assumptions

Assumption	Rationale
The included obesity-related outcomes (i.e., T2D, CV disease, ESKD, cirrhosis, hip or knee replacement, and OSA) and the direct impact of BMI on QoL are expected to reasonably capture the clinical benefits of weight-lowering medications.	Although weight-lowering medications may provide a broad range of clinical benefits, the selected obesity-related outcomes reflect those most likely impacted by weight loss—based on clinical trial data and expert opinion—and are associated with significant effects on life expectancy, quality of life, and healthcare costs.[63,75-79] While prior models have focused primarily on cardiovascular disease and T2D, our model was expanded to include additional obesity-related outcomes informed by emerging evidence to more comprehensively capture treatment effects.[74,80-82] Including further outcomes could enhance comprehensiveness but may also add unnecessary complexity and increase the risk of double-counting. To account for residual benefits from outcomes not explicitly modeled, we incorporated BMI-based quality-of-life improvements that are independent of the modeled outcomes.
Weight-lowering medications may have direct effects on preventing obesity-related outcomes, independent of weight loss-mediated benefits.	Studies suggest that weight-loss treatments may prevent obesity-related outcomes through direct mechanisms independent of weight loss or metabolic changes, particularly for cardiovascular outcomes and diabetes.[44,61,64,79] Whenever possible, we used direct treatment effects on these outcomes—beyond weight and modeled metabolic risk factors—rather than indirect effects estimated through risk functions or weight-related associations. Relying solely on indirect mechanisms may incorrectly estimate the exact benefits of treatment.

Assumption	Rationale
Direct cardiovascular effects of weight-lowering medications demonstrated in patients with diabetes can be extrapolated to estimate effects in obesity populations where direct measurements have not been performed.	The direct cardiovascular effects of oral semaglutide and tirzepatide have been evaluated only in populations with T2D.[44,49] However, these effects may reasonably be extrapolated to individuals with obesity without T2D, given the doses used and the overlapping cardiovascular risk profiles of the two populations, as well as data on semaglutide in patients with and without T2D. In the absence of dedicated cardiovascular outcomes trials in people without T2D, this serves as the best available evidence for the potential direct cardiovascular effects of weight-lowering medications. How these extrapolations were executed is discussed in the text.
Treatment discontinuation rates are based on the trial's intention-to-treat (ITT) population.	Obesity is widely recognized by experts as a chronic metabolic condition requiring long-term treatment. Although some real-world studies suggested low persistence with weight-lowering medications, robust data to accurately model long-term treatment patterns and associated outcomes (e.g., effects on BMI and direct effects on obesity-related outcomes) remain limited.[41,83,84] Furthermore, experts have noted recent improvements in utilization rates, particularly following the resolution of major barriers such as drug shortages that may have influenced earlier study results.
Patients remaining on treatment during the trial period remain on therapy for the duration of the model and the weight loss achieved in the trial is maintained.	Obesity is recognized as a chronic condition requiring lifetime management. Clinical trial data demonstrate sustained weight maintenance following maximum weight reduction while on treatment.[85,86] While natural weight fluctuations may occur over time, previous economic models have shown that assumptions about natural weight gain have minimal impact on estimated economic value; therefore, it was examined in a sensitivity analysis.[74,87]
Weight loss with a treatment is based on the weight loss observed in trials with the highest dose of that treatment.	While multiple dosing options exist and individual dosing may vary, clinical practice typically targets either the maximal effective dose unless limited by tolerability or the dose that results in appropriate weight loss if this is lower than the maximal dose. Consequently, average patients are expected to

Assumption	Rationale
	achieve weight loss consistent with the highest trial doses.
Age and sex-specific US general population mortality rates can be used for individuals with obesity who have no obesity-related outcomes.	There are a lack of mortality data specific to individuals with obesity but without modeled obesity-related outcomes. Using general population mortality rates may underestimate mortality by not fully capturing the excess risk of obesity, although our assumption that hyperlipidemia is optimally managed with statins helps mitigate one source of potential underestimation by addressing unmanaged lipid-related mortality risk. Conversely, we may overestimate mortality by including deaths from each obesity-related outcome separately. Balancing these considerations, we believe that using general population mortality rates—while separately accounting for increased mortality risk based on comorbidity status—is the most appropriate approach among the available options and is consistent with the approach used in a previous ICER model.[74]
For cohorts with multiple obesity-related outcomes, quality-of-life effects are combined multiplicatively, and healthcare costs are combined additively.	This approach is commonly used in cost-effectiveness models involving multiple comorbid conditions, including prior obesity models, and is also recommended by the Decision Support Unit (DSU) at the National Institute for Health and Care Excellence (NICE).[74,87-90] To minimize the risk of double-counting when combining multiple outcomes, we selected quality-of-life and cost inputs that were, where possible, adjusted for relevant clinical characteristics and comorbidities.

BMI: Body mass index, CVD: Cardiovascular Diseases, ESKD: End-stage kidney disease, QoL: Quality of life, US: United States

Key Model Inputs

Key model inputs are shown in Table 4.2.

Clinical Inputs

The percentage change in body weight from baseline for each treatment was derived from the ICER meta-analysis of intention to treat (ITT) populations, as well as the ITT populations of relevant clinical trials. The model assumed weight reduction occurs during the first year after treatment initiation, reaching maximum reduction by year two. From year two onward, BMI remained stable, reflecting sustained weight maintenance with continued treatment in the base case. Natural age-related weight gain from year two was explored in a sensitivity analysis.

The metabolic risk factors used to estimate the risk of obesity-related outcomes included the proportion of patients treated for hypertension (HTN), systolic blood pressure (SBP) among those treated and untreated for HTN, and glycemic control. The prevalence of treated HTN was estimated as a function of BMI, based on relationships reported in the literature and consistent with the approach used in the previous ICER model.[74,91] An average systolic blood pressure (SBP) of 125 mmHg and 135 mmHg was assumed for patients without HTN and with (treated) HTN, respectively.[74,92,93] Treatment effects on glycemic control were captured through the modeled risk of developing T2D. The annual probability of developing diabetes without interventions was derived from studies tracking incident T2D among individuals with obesity who were diabetes-free at baseline and received lifestyle modification alone.[61 64,94-96] The direct antidiabetic effect of the interventions was estimated using trial data comparing the interventions to lifestyle modification in this population.[61,64]

The risk of developing obesity-related outcomes was estimated using direct effects of treatment on obesity-related outcomes beyond those mediated by weight loss (e.g., direct CV effects), where data allowed. Otherwise, these effects were estimated indirectly through changes in weight and related risk factors, using existing risk equations or established associations between weight and the risk of onset.

Annual risk of primary CV disease was estimated using the office-based, non-laboratory prediction model from the Framingham Heart Study and recurrent CV disease risks were obtained from existing literature in the lifestyle modification arm.[74 97-99] In the intervention arms, both primary and recurrent CV disease risks were reduced according to the direct cardiovascular effects observed in clinical trials.[45,49,79] Given the limited availability of direct CV outcome data that perfectly align with the modeled population (patients with obesity without diabetes), CV effects were derived from the most relevant available clinical trials for each intervention.

For injectable semaglutide, CV effects were obtained from the SELECT trial, which enrolled patients with obesity, without diabetes, and with a history of CV disease (HR=0.8).[79] ICER's prior report on medications for obesity noted that semaglutide appeared to have greater CV benefits in patients with T2D than would be explained by improvements in A1C.[22] In the semaglutide cardiovascular outcomes trial in T2D (SUSTAIN-6), there were too few events in patients without known CV disease to compare the reduction in the primary composite CV outcome to that seen in those with known CV disease, but in patients with prior stroke or MI – potential markers for more significant CV disease – reductions in the primary outcome were not superior to those without such events (HR 0.76 versus 0.70; NS).[100] In meta-analyses of trials of statins, a class of medications that like semaglutide seems to have pleiotropic effects on CV risk, statins reduce a CV composite by 26% in primary prevention, and by 19% in secondary prevention.[101,102] Given the lack of consistent directionality of relative efficacy effect modification by primary versus secondary prevention or treatment in T2D versus treatment in those without T2D, we feel that using the reduction seen in SELECT (HR 0.8) is a reasonable choice for modeling CV risk reduction in patients without T2D since SELECT used semaglutide at the doses we are modeling.

For oral semaglutide, no CV outcome data exists for patients with obesity without diabetes; therefore, effects were derived from a meta-analysis of the SOUL trial and PIONEER6 trial, which enrolled individuals with T2D (HR=0.86).[44,45] Acknowledging that these trials evaluated a lower dose of oral semaglutide (14 mg) than the dose used in the model (25 mg), we explored alternative approaches: 1) adjusting the direct CV effect of injectable semaglutide using the ratio of weight loss between injectable and oral formulations and 2) applying an indirect approach based on Framingham risk equations. These approaches produced less favorable results than what was estimated from the meta-analysis of the SOUL and PIONEER 6 trials; therefore, we considered the meta-analysis estimate to represent the most optimistic scenario.

For tirzepatide, CV effects were assumed to be equivalent to those of injectable semaglutide due to insufficient data from SURPASS-CVOT to estimate effects in the ITT population (HR=0.8).[49] The tirzepatide CV efficacy estimates may be updated when full SURPASS-CVOT results become available. Tirzepatide uses similar doses for treatment of DM and obesity, making such an extrapolation more direct than it would have been for injectable semaglutide.

ESKD incidence rates for each treatment arm were estimated by applying BMI-related risk multipliers to a reference ESKD incidence rate in the US general population, used as a proxy for risk at a BMI of 30 (approximating the US average BMI). [103-106] The risk of cirrhosis and knee and hip replacements was modeled similarly, using US general population incidence rates as a reference, with risks adjusted based on key risk factors including BMI. [105,107-112] To estimate the proportion of patients with OSA in each treatment arm over time, the baseline prevalence was adjusted using odds ratios from a study that examined BMI subgroups and OSA prevalence associations via individual patient data meta-analysis.[84,113]

Mortality was estimated using all-cause mortality from US life tables as the baseline, with additional excess mortality applied for patients who develop obesity-related outcomes or experience acute events such as MI and stroke.[114]

The discontinuation rate reflected all-cause discontinuation observed in the trials among the ITT population, based on data from the ICER meta-analysis and relevant clinical trials.[46,85] All treatment discontinuations within the first two years of initiation were captured, consistent with the trial follow-up period and the timeframe from which efficacy data were obtained. Individuals remaining on treatment after two years were assumed to continue for life based on the rationale provided in Table 4.1. Discontinuation impacted only drug costs, as treatment efficacy estimates from the ITT population already account for the effects of discontinuation.

Severe GI AEs were modeled in the analysis. The proportion of patients experiencing severe GI AEs for each treatment was informed by the ICER meta-analysis and relevant clinical trials.[46,85]

Additional details can be found in Table 4.2 and Supplement E2.

Health State Utility Inputs

The impact of weight loss on quality of life was modeled in two ways: through its effect on reducing the risk of obesity-related outcomes that diminish quality of life, and through additional quality-of-life gains directly associated with reductions in BMI, independent of obesity-related outcomes.

Age-specific utilities from the general US population served as baseline values, with condition-specific utility decrements applied for patients who have developed obesity-related outcomes.[74,115] For health states with multiple obesity-related outcomes, disutilities were combined multiplicatively using disutility multipliers. Short-term disutilities from acute events were applied additively, assuming that that their temporary impact is likely independent and occurs on top of the baseline impairment associated with chronic conditions. Additionally, the utility decrement associated with BMI, independent of the modeled obesity-related outcomes, was applied. Based on a study examining the relationship between BMI and EQ-5D–measured quality of life, each one-unit increase in BMI was associated with a 0.006 reduction in utility, after adjusting for key obesity-related comorbidities.[116]

The model did not incorporate potential quality-of-life differences between oral and injectable administration due to limited and conflicting evidence. One vignette study suggested higher quality of life with oral semaglutide, while another survey found no significant preference differences.[117,118]

Additional details can be found in Table 4.2 and Supplement E2.

Economic Inputs

The annual net prices for injectable semaglutide and tirzepatide were derived directly from SSR Health as of Q1 2025, as its estimates reflect aggregated net prices that account for the use of direct-to-patient options available through NovoCare and LillyDirect.[119] As the price of oral semaglutide is not yet available, it was assumed to be the same as that of injectable semaglutide. The annual cost of lifestyle modification was assumed to be approximately $605, based on a prior economic evaluation.[74]

Non-drug healthcare costs included both related and unrelated components. Related healthcare costs attributable to each obesity-related outcome were sourced from existing literature. An additive approach was used to estimate costs for health states involving multiple outcomes, consistent with the previous cost-effectiveness studies in obesity.[74,88,89] In addition, related healthcare costs for short-term events—such as MI, stroke, knee or hip replacements, and G3-4 GI AEs—were applied additively to individuals who experience these events. Gender- and age-specific unrelated health care costs were additive to the related health care costs associated with obesity-related outcomes or events and were obtained from Jiao et al.[120] For the modified societal perspective, the model included productivity costs associated with chronic conditions, as these represent the primary drivers of overall productivity impact.

All non-drug costs used in the model were updated to 2024 dollars using the using the consumer price index for health care via Bureau of Economic Analysis data.[121]

Additional details can be found in Table 4.2 and Supplement E2.

Table 4.2. Key Model Inputs

Parameter	Input	Source
Patient Characteristics		
Mean Age	46 years	Gleason, 2024; Ruseva, 2025[41,42]
Percent Female	79%	Rodriguez, 2025[84]
Mean BMI	37.6 kg/m^2	Rodriguez, 2025[84]
Mean SBP for those without HTN	125 mmHg	Steven J Atlas, 2022[74]
Mean SBP for those with HTN	135 mmHg	Rodriguez, 2014; Mackenzie, 2022[92,93]
Percent Smoking	14.6%	CDC[122]
Treatment Effects on Body Weight		
Change in Weight from Baseline by Year 1 (%), LSM	-3.41%	ICER Pooled data*
Change in Weight from Baseline by Year 2 (%), LSM	-2.60%	Garvey, 2022[85]
Absolute Difference in % Weight Change by Year 1, Injectable Semaglutide vs. LSM	-13.14%	ICER MA; Table D1.12

Parameter	Input	Source
Absolute Difference in % Weight Change by Year 2, Injectable Semaglutide vs. LSM	-14.00%	Garvey, 2022[85]
Absolute Difference in % Weight Change by Year 1, Oral Semaglutide vs. LSM	-11.40%	Wharton, 2025[43]
Absolute Difference in % Weight Change by Year 2, Oral Semaglutide vs. LSM†	-12.46%	Author's calculation; Wharton, 2025; Garvey, 2022[43,85]
Absolute Difference in % Weight Change by Year 1, Tirzepatide vs. LSM‡	-18.97%	Jastreboff, 2025[64]
Absolute Difference in % Weight Change by Year 2, Tirzepatide vs. LSM‡	-18.97%	Assumed to be the same as Year 1 data
Treatment Effects on Glycemic Control		
Annual Probability of T2D for LSM	2.3%	Kahn, 2024; Torgerson, 2004; Jastreboff, 2025; Le Roux, 2017; Edelman, 2004[61,94 64,95,96]
HR for T2D with Injectable Semaglutide vs. LSM	0.27	Kahn, 2024[61]
HR for T2D with Oral Semaglutide vs. LSM	0.27	Assumed to be the same as injectable semaglutide
HR for T2D with Tirzepatide vs. LSM	0.07	Jastreboff, 2025[64]
Risk of CVD		
Annual Probability of CVD for LSM	Estimated based on the risk function from the Framingham Heart Study	D'Agostino Sr, 2008[97]
HR for CVD with Injectable Semaglutide vs. LSM	0.80	Lincoff, 2023[79]
HR for CVD with oral Semaglutide vs. LSM	0.86	Husain, 2019; McGuire 2025[44,45]
HR for CVD with Tirzepatide vs. LSM§	0.80	Assumed to be the same Injectable Semaglutide
Treatment Discontinuation		
% Discontinued treatment by Year 1, LSM	19.46%	ICER Pooled data#
% Discontinued treatment by Year 2, LSM	27.00%	Garvey, 2022[85]
% Discontinued treatment by Year 1, Injectable Semaglutide	14.60%	ICER MA
% Discontinued treatment by Year 2, Injectable Semaglutide#	14.60%	Assumed to be the same as Year 1§
% Discontinued treatment by Year 1, Oral Semaglutide	14.21%	Garvey, 2024[123]
% Discontinued treatment by Year 2, Oral Semaglutide§	14.21%	Assumed to be the same as Year 1
% Discontinued treatment by Year 1, Tirzepatide	11.09%	Jastreboff, 2022[46]

Parameter	Input	Source
% Discontinued treatment by Year 2, Tirzepatide¤	11.09%	Assumed to be the same as Year 1
Adverse Events		
% Experiencing severe GI AEs, LSM	1.31%	ICER Pooled data#
% Experiencing severe GI AEs, Injectable Semaglutide	3.20%	ICER MA
% Experiencing severe GI AEs, Oral Semaglutide	0.66%	Garvey, 2024[123]
% Experiencing severe GI AEs, Tirzepatide	4.01%	Jastreboff, 2022[46]
Drug Costs		
Annual Net Price, Injectable Semaglutide**	$6,829	SSR Health
Annual Net Price, Oral Semaglutide	$6,829	Assumed to be the same as injectable semaglutide
Annual Net Price, Tirzepatide**	$7,973	SSR Health

AE: Adverse Events, BMI: Body mass index, CVD: Cardiovascular Disease, T2D: Type 2 Diabetes, GI: Gastrointestinal, HR: Hazard ratio, HTN: Hypertension, ICER MA: ICER'S Meta Analysis, kg: kilogram, LSM: Lifestyle modification, m: meter, mmHg: millimeter of mercury, SBP: Systolic blood pressure

*Pooled from STEP 1, STEP 3, STEP 5, STEP 8, OASIS 4, and SURMOUNT 1 using unadjusted data

†Due to the lack of year 2 data for oral semaglutide, the absolute difference in % weight change at Year 1 for oral semaglutide was adjusted by multiplying it by the ratio of the absolute difference in % weight change at Year 2 to that at Year 1 for injectable semaglutide.

‡The estimate was derived from individuals with obesity and prediabetes due to the lack of an unadjusted efficacy estimate for the overall population; The absolute difference in % weight change at Year 2 was assumed to be the same as at Year 1, due to the absence of Year 2–specific data and consistent with the long-term BMI trend observed in Jastreboff et al. [64]

§This value may be revised once the detailed results of the SURPASS-CVOT trial become available. [49]

#Pooled from STEP 1, STEP 3, STEP 4, STEP 8, OASIS 4, and SURMOUNT 1

¤The percentage discontinued by Year 2 was assumed to be the same as Year 1 for the following reasons: Although Year 2 discontinuation data for injectable semaglutide are available from the STEP 5 trial, the cumulative discontinuation by Year 2 reported in STEP 5 (13.2%) is lower than the cumulative discontinuation by Year 1 estimated in the ICER MA, which is illogical. No Year 2–specific discontinuation data are available for oral semaglutide and tirzepatide.

**Price as of Q1 2025; The annual net price already accounts for the use of direct-to-patient option available through NovoCare and LillyDirect.

4.3. Results

Base-Case Results

Table 4.3 presents the discounted intervention costs, total costs, quality-adjusted life years (QALYs), equal-value life years (evLYs), and life years, as well as the undiscounted number of stroke and MI events, for injectable semaglutide, oral semaglutide, and tirzepatide added to lifestyle modification compared with lifestyle modification alone. Tables 4.4 and 4.5 present the discounted incremental results as well as incremental cost-effectiveness ratios estimated based on the clinical and cost

outcomes shown in Table 4.3. For oral semaglutide, the results are based on the assumption that its price is equal to that of injectable semaglutide.

Table 4.3. Discounted Base-Case Results for the Interventions versus Lifestyle Modification

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI Events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$132,229	$447,925	47	16.79	16.81	20.39
Oral Semaglutide*‡	$132,475	$449,980	51	16.68	16.70	20.35
Tirzepatide*	$158,493	$459,490	45	17.16	17.18	20.49
Lifestyle Modification	$9,036	$370,644	69	15.63	15.63	20.01

evLYs: equal value of life years, QALY: quality-adjusted life year, MI: Myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

†Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

Table 4.4. Discounted Incremental Results for the Interventions versus Lifestyle Modification

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI Events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$123,193	$77,281	-22	1.16	1.18	0.38
Oral Semaglutide*‡	$123,438	$79,337	-18	1.05	1.07	0.34
Tirzepatide*	$149,456	$88,846	-24	1.54	1.55	0.48
Lifestyle Modification	Reference					

evLYs: equal value of life years, QALY: quality-adjusted life year, MI: Myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

†Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

Table 4.5. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per MI or Stroke Avoided†
Injectable Semaglutide*	Lifestyle Modification	$66,355	$65,280	$202,949	$669,832
Oral Semaglutide*‡	Lifestyle Modification	$75,456	$74,143	$233,969	$861,284
Tirzepatide*	Lifestyle Modification	$57,779	$57,188	$185,135	$711,151

evLYs: equal value of life years, QALY: quality-adjusted life year, MI: Myocardial infarction

*Each treatment is added to lifestyle modification

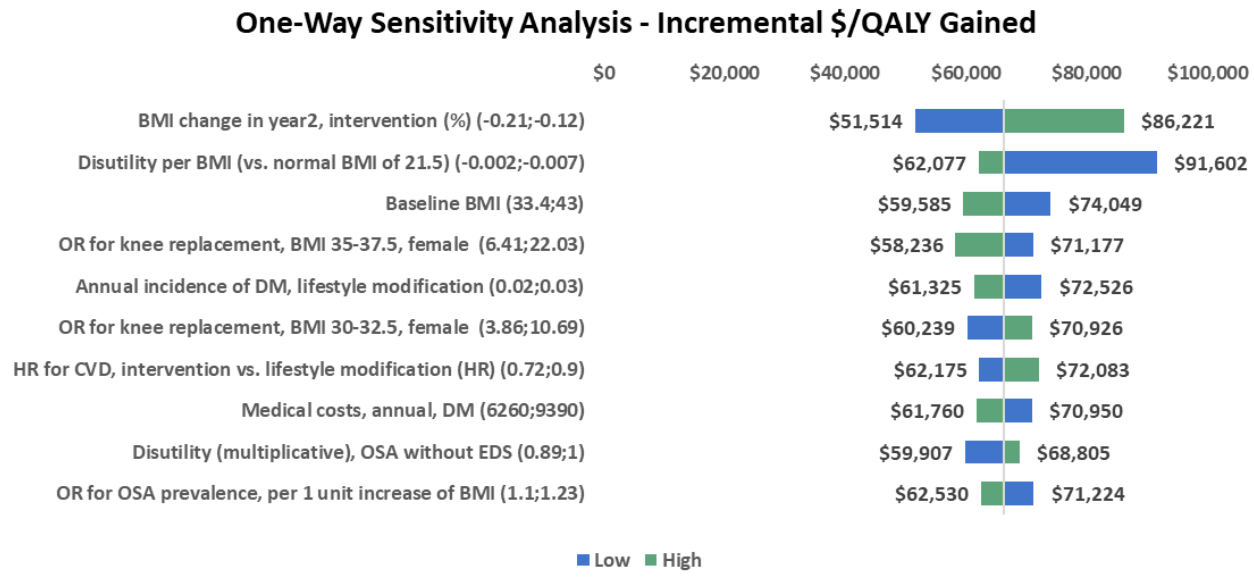
†Estimated using discounted values for the number of stroke or MI events to ensure consistency with the discounted costs used in the numerator: 25, 27, 24, and 36 per 100 individuals for injectable semaglutide, oral semaglutide, tirzepatide, and lifestyle modification, respectively.

‡Based on an assumed price

Sensitivity Analyses

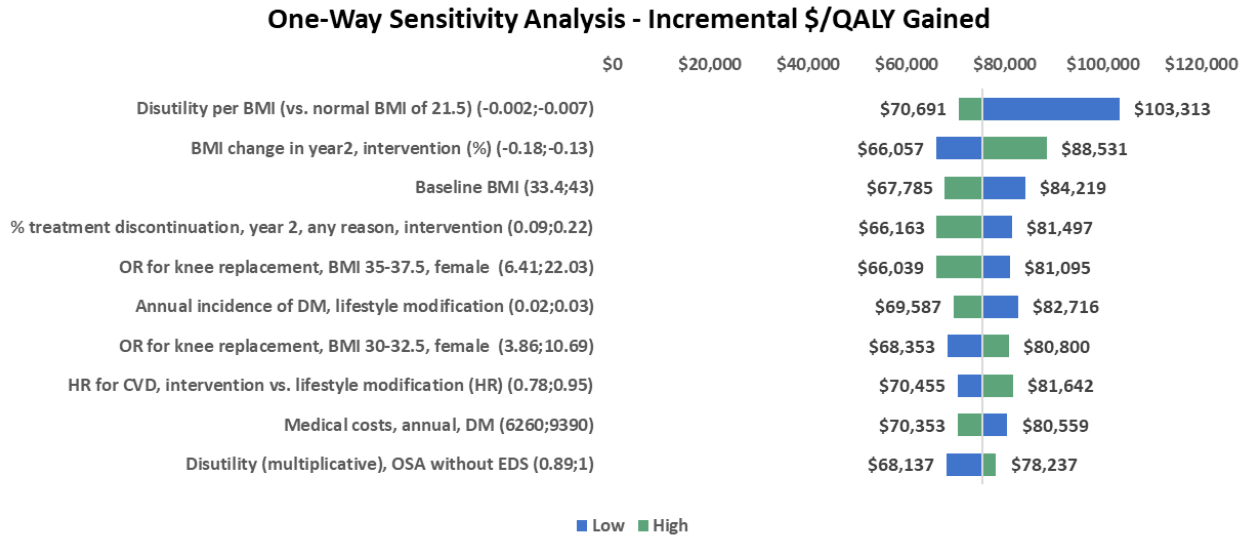
Figures 4.2, 4.3, and 4.4 show the inputs with the greatest influence on the incremental cost-effectiveness ratio per QALY for injectable semaglutide, oral semaglutide, and tirzepatide, respectively. The parameters with the greatest influence on the cost-effectiveness results across all three interventions were the treatment effect on BMI at Year 2 and the quality-of-life change associated with BMI independent of modeled outcomes.

Figure 4.2. Tornado Diagram for Injectable Semaglutide Added to Lifestyle Modification versus Lifestyle Modification Alone



BMI: Body Mass Index, DM: type 2 diabetes, OR: Odds ratio, HR: hazard ratio, CVD: cardiovascular disease, OSA: Obstructive sleep apnea
Note: Only the 10 most influential model parameters are shown.

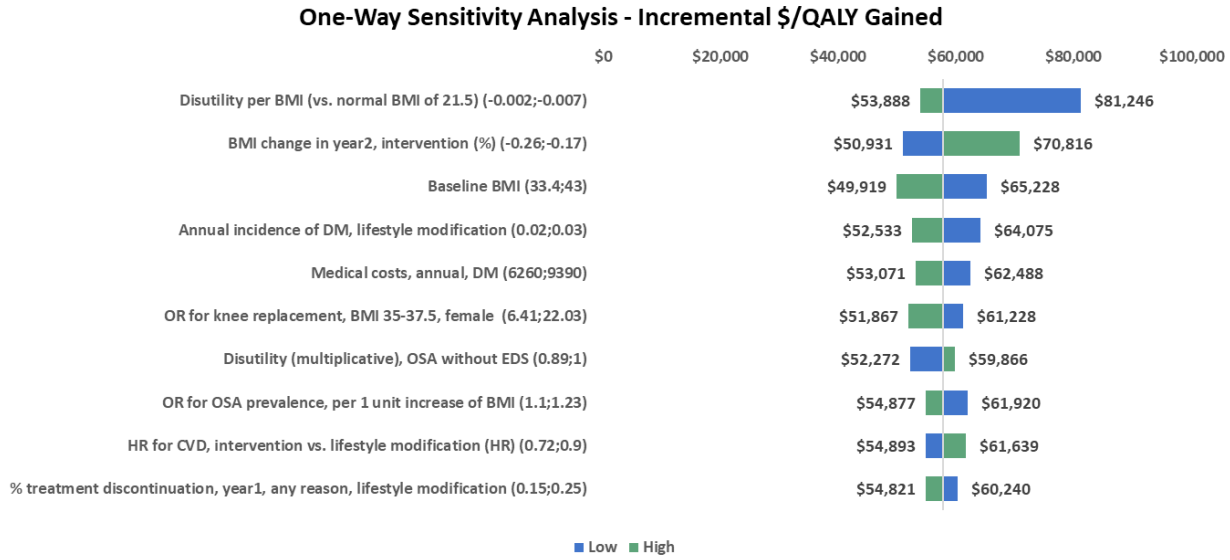
Figure 4.3. Tornado Diagram for Oral Semaglutide Added to Lifestyle Modification versus Lifestyle Modification Alone*



BMI: Body Mass Index, DM: type 2 diabetes, OR: Odds ratio, HR: hazard ratio, CVD: cardiovascular disease, OSA: Obstructive sleep apnea
Note: Only the 10 most influential model parameters are shown.

*Based on an assumed price of oral semaglutide

Figure 4.4. Tornado Diagram for Tirzepatide Added to Lifestyle Modification versus Lifestyle Modification Alone



BMI: Body Mass Index, DM: type 2 diabetes, OR: Odds ratio, HR: hazard ratio, CVD: cardiovascular disease, OSA: Obstructive sleep apnea
Note: Only the 10 most influential model parameters are shown.

Tables 4.6 and 4.7 present the probability of injectable semaglutide, oral semaglutide, and tirzepatide added to lifestyle modification being cost-effective at common thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively. Please refer to Supplement Section E4 for the mean and 95% credible intervals for model outcomes.

Table 4.6. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Injectable Semaglutide, Oral Semaglutide, and Tirzepatide Added to Lifestyle Modification versus Lifestyle Modification Alone

	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
Injectable Semaglutide	14.9%	99.8%	100.0%	100.0%
Oral Semaglutide*	4.5%	96.0%	100.0%	100.0%
Tirzepatide	33.3%	99.9%	99.9%	100.0%

QALY: quality-adjusted life year

*Based on an assumed price

Table 4.7. Probabilistic Sensitivity Analysis Cost per evLY Gained Results: Injectable Semaglutide, Oral Semaglutide, and Tirzepatide Added to Lifestyle Modification versus Lifestyle Modification Alone

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Injectable Semaglutide	16.9%	99.9%	100.0%	100.0%
Oral Semaglutide*	5.4%	96.4%	100.0%	100.0%
Tirzepatide	35.6%	99.9%	99.9%	100.0%

evLYs: equal value of life years gained

*Based on an assumed price

Scenario Analyses

We conducted several scenario analyses to examine the uncertainty and potential variations in the findings. Additionally, the cost-effectiveness of treatment was estimated separately based on baseline obesity status (e.g., overweight, obesity, and severe obesity), as individuals with higher initial BMI tend to achieve greater absolute weight loss or may experience differential treatment effects. We performed a subgroup analysis for patient groups stratified by the following baseline BMI: BMI <30, BMI ≥30, BMI ≥35, and BMI ≥40.

The scenario analyses examined are outlined below in Tables 4.8 to 4.10. Additional details are detailed in Supplement Section E5.

1. Modified societal perspective that includes patient productivity costs
2. Exclusion of unrelated health care costs
3. Alternative source for the association between BMI and ESKD risk: Hsu 2006 [124]
4. Alternative direct diabetic impacts of injectable and oral semaglutide to account for differences in the source populations between semaglutide and tirzepatide
5. Alternative baseline incidence of diabetes: Edelman 2004.[96]
6. Subgroup analysis based on the baseline BMI:
    - BMI <30
    - BMI ≥30
    - BMI ≥35
    - BMI ≥40

Table 4.8. Scenario and Subgroup Analysis Results for Injectable Semaglutide Added to Lifestyle Modification versus Lifestyle Modification Alone

Scenario	Cost per QALY Gained	Cost per evLY Gained
Base-Case	$66,355	$65,280
Modified Societal Perspective	$53,831	$52,960
Exclusion of Unrelated Medical Costs	$61,723	$60,723
Alternative Source for the Impact of BMI on ESKD Risk	$59,796	$58,752
Alternative Direct Diabetic Impacts of Injectable and Oral Semaglutide	$55,883	$54,974
Alternative Baseline Incidence of Diabetes	$51,670	$50,670
Subgroup Analysis: BMI <30	$81,655	$81,409
Subgroup Analysis: BMI ≥30	$66,458	$65,329
Subgroup Analysis: BMI ≥35	$57,654	$56,588
Subgroup Analysis: BMI ≥40	$66,351	$64,554

QALY: quality-adjusted life year, evLY: equal value of life year; BMI: Body mass index; ESKD: End-stage kidney disease

Table 4.9. Scenario and Subgroup Analysis Results for Oral Semaglutide Added to Lifestyle Modification Versus Lifestyle Modification Alone*

Scenario	Cost per QALY Gained	Cost per evLY Gained
Base-Case	$75,456	$74,143
Modified Societal Perspective	$62,494	$61,406
Exclusion of Unrelated Medical Costs	$70,885	$69,652
Alternative Source for the Impact of BMI on ESKD Risk	$67,836	$66,552
Alternative direct diabetic impacts of injectable and oral semaglutide	$64,311	$63,168
Alternative Baseline Incidence of Diabetes	$58,442	$57,221
Subgroup Analysis: BMI <30	$87,253	$86,875
Subgroup Analysis: BMI ≥30	$74,584	$73,089
Subgroup Analysis: BMI ≥35	$71,239	$69,703
Subgroup Analysis: BMI ≥40	$72,454	$70,259

QALY: quality-adjusted life year, evLY: equal value of life year; BMI: Body mass index; ESKD: End-stage kidney disease

*Based on an assumed price of oral semaglutide

Table 4.10. Scenario and Subgroup Analysis Results for Tirzepatide Added to Lifestyle Modification versus Lifestyle Modification Alone

Scenario	Cost per QALY Gained	Cost per evLY Gained
Base-Case	$57,779	$57,188
Modified Societal Perspective	$45,389	$44,925
Exclusion of Unrelated Medical Costs	$53,348	$52,802
Alternative Source for the Impact of BMI on ESKD Risk	$50,166	$49,609
Alternative Baseline Incidence of Diabetes	$42,016	$41,510
Subgroup Analysis: BMI <30	$76,332	$76,483
Subgroup Analysis: BMI ≥30	$61,120	$60,429
Subgroup Analysis: BMI ≥35	$53,799	$53,062
Subgroup Analysis: BMI ≥40	$54,176	$53,144

QALY: quality-adjusted life year, evLY: equal value of life year; BMI: Body mass index; ESKD: End-stage kidney disease

Threshold Analyses

Tables 4.11 and 4.12 report the threshold prices at $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively.

Table 4.11. QALY-Based Threshold Analysis Results

	Annual Net Price*	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Injectable Semaglutide	$6,829	$5,700	$9,100	$12,400	$15,700
Oral Semaglutide†	$6,829	$5,300	$8,300	$11,300	$14,300
Tirzepatide	$7,973	$7,300	$11,500	$15,700	$19,900

QALY: quality-adjusted life year

*Annual price paid by payers after accounting for all discounts, rebates, coupons, or other financial concessions as estimated by SSR Health.

†The annual net price of oral semaglutide was assumed to be the same as that of injectable semaglutide.

Table 4.12. evLY-Based Threshold Analysis Results

	Annual Net Price*	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Injectable Semaglutide	$6,829	$5,800	$9,200	$12,500	$15,900
Oral Semaglutide†	$6,829	$5,400	$8,400	$11,400	$14,500
Tirzepatide	$7,973	$7,400	$11,600	$15,800	$20,100

evLYs: equal value of life years gained, WAC: wholesale acquisition cost

*Annual price paid by payers after accounting for all discounts, rebates, coupons, or other financial concessions as estimated by SSR Health.

†The annual net price of oral semaglutide was assumed to be the same as that of injectable semaglutide.

Model Validation

Model validation followed standard practices in the field. All mathematical functions were tested to ensure consistency with the report and supplemental appendix materials. Stress testing using null input values confirmed that the model produced results aligned with expectations. An independent modeler also verified the mathematical functions, inputs, and outputs. Validation also included comparisons with findings from similar models identified in the literature, focusing on those with comparable populations, settings, perspectives, and treatments. Specifically, we compared our model's outcomes, inputs, and assumptions with other published models to evaluate face validity and identify key similarities and differences (Supplement E6). Additionally, the model analysis plan and/or draft evidence report were reviewed by multiple stakeholders—including manufacturers and clinical and economic experts—and changes were made based on their feedback.

Uncertainty and Controversies

There are several limitations and areas of uncertainty in our model:

- Uncertainty around long-term treatment effects beyond the trial period: We assumed that weight loss achieved by year 2 is maintained throughout the treatment duration. Similarly, direct treatment effects on diabetes and CV diseases observed in the trials were maintained lifelong. These assumptions were informed by the longest available follow-up trial data–104 weeks for semaglutide and 176 weeks for tirzepatide–which showed sustained weight reduction while patients remained on treatment.[64,125] However, more data on the long-term durability of treatment benefits are needed to accurately capture the lifetime impact of these interventions. Depending on the long-term trajectory of treatment effects, our results could be biased in either direction, with the magnitude of bias remaining uncertain.
- Uncaptured treatment benefits: Although we modeled several key obesity-related outcomes and applied BMI-based quality-of-life adjustments independent of these outcomes, additional benefits from unmodeled conditions may exist (e.g., cost or mortality impacts related to those outcomes). Furthermore, limited data on direct treatment effects for outcomes such as ESKD and cirrhosis may have led to an under- or overestimation of treatment benefits. Including more obesity-related outcomes (e.g., cancer, infertility, etc.) would likely improve the estimated cost-effectiveness of these interventions. However, the selection of obesity-related outcomes was guided by clinical evidence, expert input, and public comments and is considered to capture the primary benefits of the interventions.
- Risk of double counting: It is possible that treatment benefits may have been overestimated due to double counting. We obtained mortality, utility, and cost estimates for each obesity-related outcome, which were combined multiplicatively or additively when health states involved multiple conditions. However, if these estimates were not fully adjusted for

coexisting conditions modeled separately, combining them could lead to an overestimation of the true impact of comorbidities. Since most of our estimates were adjusted for key clinical characteristics or comorbidities, and we focused on a limited set of obesity-related outcomes, the risk of double-counting is unlikely to be substantial.

- Generalizability of the Framingham Heart Study: The Framingham Heart Study was conducted primarily among white participants and may have somewhat limited generalizability to non-white populations. [126,127] Although White adults account for the majority of the modeled population (approximately 75% White, 14% Black, 2% Asian, and 9% other or unknown racial/ethnic groups, based on a study of real-world users of weight-lowering medications), the Framingham risk equations may not completely capture CV disease risk in the modeled population, as risk can vary by race.[84] Although we varied the coefficients of the Framingham risk equations in sensitivity analyses to account for uncertainty in CV disease risk, there is likely some residual uncertainty in the results. However, there is no strong evidence to suggest that the relative effects of the treatments vary by race or ethnic group.
- Generalizability of direct CV disease effects from populations with diabetes: The direct treatment effect of oral semaglutide on CV outcomes was evaluated in the SOUL trial and PIONEER6 trial both of which included only individuals with T2D. There could be uncertainty regarding the generalizability of these findings to the obesity population without T2D.
- Uncertainty around the real-world treatment patterns and outcomes associated with treatment discontinuation and adherence: we assumed that treatment discontinuation patterns mirrored those observed in the ITT population of the clinical trials during the trial period and those who remained on therapy during the trial period continue treatment for the duration of the model. We did not model alternative discontinuation scenarios for several reasons. First, obesity is now widely recognized by clinical experts as a chronic condition that requires long-term management. During the scoping phase, most clinical experts indicated that lifelong pharmacologic treatment is the preferred approach for managing obesity, given the high likelihood of weight regain after discontinuation. Moreover, although earlier real-world studies suggested low persistence with weight-lowering medications, experts noted recent improvements in drug utilization following the resolution of barriers like drug shortages.[41,83,84] Finally, limited data on long-term real-world treatment patterns and their effects on weight and obesity-related outcomes make it difficult to accurately model real-world use. While studies demonstrate that treatment discontinuation leads to weight regain, insufficient evidence exists regarding complex real-world patterns—such as treatment switching, restarting, or drug holidays—and their effects on BMI. Additionally, the impact of these patterns on direct obesity-related outcomes (e.g., cardiovascular or antidiabetic effects) has not been studied. Therefore, modeling alternative real-world scenarios would be premature given the numerous assumptions and high

uncertainty required. Treatment persistence in this model may be higher than in real-world settings, resulting in greater clinical benefits and costs of the treatments.

- Uncertainty around net drug prices: Although SSR pricing data provides the best available estimate of net prices, these values may be volatile given the rapidly evolving pricing environment and the recent implementation of direct purchase programs such as Novocare and Lilly Direct.
- Comparison limited to lifestyle modification: Comparisons between interventions were out of scope and therefore not conducted. The results presented cannot be used to estimate the cost-effectiveness of one intervention versus another. Such comparisons were conducted only for the comparative clinical effectiveness assessment.

4.4 Summary and Comment

Cost-effectiveness analyses indicate that injectable semaglutide, oral semaglutide, and tirzepatide, when added on to lifestyle modification, provide greater clinical benefits than lifestyle modification alone. Although these treatments increase intervention costs, they yield long-term savings in non-intervention costs. At current net prices, their incremental cost-effectiveness ratios were below commonly used cost-effectiveness thresholds. Results were most influenced by the treatment effect on BMI at Year 2 and the quality-of-life change associated with BMI independent of modeled outcomes, though the overall conclusions remained unchanged across all sensitivity and scenario analyses. The model also found that these interventions were generally cost-effective across a range of BMI cut points, although there was somewhat greater cost effectiveness in patients with higher baseline BMI.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities 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. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	More than 40% of the US population is living with obesity. Despite the number of therapies available, there remain challenges to accessing highly effective obesity medications and thus additional options for treatment may be beneficial in closing the treatment gap. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported for the modeled population below. Individuals who manage obesity with lifestyle modifications were used as a reference group. evLY shortfalls: Absolute shortfall: 6.23 Proportional shortfall: 20.41% QALY shortfalls: Absolute shortfall: 4.99 Proportional shortfall: 17.02% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.

This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.	The overall prevalence of obesity in the US at least 40% but with differences according to racial and ethnic background. Black adults and Hispanic adults have a higher prevalence of disease compared to White and Asian adults. The Health Improvement Distribution Index (HIDI) was calculated for the following subgroups: Non-Hispanic Blacks: 49.9%/41.9% = 1.2 Hispanic adults: 45.6%/41.9% = 1.1
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	These treatments are not immediately expected to have a substantial impact on caregivers' quality of life. Long-term, prevention of obesity-related complications may decrease caregiver burden.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	The availability an oral formulation of semaglutide provides an alternative to those patients who are not able to or do not wish to use injectable GLP-1 RA medications.

6. Health Benefit Price Benchmark

The threshold prices for injectable semaglutide, oral semaglutide, and tirzepatide from the health care sector perspective, based on both evLYs and QALYs gained, are presented in Table 6.1 below. The Health Benefit Price Benchmark (HBPB) for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 per QALY and $150,000 per evLY gained. At the current net price – or the assumed net price in the case of oral semaglutide – we estimate no discounts are needed for any of the three drugs.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Injectable Semaglutide, Oral Semaglutide, and Tirzepatide

Annual Prices Using…	Annual Net Price	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from Net Price to Reach Threshold Prices
Injectable Semaglutide				
QALYs Gained	$6,829	$9,100	$12,400	No discount needed
evLYs Gained	$6,829	$9,200	$12,500	No discount needed
Oral Semaglutide				
QALYs Gained	$6,829*	$8,300	$11,300	No discount needed*
evLYs Gained	$6,829*	$8,400	$11,400	No discount needed*
Tirzepatide				
QALYs Gained	$7,973	$11,500	$15,700	No discount needed
evLYs Gained	$7,973	$11,600	$15,800	No discount needed

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

*The net price of oral semaglutide was assumed to equal that of injectable semaglutide.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of the interventions of interest (injectable semaglutide, oral semaglutide, and tirzepatide) for the population of adults with a BMI ≥30 or ≥27 with at least one weight-related comorbidity (excluding the T2D population). All costs were undiscounted and estimated over a five-year time horizon. We used the annual net price ($6,829 for injectable semaglutide and oral semaglutide, $7,973 for tirzepatide) and the threshold prices (at $50,000, $100,000, $150,000 and $200,000 per evLYG) for each drug in our estimates of budget impact. As previously stated, since the price of oral semaglutide is not yet available, it was assumed to be the same as that of injectable semaglutide.

To estimate the size of the potential candidate population for treatment, we used inputs for the prevalence of adults in the US with obesity (42.4%), and the prevalence of adults in the US who are overweight (30.7%)[128] multiplied by the percentage of overweight adults in the US that have multimorbidity (39.5%).[129] From this population, we excluded those who are already receiving medication treatment for obesity (22%).[130] We also excluded the population of US adults with type 2 diabetes (approximately 9.5% of the total population)[131] multiplied by the percentage of T2D patients who are overweight or obese (approximately 90% of the T2D population).[132,133] Applying these sources to the total US adult population averaged over the next five years (~270,900,000)[111] results in estimates of ~92,000,000 eligible patients.

We first conducted individual budget impact analyses for each intervention of interest (Figure 7.1), assuming that 20% of the eligible population would initiate the treatment in each of the five years, or ~18,400,000 patients per year. In these individual analyses, the new uptake was comprised solely of patients starting the intervention of interest (i.e. in the injectable semaglutide analysis, the new uptake comprised only patients starting injectable semaglutide). Separately, in a blended budget impact analysis (Figure 7.2), to account for multiple interventions of interest, we assumed that the 20% uptake includes patients initiating all three interventions of interest equally (i.e., 6.7% of patients initiating injectable semaglutide, 6.7% of patients initiating oral semaglutide, and 6.7% of patients initiating tirzepatide), with ~30,700,000 patients initiating each treatment over the next five years, or ~6,100,000 patients per treatment each year. For both the individual and blended budget impact analyses, we assumed that all patients are on lifestyle modification alone at baseline.

7.2. Results

Figure 7.1 illustrates the cumulative per patient budget impact for each individual intervention of interest compared to lifestyle modification. At the injectable semaglutide net price of $6,829, the average annual budget impact per patient was $6,607 in year one, with cumulative annual budget impact per patient increasing to $16,426 by year five. At the oral semaglutide assumed net price of $6,829, the average annual budget impact per patient was $6,405 in year one, with cumulative annual budget impact per patient increasing to $16,402 by year five. At the tirzepatide net price of $7,973, the average annual budget impact per patient was $7,711 in year one, with cumulative annual budget impact per patient increasing to $19,460 by year five.

Figure 7.1. Cumulative Annual Per Patient Budget Impact for Each Intervention

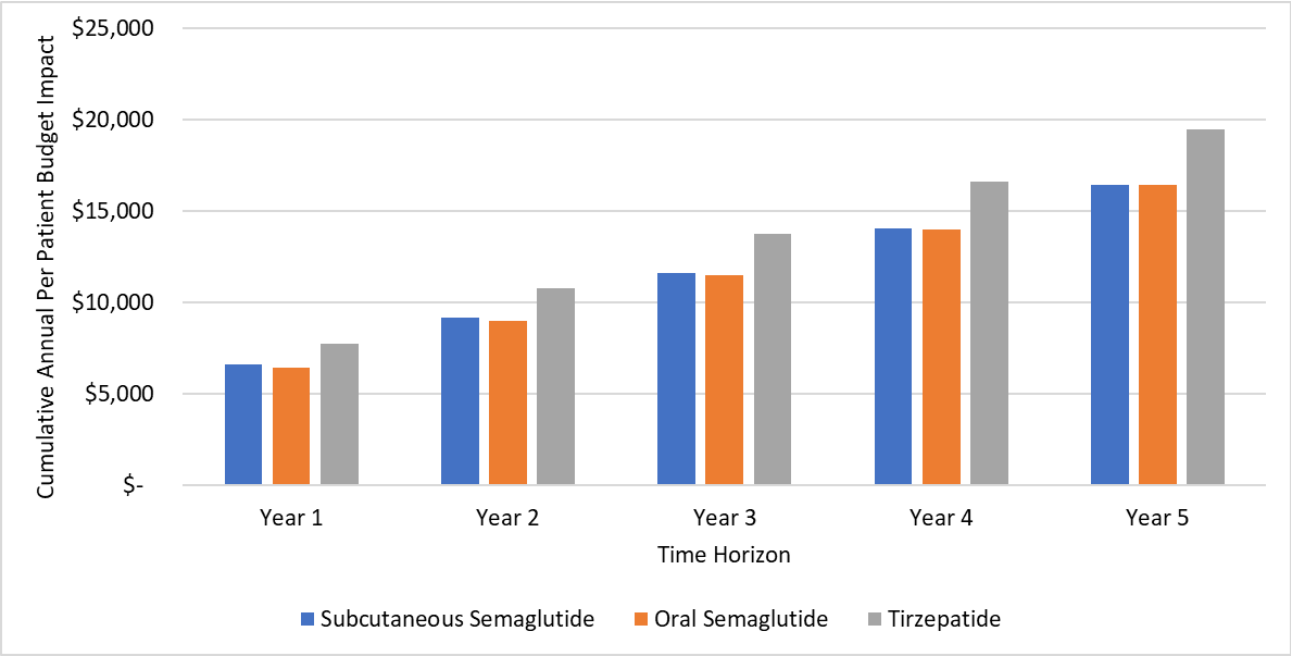
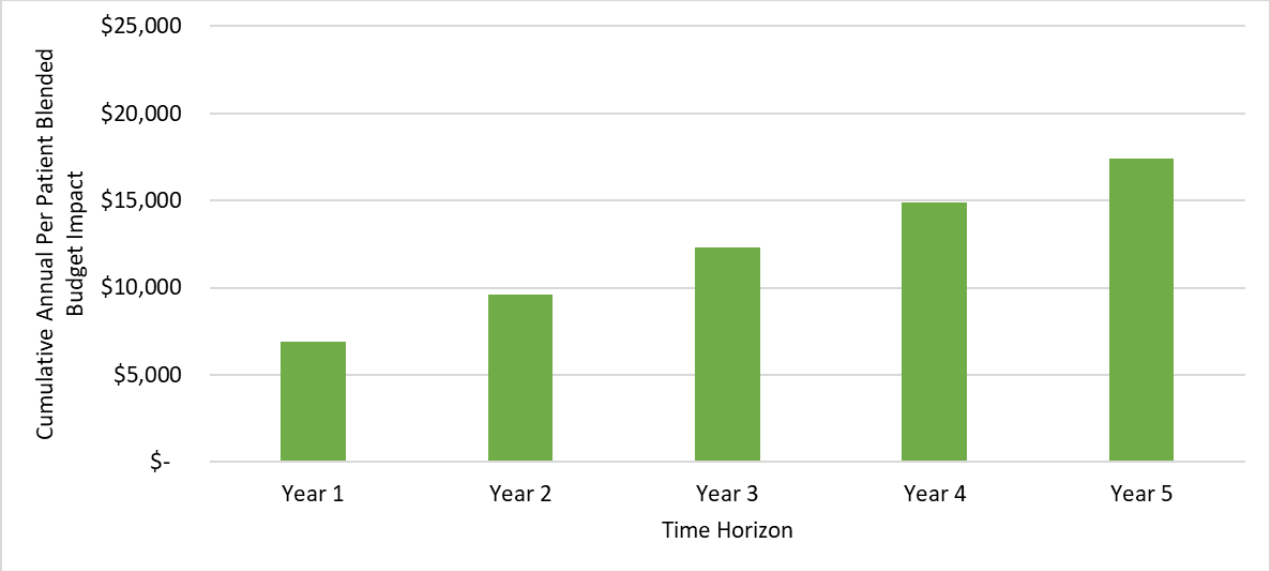


Figure 7.2 illustrates the cumulative per patient treated blended budget impact assuming a combined uptake of all interventions of interest compared to lifestyle modification. At the net prices of each intervention of interest, the average annual budget impact per patient was $6,908 in year one, with cumulative annual budget impact per patient increasing to $17,429 by year five.

Figure 7.2. Cumulative Annual Per Patient Blended Budget Impact of a Combined Uptake of all Interventions



Across all interventions, fewer than 1% of eligible patients could receive treatment before the potential budget impact threshold is met.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Overweight and obesity: Body mass index (BMI), calculated based on height and weight in kg/m^2, is the most common way that obesity is defined in clinical practice. An individual is considered overweight at a BMI of ≥25 kg/m^2. Obesity is defined as a BMI ≥30 kg/m^2 and individuals with a BMI ≥40 kg/m^2 are considered to have severe obesity.[134] BMI is often expressed without units.

Weight-related comorbid conditions: Clinical guidelines recommend adjunctive pharmacotherapy for adults with overweight who have coexisting conditions, including but not limited to hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease.[135]

Important Outcomes

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.[23]

Categorical weight loss: Represents the proportion of individuals who achieve a specified threshold change in body weight from baseline to follow-up assessment. Weight loss was assessed using thresholds of ≥5%, ≥10%, ≥15%, ≥20%.[23]

Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT): The IWQOL is a quality of life instrument specifically developed to assess individuals with obesity. It measures eight domains: health, social/interpersonal, work, mobility, self-esteem, sexual life, activities of daily living, and comfort with food. The IWQOL-Lite Clinical Trials Version (IWQOL-Lite-CT) is a shorter version developed and validated for use in clinical trials.[136,137] 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 reflects an improvement in health status, with anchor-based analyses supporting a minimal clinically important difference ranging from 13.5 to 16.6 points across composite scores.[138]

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.[139] 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). 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 reflects an improvement in health status, with a 3.7-point increase representing the threshold for a clinically meaningful improvement.[23]

EQ-5D-5L: The EQ-5D-5L is a standardized five-item tool used to assess health-related quality of life (HRQoL) across various conditions. It covers mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A single index score is derived, ranging from less than 0 (worse than death) to 1 (perfect health). Additionally, a visual analogue scale (0–100) captures the respondent's self-rated health.[140]

Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain subscale: A clinical tool used to measure the severity of knee pain during daily activities. It includes 5 items assessing pain during walking, stair climbing, sitting, lying down, and standing, rated on a 5-point Likert scale from "none" to "extreme." Higher total scores indicate greater pain, stiffness, and functional limitations. The minimal clinically important difference for the WOMAC is 4.2 points for the pain subscale.[62,141]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[142] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[143,144] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to

vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

A2. Potential Cost-Saving Measures in Obesity

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, please reference ICER's Value Assessment Framework). These services are ones that would not be directly affected by therapies for obesity (e.g., hospitalizations for myocardial infarction), 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 patients with obesity that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive any feedback on this inquiry.

B. Stakeholder Input: Supplemental Information

B1. Patient Community Insights: Methods

We spoke with eight individuals living with obesity and two patient advocacy groups to gain perspectives on living with obesity and experiences with obesity treatment. The eight individuals were men and women living in various areas of the US and at various life stages and were recommended by patient advocacy groups.

B2. Clinical Expert Input: Methods

We spoke with clinical experts ranging from primary care physicians who are board-certified in obesity medicine to endocrinologists specializing in the treatment of genetic obesity syndromes. Clinical experts practiced in a variety of settings, from academic medical centers to weight management companies. We also spoke with one clinical specialty society, as well as one payer.

C. Clinical Guidelines

Clinical practice guidelines for obesity range cover topics ranging from diagnosis and treatment to recommendations for addressing weight stigma and bias. We targeted clinical practice guidelines focused on the treatment of obesity, and these guidelines are summarized below.

American Gastroenterology Association (AGA) Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity[16]

The 2022 AGA Clinical Practice Guidelines focused on reviewing evidence on pharmacological interventions for adults with obesity. The guidelines were developed by a multidisciplinary panel of content experts and guideline methodologists, and drugs evaluated for this guideline included semaglutide, liraglutide, phentermine-topiramate, naltrexone-buproprion, orlistat, and phentermine. The panel made the following recommendations for adults with obesity or overweight with weight-related complications: 1) The addition of pharmacological agents to treatment is recommended if there is an inadequate response to lifestyle interventions alone; 2) Semaglutide 2.4 mg should be prioritized over other approved anti-obesity medications for the long-term treatment of obesity for most patients; 3) Liraglutide, phentermine-topiramate, and naltrexone-buproprion are also recommended for long-term management of obesity; 4) Orlistat is not recommended for treatment of obesity; 5) Phentermine monotherapy is approved for short-term management of obesity (12 weeks) and is recommended for management of obesity.

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity[135]

The 2016 AACE/ACE clinical practice guidelines provides evidence-based recommendations about the management of obesity as a chronic disease, targeting both weight-related complications and adiposity to improve overall health and quality of life. The guidelines cover screening and diagnosis of obesity and obesity-related complications, recommendations for lifestyle modifications, pharmacotherapy, and bariatric surgery. The guidelines recommend that pharmacotherapy be used as an adjunct to lifestyle modifications and should be used for the chronic treatment of the disease. The guidelines further recommend that pharmacotherapy decisions should be individualized clinicians and their patients should have access to all approved medications to allow for appropriate individualization of therapy. The guideline further evaluates and recommends treatment based on specific clinical scenarios (e.g., chronic kidney disease, liver disease, hypertension, cardiovascular disease, etc.). Finally, individuals with a BMI ≥40 or BMI ≥35 and 1 or more severe obesity-related complication should be eligible for bariatric surgery.

American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) Guideline for the Management of Overweight and Obesity in Adults[145]

The 2013 AHA/ACC/TOS guidelines offered comprehensive recommendations on identifying and treating individuals living with obesity. Recommendations included both counseling about lifestyle modifications and pharmacologic treatment, including offering or referring for high-intensity comprehensive lifestyle interventions, adding pharmacotherapy as an adjunct in individuals with BMI ≥30 or BMI ≥27 and ≥1 obesity-associated comorbid condition(s), and offering referral to a bariatric surgeon for consultation for individuals with BMI ≥40 or BMI ≥35 with obesity-related comorbid conditions. The guideline did not make recommendations for specific pharmacotherapy, though many modern drugs were approved after the publication of this clinical practice guideline.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for this review is adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition, who are actively seeking medical management for weight loss; adults with established diabetes are excluded.

Data permitting, we will seek to examine the following patient subgroups, including but not limited to: age, sex at birth, race and ethnicity, BMI categories, use and intensity of lifestyle interventions, established cardiovascular disease, and prior bariatric surgery.

Interventions

The full list of interventions is as follows:

- Semaglutide, injectable administered weekly
- Semaglutide, oral administered daily
- Tirzepatide, injectable administered weekly

Each of these may be administered in combination with lifestyle modification (e.g., reduced calorie diet and increased physical activity) or alone.

Comparators

We intend to compare these interventions to lifestyle modification alone, to no treatment, and to each other.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Weight reduction (e.g., mean % change in body weight loss, categorical weight loss [e.g., ≥5%, ≥10%, ≥15%, ≥20% etc.], and change in BMI from baseline)
    - Weight re-gain
    - Quality of life (e.g., short form [SF]-36, impact of weight on quality of life-lite for clinical trial [IWQoL-Lite-CT], impact of weight on daily activities questionnaire [IWDAQ]) and functional status)
    - Mental health outcomes (e.g., anxiety and depression)
    - Physical functioning (e.g., six-minute walk test)
    - Obesity-related complications, including but not limited to:
        - Cardiovascular events (e.g., major adverse cardiovascular events [MACE]-3 or MACE-5, non-fatal MI, and non-fatal stroke)
        - Sleep apnea
        - Diabetes requiring treatment
        - Heart failure
        - Hyperlipidemia requiring treatment
        - Hypertension requiring treatment
        - End-stage kidney disease
        - Cirrhosis
        - Symptomatic degenerative joint disease
        - Joint replacement surgery
        - Fractures
        - Infertility
        - Cancer
        - Mortality
    - Adverse events including
        - Gastrointestinal events (e.g., nausea, vomiting, diarrhea, constipation, etc.)
        - Muscle loss leading to weakness
        - Serious adverse events
        - Adverse events leading to treatment discontinuation
- Other Outcomes
    - Body composition
    - Bone density
    - Chronic kidney disease (CKD)
    - Metabolic-associated liver disease
    - Polycystic ovarian syndrome

Timing

Evidence on intervention effectiveness will be derived from studies of at least 26 weeks duration and evidence on harms from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. High-quality comparative observational studies will also be included.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
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.

Section and Topic	Item #	Checklist Item
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)).
	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 estimate 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.

Section and Topic	Item #	Checklist Item
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
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 injectable semaglutide, oral semaglutide, and tirzepatide for obesity followed established best research methods.[146,147] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[148] The PRISMA guidelines include a checklist of 27 items (see **Table D1.1**).

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 the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

#	Search Term
1	exp Obesity/
2	exp Weight Loss/
3	exp Overweight/
4	(obes* or overweight or "over weight" or "over-weight" or "body mass ind*" or "BMI").ti,ab.
5	1 or 2 or 3 or 4
6	('ozempic' or 'rybelsus' or 'wegovy' or 'semaglutide' or 'NN 9535' or 'NN9535' or 'NN-9535').ti,ab.
7	('tirzepatide' or 'zepbound' or 'mounjaro' or 'LY 3298176' or 'LY3298176' or 'LY-3298176').ti,ab.
8	6 or 7
9	5 and 8
10	9 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 "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 "video-audio media").pt.
11	10 not (animals not (humans and animals)).sh.
12	limit 11 to english language
13	remove duplicates from 12

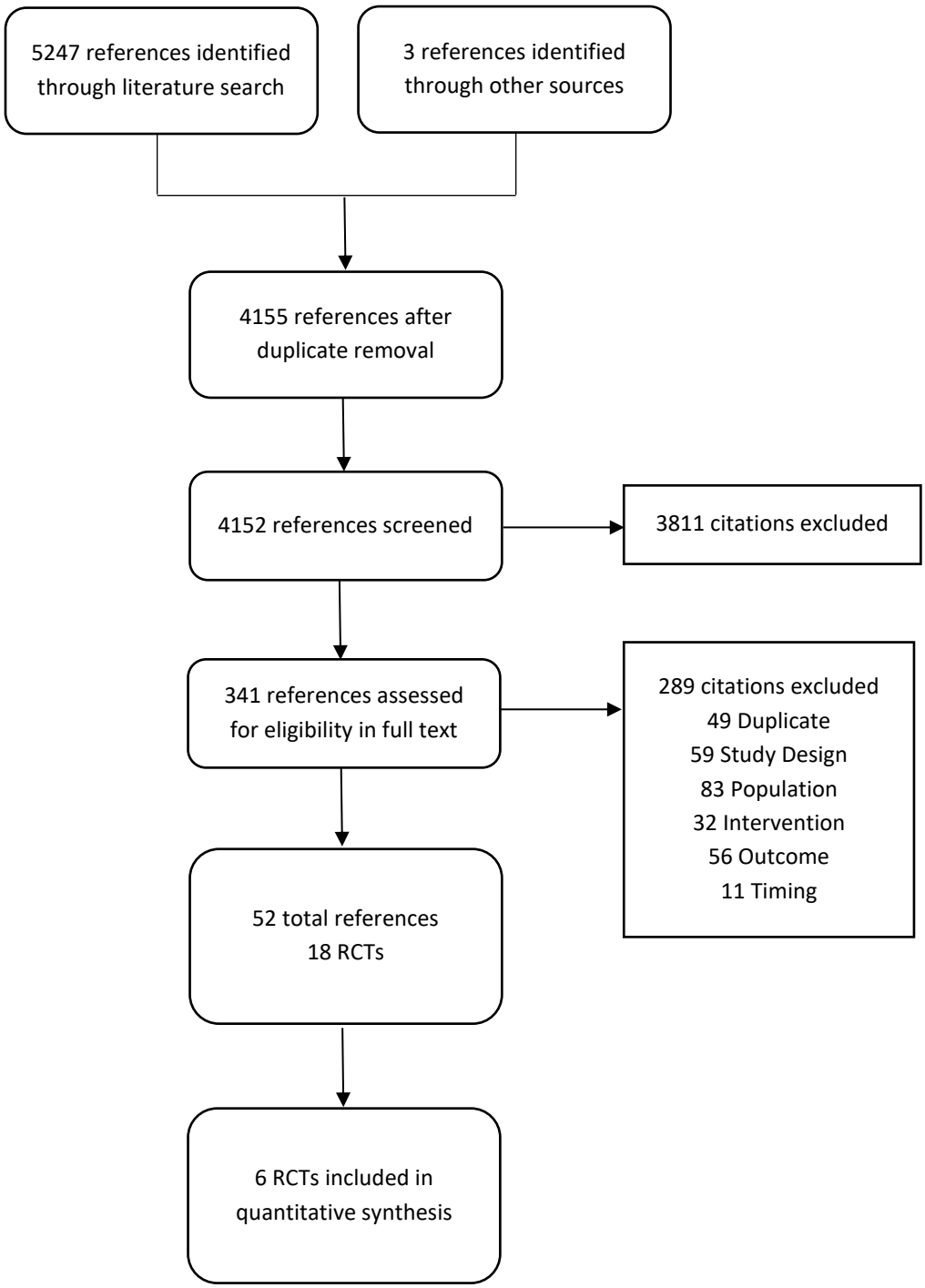
Date of last search: 09/23/2025

Table D1.3. Search Strategy of EMBASE SEARCH

#	Search Term
1	'obesity'/exp OR 'obesity'
2	'body weight loss'/exp OR 'body weight loss'
3	'overweight'/exp OR 'overweight' OR ‘over-weight’ OR ‘over-weight’
4	'obes*':ti,ab OR 'body mass ind*':ti,ab OR ‘BMI’:ti,ab
5	#1 OR #2 OR #3 OR #4
6	(‘ozempic’ OR ‘rybelsus’ OR ‘wegovy’ OR ‘semaglutide’ OR ‘NN 9535’ OR ‘NN9535’ OR ‘NN-9535’):ti,ab
7	(‘tirzepatide’ OR ‘zepbound’ OR ‘mounjaro’ OR ‘LY 3298176’ OR ‘LY3298176’ OR ‘LY-3298176’):ti,ab
8	#6 OR #7
9	#5 AND #8
10	#9 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)
11	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
12	#10 NOT #11
13	#12 AND [english]/lim
14	#13 NOT [medline]/lim

Date of last search: 09/23/2025

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. 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

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[147,149] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the primary outcomes of all key trials included in this review. See Table D1.4-D1.5.

Table D1.4. Risk of Bias Assessments for Primary Endpoints of Key Trials Assessing Body Weight Change from Baseline

Study	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Injectable Semaglutide						
STEP 1	Low	Low	Low	Low	Low	Low
	Notes:					
STEP 3	Low	Low	Low	Low	Low	Low
	Notes:					
STEP 4	Low	Some concerns	Low	Low	Low	Some concerns
	Notes: Participants may have been unblinded by changes in weight and side effects due to switching to a placebo after treatment with injectable semaglutide in the 20 week lead-in period.					
STEP 5	Low	Low	Some concerns	Low	Low	Some concerns
	Notes: More participants had missing data and discontinued the trial in the placebo group for documented reasons (i.e., lack of efficacy, withdrawal of consent, and lost to follow-up) compared to the semaglutide group.					
STEP 8	Low	Low	Low	Low	Low	Low
	Notes: Our rating only reflects the semaglutide versus placebo comparison; we did not consider the other trial arms in our ratings.					
STEP 10	Low	Low	Low	Low	Low	Low
	Notes:					
Oral Semaglutide						
OASIS-4	Low	Low	Low	Low	Low	Low
	Notes:					
Tirzepatide						
SURMOUNT 1	Low	Low	Some concerns	Low	Low	Some concerns
	Notes: More participants had missing data and discontinued the trial in the placebo group for documented reasons (lost to follow-up and withdrawal of consent) compared to the tirzepatide group.					
SURMOUNT 3	Low	Low	Low	Low	Low	Low
	Notes:					
SURMOUNT 4	Low	Some concerns	Low	Low	Low	Some concerns

Study	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
	Notes: Participants may have been unblinded based on changes in weight and adverse events due to switching to placebo after taking tirzepatide for the 36 weeks lead-in period.					
Direct Comparison						
SURMOUNT 5	Low	Some Concerns	Low	Low	Low	Some Concerns
	Notes: Due to open-label study design					

OASIS-4 was excluded due to the lack of availability of a publication and a protocol.

Table D1.5. Risk of Bias Assessments for Primary Endpoints of Key Trials Assessing Cardiovascular Outcomes and Obesity-Related Complications

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Injectable Semaglutide						
STEP 9	Low	Low	Low	Low	Low	Low
	Notes:					
SELECT		Low	Low	Low	Low	Low
	Notes:					
STEP-HFpEF	Low	Low	Low	Low	Low	Low
	Notes:					
ESSENCE	Low	Low	Low	Low	Low	Low
	Notes:					
Tirzepatide						
SUMMIT	Low	Low	Low	Low	Low	Low
	Notes:					
SURMOUNT OSA	Low	Low	Some Concerns	Low	Low	Some Concerns
	Notes: More participants had missing data and discontinued the trial in the placebo group for documented reasons (i.e., withdrawal by subject) compared to the semaglutide group.					

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[56] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates[150-152], using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.7 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.8.

Table D1.6. Demographic Characteristics and Categories

Demographic Characteristics	Categories
Race and Ethnicity*	Racial categories: White Black or African American Asian American Indian and Alaskan Native Native Hawaiian and Other Pacific Islanders Ethnic Category: Hispanic or Latino
Sex	Female Male
Age	Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.7. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.8. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results

Table D1.9. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
STEP-1	Fair	Fair	NR
STEP-3	Good	Poor	NR
STEP-4	Fair	Poor	NR
STEP-5	Fair	Poor	NR
STEP-8	Good	Poor	NR
STEP-9	Poor	Poor	Good
STEP-10	Fair	Fair	NR
OASIS-4	Poor	Poor	NR
SURMOUNT-1	Fair	Fair	Poor
SURMOUNT-3	Fair	Fair	NR
SURMOUNT-4	Good	Fair	Fair
SURMOUNT-5	Good	Fair	Poor
SURMOUNT-OSA	Fair	Fair	NR
SELECT	Fair	Fair	Good
SURPASS-CVOT	NR	Fair	NR
STEP-HFpEF	Poor	Good	NR
ESSENCE	Fair	Good	NR
SUMMIT	Fair	Good	NR

NE: Not Estimated, NR: Not Reported. OASIS-4 was excluded due to the lack of availability of a publication describing the relevant categories.

*The ratings presented above reflect representation based on estimates for the U.S. obesity population. CDR ratings may vary when adjusted for the specific disease prevalence within populations enrolled in individual trials.

Table D1.8. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for 18 trials. Given that these are multinational clinical trials and US-specific enrollment data is not publicly available, each trial was rated using the full sample.

Table D1.10. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Prevalence/ Incidence	79.06%	16.74%	2.72%	21.23%	-	-	1.06%	0.29%
STEP-1	75.10%	5.70%	13.30%	12.00%	-	-	NR	NR
PDRR	0.95	0.34	4.89	0.57	-	-	0	0
Score	3	1	3	2	9	Fair	NC	NC
STEP-3	76.10%	18.90%	1.80%	19.80%	-	-	0.16%	0.49%
PDRR	0.96	1.13	0.66	0.93	-	-	0.15	1.69
Score	3	3	2	3	11	Good	NC	NC
STEP-4	83.70%	13.00%	2.40%	NR	-	-	NR	NR
PDRR	1.06	0.78	0.88	NC	-	-	0	0
Score	3	2	3	0	8	Fair	NC	NC
STEP-5	93.10%	3.90%	0.66%	12.80%	-	-	0.99%	NR
PDRR	1.18	0.23	0.24	0.60	-	-	0.93	0
Score	3	1	1	2	7	Fair	NC	NC
STEP-8	73.30%	18.90%	3.80%	11.50%	-	-	NR	NR
PDRR	0.93	1.13	1.40	0.54	-	-	0	0
Score	3	3	3	2	11	Good	NC	NC
STEP-9	60.90%	7.60%	13.80%	NR	-	-	11.90%	NR
PDRR	0.77	0.45	5.07	NC	-	-	11.23	0
Score	2	1	3	0	6	Poor	NC	NC
STEP-10	88.00%	4.00%	4.00%	3.40%	-	-	0.48%	NR
PDRR	1.11	0.24	1.47	0.16	-	-	0.45	0
Score	3	1	3	1	8	Fair	NC	NC
OASIS-4	91.53%	7.16%	0.60%	7.80%	-	-	NR	NR
PDRR	1.16	0.43	0.22	0.37	-	-	0	0
Score	3	1	1	1	6	Poor	NC	NC
SURMOUNT-1	70.60%	7.90%	10.90%	47.80%	-	-	9.09%	0.35%
PDRR	0.89	0.47	4.01	2.25	-	-	8.58	1.21
Score	3	1	3	3	10	Fair	NC	NC
SURMOUNT-3	86.00%	10.90%	0.70%	53.90%	-	-	1.03%	NR
PDRR	1.09	0.65	0.26	2.54	-	-	0.97	0
Score	3	2	1	3	9	Fair	NC	NC
SURMOUNT-4	80.10%	11.20%	7.20%	44.20%	-	-	NR	0.29
PDRR	1.02	0.67	2.65	2.08	-	-	0	1

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Score	3	2	3	3	11	Good	NC	NC
SURMOUNT-5	76.10%	19.20%	2.40%	26.10%	-	-	0.80%	NR
PDRR	0.96	1.15	0.88	1.23	-	-	0.75	0
Score	3	3	3	3	12	Good	NC	NC
SURMOUNT-OSA	69.30%	5.10%	17.10%	37.10%	-	-	7.89%	NR
PDRR	0.88	0.30	6.29	1.75	-	-	7.44	0
Score	3	1	3	3	10	Fair	NC	NC
SELECT	84.00%	3.80%	8.20%	NR	-	-	NR	NR
PDRR	1.06	0.23	3.01	NC	-	-	0	0
Score	3	1	3	0	7	Fair	NC	NC
SURPASS-CVOT	NR	NR	NR	NR	NR	NR	NR	NR
PDRR	0	0	0	0	0	0	0	0
Score	NC	NC	NC	NC	NC	NC	NC	NC
STEP-HFpEF	95.80%	4.00%	0%	6.80%	-	-	NR	NR
PDRR	1.21	0.24	0.00	0.32	-	-	0	0
Score	3	1	0	1	5	Poor	NC	NC
ESSENCE	67.50%	0.63%	27.00%	18.30%	-	-	NR	NR
PDRR	0.86	0.04	9.93	0.86	-	-	0	0
Score	3	1	3	3	10	Fair	NC	NC
SUMMIT	70.00%	4.90%	17.90%	NR	-	-	6.84%*	
PDRR	0.89	0.29	6.58	NC	-	-	NC	NC
Score	3	1	3	0	7	Fair	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio
*Not calculate because reported as "Native American, Alaska Native, or Pacific Islander"
OASIS-4 was excluded due to the lack of a publication or presentation describing the relevant categories.

Table D1.11. Sex and Age

	Sex				Age		
	Male	**Female**	**Score**	**Rating**	**Older Adults (≥65 years)**	**Score**	**Rating**
Prevalence/ Incidence	**48.35%**	**51.65%**	**-**	**-**	**16.56%**	**-**	**-**
STEP-1	25.90%	74.10%	-	-	NR	-	-
PDRR	0.54	1.43	-	-	NC	-	-
Score	2	3	5	Fair	NC	NC	NC
STEP-3	19.00%	81.00%	-	-	NR	-	-
PDRR	0.39	1.57	-	-	NC	-	-
Score	1	3	4	Poor	NC	NC	NC
STEP-4	21.00%	79.00%	-	-	NR	-	-
PDRR	0.43	1.53	-	-	NC	-	-
Score	1	3	4	Poor	NC	NC	NC
STEP-5	22.40%	77.60%	-	-	NR	-	-
PDRR	0.46	1.50	-	-	NC	-	-
Score	1	3	4	Poor	NC	NC	NC
STEP-8	21.60%	78.40%	-	-	NR	-	-
PDRR	0.45	1.52	-	-	NC	-	-
Score	1	3	4	Poor	NC	NC	NC
STEP-9	18.40%	81.60%	-	-	18.90%	-	-
PDRR	0.38	1.58	-	-	1.14	-	-
Score	1	3	4	Poor	3	3	Good
STEP-10	29.00%	71.00%	-	-	NR	-	-
PDRR	0.60	1.37	-	-	NC	-	-
Score	2	3	5	Fair	NC	NC	NC
OASIS-4	48.35%	51.65%	-	-	NR	-	-
PDRR	0.44	1.53	-	-	NC	-	-
Score	1	3	4	Poor	NC	NC	NC
SURMOUNT-1	32.50%	67.50%	-	-	6.00%	-	-
PDRR	0.67	1.31	-	-	0.36	-	-
Score	2	3	5	Fair	1	1	Poor
SURMOUNT-3	37.10%	62.90%	-	-	NR	-	-
PDRR	0.77	1.22	-	-	NC	-	-
Score	2	3	5	Fair	NC	NC	NC
SURMOUNT-4	29.40%	70.60%	-	-	10.00%	-	-
PDRR	0.61	1.37	-	-	0.60	-	-
Score	2	3	5	Fair	2	2	Fair

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
SURMOUNT-5	35.30%	64.70%	-	-	7.90%	-	-
PDRR	0.73	1.25	-	-	0.48	-	-
Score	2	3	5	Fair	1	1	Poor
SURMOUNT-OSA	69.70%	30.30%	-	-	NR	-	-
PDRR	1.44	0.59	-	-	NC	-	-
Score	2	3	5	Fair	NC	NC	NC
SELECT	72.30%	27.70%	-	-	38.20%	-	-
PDRR	1.50	0.54	-	-	2.31	-	-
Score	3	2	5	Fair	3	3	Good
SURPASS-CVOT	71.10%	28.90%	-	-	NR	-	-
PDRR	1.47	0.56	-	-	NC	-	-
Score	3	2	5	Fair	NC	NC	NC
STEP-HFpEF	43.90%	56.10%	-	-	NR	-	-
PDRR	0.91	1.09	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
ESSENCE	42.90%	57.10%	-	-	NR	-	-
PDRR	0.89	1.11	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
SUMMIT	46.20%	53.80%	-	-	NR	-	-
PDRR	0.96	1.04	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio; OASIS-4 was excluded due to lack of a publication or presentation describing the relevant data.

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.[153,154]

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 treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: “Obesity”, “Semaglutide”, and “Tirzepatide”. 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.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Section D3) and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcomes.

Meta-Analyses Methods

We conducted random-effects pairwise meta-analyses to compare injectable semaglutide with placebo across multiple pre-specified efficacy and safety outcomes. The assessed efficacy outcomes included percent change in body weight loss from baseline, mean change in SBP from baseline, and mean change in HbA1C from baseline. Safety outcomes included all-cause discontinuations, discontinuations due to AEs, and severe GI side effects. For continuous outcomes (percent body weight loss, SBP, and HbA1C), we used restricted maximum-likelihood estimator (REML) to address heterogeneity and the classical inverse variance formula to calculate the variance of the pooled estimate. Results for continuous outcomes were presented as mean difference (MD) with 95% confidence intervals. For binary outcomes (discontinuations and GI side effects), we used Paule-Mandel estimator (PM) to address heterogeneity and classical inverse variance formula to calculate the variance of the pooled estimate. Results for binary outcomes were presented as rate ratios (RR) with 95% confidence intervals. All statistical analyses were performed using R Statistical Software (version 4.2.1) and data packages tidyverse, meta, and dmetar. Results of the meta-analyses are discussed throughout the report and summarized here in Table D1.12.

Table D1.12 Meta-Analysis Results for Injectable Semaglutide and Oral Semaglutide

Outcomes	Sources	Mean Difference or Relative Risk (95% CI; Heterogeneity)
Injectable Semaglutide		
Percent weight change from baseline (unadjusted)	STEP 1, 3, 5, and 8	MD -13.1% (-15 to -11.3; I^2 83%)
Percent weight change from baseline (adjusted)	STEP 1, 3, 5, and 8	MD -12.0% (-13.9 to -10.2; I^2 77%)
Mean SBP change from baseline	STEP 1, 3, and 8	MD -5.96 (-8.96 to -2.95; I^2 70%)
Mean HbA1C change from baseline	STEP 1, 3, and 8	MD -0.31 (-0.40 to -0.22; I^2 86%)
All-cause discontinuations	STEP 1, 3, 4, and 8	RR 0.75 (0.61 to 0.91; I^2 17%)
Discontinuations due to adverse events	STEP 1, 3, 4, and 8	RR 1.89 (1.31 to 2.74; I^2 0%)
Severe gastrointestinal side effects	STEP 1, 3, 4, and 8	RR 2.44 (0.50 to 11.97; I^2 66%)
Oral Semaglutide		
Major adverse cardiovascular events	SOUL, PIONEER 6	RR 0.86 (0.78 to 0.95; I^2 0%)

CI; confidence interval, MD: mean difference, RR: relative risk, SBP: systolic blood pressure

Feasibility of Conducting Indirect Treatment Comparison

We examined the feasibility of conducting indirect comparisons because direct evidence for the cardiovascular outcomes of tirzepatide versus placebo for patients with obesity was not available. Tirzepatide was compared against dulaglutide in the SURPASS CVOT trial while dulaglutide was compared against placebo in the REWIND trial. We examined whether there were notable differences in study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality of these two trials. Both trials were deemed sufficiently similar in terms of design, intervention type, outcome definitions or measurement, and analytic methods. However, there were some notable differences between the inclusion criteria of these two trials. Additionally, although a peer-reviewed REWIND publication and a conference presentation from the SURPASS CVOT trial were available, we did not have access to individual patient-level data. As such, due to data limitations, we were not able to conduct the indirect treatment comparison at the time of this report.

All data analyses were validated by an independent member of the research team. The validator reviewed and confirmed the data analysis methods, data format, and analysis code. The validator re-ran the analysis, validated the results, and confirmed the appropriateness of reported data.

D2. Additional Clinical Effectiveness Results

Additional Evidence Base

The main report includes primary sources of data and key evidence to inform our review of injectable semaglutide, oral semaglutide and tirzepatide for the treatment of obesity. In this supplement, we describe details about additional trials that are either briefly mentioned or not included in the main report.

For injectable semaglutide, we provide additional details about the STEP trials. Here, we also discussed four Phase III trials for injectable semaglutide, evaluating outcomes related to weight regain (STEP 4) and obesity-related complications such as knee osteoarthritis (STEP 9), HFpEF (STEP-HFpEF) and metabolic-dysfunction associated hepatitis (ESSENCE). No additional trials were identified for oral semaglutide at a dose 25 mg. For tirzepatide, here we provided details about three Phase III trials that assessed weight regain (SURMOUNT 4), OSA (SURMOUNT-OSA), and cardiovascular outcomes (SUMMIT). Although both ESSENCE and SUMMIT trials included participants with obesity irrespective of their diabetes status, subgroup analyses on participants without diabetes were available.

Injectable Semaglutide

The study design and baseline characteristics for STEP 1, STEP 3, STEP 5, STEP 8, and STEP 10 are briefly described in the main report. Additional exclusion criteria for all STEP trials to highlight included self-reported change in body weight >5kg or obesity medication within 90 days before screening, previous or planned bariatric surgery during the trial, history of major depressive disorder within 2 years before screening, history of suicidal attempt, diagnosis of other severe psychiatric disorders, uncontrolled thyroid disease, and history of acute pancreatitis within 180 days before screening.[23-27] STEP 1, STEP 3, and STEP 5 had co-primary endpoints of percentage change in body weight from baseline to end of trial and achievement of $\geq$5% body weight loss.[23-25] The primary endpoint for STEP 8 was percent change in body weight from randomization to week 68.[27] STEP 10 had a co-primary endpoint of change from baseline in percent body weight at week 52 and proportion of participants achieving normoglycemia (HbA1C <6%).[26] See Supplement Table D2.4. for additional details about study design. Baseline characteristics of these trials are presented in Supplement Tables D2.1 and D2.5.

Table D2.1. Overview of Key Trials of Injectable Semaglutide versus Placebo

Trials		STEP 1[23]		STEP 3[24]		STEP 5[25]		STEP 8[27]		STEP 10[26]	
Study Arms		**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**
Sample Size		**1306**	**655**	**407**	**204**	**152**	**152**	**126**	**85**	**138**	**69**
Mean Age, Years (SD)		46 (13)	47 (12)	46 (13)	46 (13)	47 (12)	47 (10)	48 (14)	51 (12)	53 (11)	53 (11)
Female, %		73%	76%	77%	88%	81%	74%	81%	78%	72%	68%
Race and Ethnicity, %	**White**	75%	76%	75%	78%	93%	93%	75%	71%	90%	86%
	Black	6%	6%	20%	18%	5%	3%	20%	22%	4%	4%
	Asian	14%	12%	1%	3%	1%	0%	3%	4%	3%	7%
	Hispanic	12%	13%	18%	23%	12%	14%	12%	8%	4%	1%
Baseline Weight (SD), kg		105 (22)	105 (22)	107 (23)	104 (23)	106 (21)	107 (23)	103 (25)	109 (23)	112 (22)	111 (24)
Baseline BMI (SD), kg/m^2		38 (7)	38 (7)	38 (7)	38 (7)	39 (7)	39 (7)	37 (7)	39 (7)	40 (7)	40 (8)
Mean HbA1C (SD), %		5.7 (0.3)	5.7 (0.3)	5.7 (0.3)	5.8 (0.3)	5.7 (0.3)	5.7 (0.4)	5.5 (0.3)	5.6 (0.4)	5.9 (0.3)	5.9 (0..3)
Mean Systolic Blood Pressure (SD), mmHg		126 (14)	127 (14)	124 (15)	124 (15)	126 (14)	125 (15)	125 (14)	123 (14)	131 (15)	129 (15)
Mean eGFR (SD), mL/min/1.73m^2		96 (19)	96 (18)	97 (21)	97 (21)	96 (17)	93 (18)	96 (21)	92 (20)	NR	NR
At Least One Comorbidity, %		75%	75%	76%	76%	NR	NR	75%	81%	80%	81%

BMI: body mass index, eGFR: estimated glomerular filtration rate, HbA1C: hemoglobin A1C, kg: kilogram, m: meter, mmHg: millimeter of mercury, mL: milliliter, min: minute, NR: not reported, PBO: placebo, SD: standard deviation, SEM: semaglutide

SELECT

The SELECT trial, a large Phase III RCT, examined the effect of injectable semaglutide 2.4 mg on CV outcomes in patients with obesity and without diabetes. A total of 17,604 patients were randomized 1:1 to injectable semaglutide or placebo as an adjunct to standard of care. Participants were eligible to enroll in the trial if they were ≥45 years old, had a BMI of ≥27, and had established CV disease defined as a previous myocardial infarction (MI), stroke, or symptomatic peripheral arterial disease (PAD). Participants were excluded if they had a diagnosis of diabetes or were treated with glucose-lowering or GLP-1 medications in the last 90 days.[19] See Supplement Table D2.4.

Baseline characteristics were similar across the arms. The mean age of trial participants was 62 years. Participants were mostly male (72%) and White (84%), with a mean BMI of 33. About 76% of the trial participants experienced a previous MI, and 23% had a stroke. The mean study follow-up period was 40 months.[19] See Supplement Table D2.9.

STEP 4

The objective of the STEP 4 trial was to study the effects of continuing versus withdrawing semaglutide on weight loss maintenance. Participants enrolled in the STEP 4 trial underwent a 20-week dose escalation period receiving semaglutide weekly and then were randomized to either semaglutide 2.4 mg plus lifestyle intervention or placebo plus lifestyle intervention for 52 additional weeks (total 68 weeks). The inclusion and exclusion criteria were similar to the other STEP trials.[155] See Supplement Table D2.4.

Prior to the run-in period, the baseline weight and BMI for all trial participants (N = 803) were 107.2 kg and 38.4. These decreased to 96 kg and 34, respectively, at the time of randomization. The mean age for trial participants was 47 years and a majority of them were female (79%) and White (86%). Over 70% of the trial participants had at least one comorbid condition. Overall, baseline characteristics were comparable between those who continued injectable semaglutide and those who switched to placebo after the run-in period.[155] See Supplement Table D2.13.

STEP 9

STEP-9 studied the effects of injectable semaglutide on adults with obesity and moderate to severe knee osteoarthritis (OA). Trial design included a 16-week dose escalation period, a 52-week on-treatment follow-up, and a 7-week off-treatment follow-up period. Adult participants were eligible if they had a BMI of ≥30, a clinical diagnosis of knee OA with moderate radiographic changes in the target knee, and had completed a 72-hour washout period of analgesics. Participants with HbA1C ≥6.5%, joint replacement in target knee, arthroscopy or injections in target knee in the last 3 months, previous or planned obesity related surgery, and uncontrolled thyroid disease were

excluded from the trial. The co-primary endpoints were percent change in body weight and changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score from baseline.[28] See Supplement Table D2.4.

Participants (271 in the semaglutide arm and 136 in the placebo arm) were around 56 years of age, female (82%), predominantly White (61%) and American Indian or Alaska Native (12%), and had a mean BMI of 40. The baseline WOMAC pain score was 71 (SD 16). Approximately half of the adult participants had hypertension and 31% had dyslipidemia.[28] Additional baseline characteristics are reported in Supplement Table D2.12.

STEP-HFpEF

The STEP-Heart Failure with Preserved Ejection Fraction (STEP-HFpEF) trial assessed cardiovascular outcomes in addition to weight loss in a population with existing HFpEF. Trial enrollees were randomized 1:1 to semaglutide 2.4 mg or placebo as an add-on to standard of care for 52 weeks. Adults ≥18 years of age were included if they had a BMI of ≥30, left ventricular ejection fraction ≥45%, New York Heart Association (NYHA) class II-IV, a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) of <90 points, and were able to perform the six minute walk distance of at least 100 meters. Participants were also required to have one of the following: elevated left ventricular filling pressure, elevated natriuretic peptide level plus echocardiographic abnormalities, or hospitalization for heart failure in the last 12 months plus ongoing treatment with diuretics or echocardiographic abnormalities. Participants with prior myocardial infarction, stroke, unstable angina pectoris, hospitalization for heart failure, or transient ischemic attack during the last 30 days were excluded. The co-primary endpoints were change in the KCCQ-CSS and percent change from baseline in body weight at week 52.[30] See Supplement Table D2.4.

The STEP-HFpEF trial participants (N=529) were mostly older adults (69 years of age), female (56%), predominantly White (96%), with a mean BMI of 37 and a median KCCQ-CSS score of 59 points. Approximately two-thirds of the trial participants were classified as NYHA functional class II; the remaining were class III or IV. The most common comorbidities among trial participants were hypertension (82%) and atrial fibrillation (52%).[30] See Supplement Table D2.11.

ESSENCE Trial

The ESSENCE trial randomized a total of 1197 participants 2:1 to receive injectable semaglutide 2.4 mg or placebo in addition to standard care for MASH or related conditions. Adult participants were enrolled if they had histologically documented steatohepatitis and liver fibrosis of stage 2 or 3 and a nonalcoholic fatty liver disease activity score (NAS) of ≥4. Participants with HbA1C ≥9.5%, chronic liver disease other than metabolic dysfunction-associated steatotic liver disease (MASLD), relevant alcohol consumption or dependence, aspartate aminotransferase (AST) >5 times the upper limit of normal (ULN), or alanine aminotransferase (ALT) >5 ULN were excluded from the trial. The trial

follow-up period was designed in two parts, with the first part ending at week 72 and the second part continuing until week 240. The 72-week endpoints were the resolution of steatohepatitis with no worsening of liver fibrosis and a reduction in liver fibrosis with no worsening of steatohepatitis. The 240-week primary endpoint was cirrhosis-free survival.[29] See Supplement Table D2.2.

Baseline characteristics were presented for the first 800 patients enrolled in the ESSENCE trial and were similar across the arms. Participants were around 56 years of age, with a mean BMI was 35. Although most participants were White (68%), the trial enrolled a substantial proportion of Asian participants (28%). Approximately 56% of the participants had type 2 diabetes.[29] See Supplement Table D2.11.

Oral Semaglutide

OASIS 4

The trial had co-primary endpoints of percent change in body weight and proportion of participants with ≥5% body weight loss.[123] The mean age for all participants was 48 years and around 80% were female, with a mean BMI of 38. The trial participants were predominantly White (92%), with Black participants (7%) representing most of the remaining sample. The mean HbA1C was 5.7% and the mean systolic blood pressure was 131 mmHg.[123] See Supplement Table D2.6.

Tirzepatide

SURMOUNT 1 and SURMOUNT 3

The co-primary endpoints for both SURMOUNT 1 and SURMOUNT 3 trials were percent change in body weight and proportion of participants achieving ≥5% body weight loss.[46,47] Participants in the SURMOUNT 1 and SURMOUNT 3 trials had largely similar baseline characteristics. Participants enrolled in SURMOUNT 1 had slightly higher baseline BMI (38) than participants in the SURMOUNT 3 trial (36).[46,47] See Supplement Tables D2.2 and D2.7.

Table. D2.2. Overview of Key Trials of Tirzepatide versus Placebo

Trials		SURMOUNT 1[46]		SURMOUNT 3[47]	
Study Arms		TZP	PBO	TZP	PBO
Sample Size		630	643	287	292
Mean Age (SD), Years		45 (12)	44 (13)	45 (13)	46 (12)
Female, %		68%	68%	63%	63%
Race and Ethnicity, %	**White**	70%	70%	86%	86%
	Black	8%	9%	11%	11%
	Asian	11%	11%	1%	1%
	Hispanic	48%	48%	53%	55%
Baseline Weight (SD), kg		106 (23)	105 (21)	103 (22)	101 (21)
Baseline BMI (SD), kg/m^2		38 (7)	38 (7)	36 (6)	36 (6)
Mean HbA1C (SD), %		5.6 (0.4)	5.6 (0.4)	5.3 (0.4)	5.4 (0.4)
Mean Systolic Blood Pressure (SD), mmHg		123 (13)	123 (13)	121 (13)	121 (12)
Mean eGFR (SD), mL/min/1.73m^2		98 (18)	98 (18)	96 (17)	97 (17)
At least One Comorbidity, %		61%	62%	67%	66%

BMI: body mass index, eGFR: estimated glomerular filtration rate, HbA1C: hemoglobin A1C, kg: kilogram, m: meter, mL: milliliter, min: minute, mmHg: millimeter of mercury, PBO: placebo, SD: standard deviation, TZP: tirzepatide

SURMOUNT 5

The primary endpoint for the SURMOUNT 5 trial was percent change from baseline in body weight at week 72.[48] Overall, baseline characteristics were similar across the arms. The trial participants were around 45 years of age and mostly female (65%). Although the majority of participants were White (76%), the trial enrolled a substantial proportion of Blacks (19%) and Hispanics (26%). Participants had a baseline BMI of 39 and a mean HbA1C of 5.6%. At baseline, the mean systolic blood pressure was 126 mm Hg and the mean eGFR was 105 mL/min/1.73 m^2. Over three-quarters of trial participants had at least one comorbid condition. Common obesity-related complications included hypertension (40%), dyslipidemia (24%), impaired glucose metabolism (19%), anxiety (18%), and OSA (15%).[48] See Supplement Table D2.8.

SURPASS CVOT

The SURPASS CVOT evaluated the CV impacts of tirzepatide 15 mg compared to dulaglutide 1.5 mg in adults with T2D and atherosclerotic cardiovascular disease (ASCVD). Participants could enroll if they were ≥40 years old, had HbA1C between 7% and 10.5%, BMI ≥25, and ASCVD. Key exclusion criteria included CV event or intervention in the 60 days prior to screening, hospitalization for heart failure in the two months prior to screening or chronic New York Heart Association (NYHA) functional classification IV heart failure, liver disease, end-stage kidney disease (ESKD) or on chronic dialysis, history of acute or chronic pancreatitis, planned coronary, carotid, or peripheral artery revascularization, or treatment with GLP-1 RA within the last three months.[49]

Baseline characteristics were not available by treatment arm for this currently unpublished trial. Overall, participants were mostly male (71%), had a mean age of 64 years, and a mean BMI of 33. About two-thirds of participants had a history of MI (47%) or stroke (19%).[49]

SURMOUNT 4

SURMOUNT 4 studied the effect of continued treatment with or withdrawal of tirzepatide on body weight. The trial included a 36-week, open-label lead-in period followed by a 52-week, double-blind period. Participants were treated with tirzepatide at maximum tolerated dose in the lead-in period and later randomized to either tirzepatide or placebo at week 36. The inclusion and exclusion criteria were similar to other SURMOUNT trials discussed in the main report. The primary endpoint was percent change in body weight from randomization to week 88, with a key secondary endpoint focusing on weight maintenance and regain.[156] See Supplement Table D2.4.

In total, 783 participants were enrolled to initiate tirzepatide and 670 of them later randomized to either tirzepatide or placebo. The baseline weight and BMI for all trial participants were 107.3 kg and 38 prior to the lead-in period, then decreased to 85 kg and 30, respectively, by the time of randomization. Systolic blood pressure also decreased from 126 mm Hg to 115 mm Hg and HbA1C slightly reduced from 5.54% to 5.04%. Baseline characteristics were comparable at randomization.[156] See Supplement Table D2.13 for additional details.

SURMOUNT OSA

SURMOUNT-OSA consisted of two identical Phase III trials that evaluated the maximum tolerated dose of tirzepatide (10 mg or 15 mg) plus lifestyle intervention versus placebo plus lifestyle intervention in adults with obesity (BMI ≥30) and moderate to severe obstructive sleep apnea (OSA). Trial 1 enrolled participants who were unable or unwilling to use positive airway pressure (PAP) therapy, while trial 2 recruited participants using PAP therapy for ≥3 months and planned to continue the therapy during the trial. Participants with type 1 or type 2 diabetes were excluded from the trial. Additional exclusion criteria included a change in body weight >5 kg in the last 3 months, planned surgery for sleep apnea or obesity, diagnosis of central or mixed sleep apnea, or major craniofacial abnormalities. The primary endpoint was the change in apnea-hypopnea index (AHI) from baseline at week 52.[21] See Supplement Table D2.4.

The investigators randomized a total of 234 participants in trial 1 and 235 participants in trial 2. Overall, baseline characteristics were similar across arms and trials. Trial 1 enrolled participants with a mean age of 48 years, most were male (67%), and White (66%). The mean BMI was 39 and the mean AHI was 52 events per hour. In trial 2, participants had a mean age of 52 years, were mostly male (72%) and White (73%). The mean BMI was 39 and the mean AHI was 50 events per hour. There were numerical differences in the sleep apnea-specific hypoxic burden between groups in both trials.[21] See Table 3.4 and Supplement Table D2.10.

SUMMIT

The SUMMIT trial examined the effects of tirzepatide in a HFpEF population. Participants were randomized 1:1 to receive tirzepatide or placebo in addition to usual therapy. Participants were eligible for the trial if they were ≥40 years, had chronic heart failure (NYHA class II-IV), a left ventricular ejection fraction ≥50%, and a BMI of ≥30. Participants were also required to have one of the following: elevated NT-proBNP, evidence of left atrial enlargement, or evidence of elevated left ventricular filling pressure. Additional inclusion criteria included a KCCQ-CSS of ≤80, a six-minute walk distance of between 100 and 425 meters, heart failure decompensation in the last 12 months, and an eGFR <70 ml/min/1.73 m^2. Participants with prior myocardial infarction, stroke, unstable angina pectoris, coronary artery bypass surgery or other major cardiovascular surgery, or transient ischemic attack during the last 90 days, or stage 5 chronic kidney disease were excluded. The co-primary endpoints were time to first event of cardiovascular death or worsening heart failure events and change in the KCCQ-CSS at week 52.[51] See Supplement Table D2.4.

In total, 731 patients (364 in the tirzepatide group and 367 in the placebo group) with obesity and HFpEF were randomized. At baseline, the mean age for participants was 65 years; 54% of them were women and 70% were White. The mean BMI was 38 and the mean KCCQ-CSS was 54 points. Approximately 48% of the trial participants had type 2 diabetes and 47% of the participants had a hospitalization or urgent care visit for worsening heart failure in the last 12 months.[51] See Supplement Table D2.11.

Observational Studies

Direct Comparison (Semaglutide vs Tirzepatide)

Rodriguez et al 2024 used electronic health record (EHR) data linked to dispensing information to assess weight loss and rates of gastrointestinal adverse events. Adults were included if they had a diagnosis code for overweight or obese in the year before their index date, defined as initiation of tirzepatide 5 mg or semaglutide 0.5 mg labeled for diabetes. The primary outcome was percent change in weight loss from baseline. Patients initiating tirzepatide were younger, mostly female, White, and had a lower prevalence of T2D compared to those initiating semaglutide. Propensity scores were used to balance treatment groups, with a sample size of 9,193 for tirzepatide and 9,192 for semaglutide after matching.[33] See Supplement Table D2.3.

Ng et al 2025 included adults with overweight or obesity and without type 2 diabetes initiating either semaglutide 2.4 mg (N = 6,794) or any off-label tirzepatide dose (N = 3,122) from the Komodo Health Database and assessed their changes in weight descriptively from index date to 12 months.[35]

Baser et al 2024 utilized a large cohort from the Kythera database, which included three anti-obesity medication groups (semaglutide, tirzepatide, and liraglutide) and one AOM non-user group. A subgroup analysis with 23,933 patients in the semaglutide and 12,854 patients in the tirzepatide group was available. Patients were required to have a clinical diagnosis of obesity before index date (i.e., first prescription claim) and continuous medical and pharmacy benefits data for the last 12 months. Participants in the tirzepatide group were slightly older and comorbidities were more common than semaglutide group. The primary outcome was incidence of OA.[32] See Supplement Table D2.3.

Anson et al 2024 conducted another large study using the TriNetX database with two adult cohorts: one with T2D (N=8,446) and another without T2D (N=13,846). The study incorporated a new user design where patients were included and followed for at least 12 months. After matching, the mean age for all patients without T2D was 48 years and 73% were female. The primary outcome was incidence of T2D.[31] See Supplement Table D2.3.

Huang et al 2024 was a retrospective study that included 8,840 propensity score matched pairs of tirzepatide and semaglutide users from the TriNetX US database. Patients were excluded if they had a history of T1D or T2D, HIV, ESKD, or any study medication use in the last six months. The outcomes of interest were ocular health outcomes, including incidence of cataracts, oculomotor binocular dysfunction, visual issues and blindness, visual disturbances, dry eye disease, and ametropic accommodative dysfunction.[34] See Supplement Table D2.3.

Injectable Semaglutide

Ruseva et al 2025 (SCOPE) used the Komodo Health Database and included 4,424 individuals treated with injectable semaglutide 2.4 mg for the management of obesity. The study endpoints included changes in body weight, BMI, and other cardiometabolic biomarkers (i.e., SBP, HbA1C, LDL etc.) with a follow-up period of 68 weeks, mimicking the clinical trials.[42] Another Ruseva et al 2025 study included 8,857 semaglutide 2.4 mg-treated patients and matched them to 35,428 non-treated patients using the Komodo database to assess both weight loss and cardiometabolic risk factors from index date to 12 months.[38] The SCORE real-world study identified overweight or obese individuals aged ≥45 years with ASCVD and without diabetes who initiated semaglutide 2.4 mg (N = 9,321) and matched them to non-users (N = 18,642) to assess multiple CV outcomes, including revised MACE-3, revised MACE-5, MACE-3, MACE-5, and their individual components.[39] Baser et al 2024 identified 1,360 individuals with obesity diagnosis receiving semaglutide and compared them with 39,891 obese individuals not taking semaglutide to assess the risk of osteoarthritis.[37] Wang et al 2023 investigated the risk of suicidal ideation associated with semaglutide compared with non-GLP1 medications.[40] Able et al 2024 identified total of 3,094 non-diabetic obese men using semaglutide were matched with non-user controls from TriNetX database to assess the risk of erectile dysfunction.[36] Gleason et al 2024 measured adherence and persistence to GLP-1 treatments for obesity using data from integrated pharmacy and medical claims. Their cohort comprised 4,066

patients with obesity using different GLP-1 products, excluding those with a diagnosis of diabetes. Persistence and adherence data relevant to only Wegovy® and Rybelsus® (off-label use) were extracted from this study.[41] See Supplement Table D2.3.

Tirzepatide

Hankosky et al 2024 first evaluated persistence, changes in body weight, and BMI among 20,998 non-diabetic, anti-obesity medication-eligible individuals using the Optum's Market Clarity Database.[52] Subsequently, Hankosky et al 2025 published a study of 4,177 individuals from the Healthcare Integrated Research Database assessing persistence, utilization patterns, and changes in body weight.[53] Hunter Gibble et al 2025 included adults with at least one tirzepatide claim and no type 2 diabetes from MarketScan database (N = 15,534) and Optum (N = 6,800) to evaluate their treatment persistence at 6 months post index.[157] Hunter Gibble et al 2024 investigated the real-world use of tirzepatide (i.e., adherence and persistence) among anti-obesity medication-eligible cohort of patients (N=10,193) using the Verdigm database.[54] Additionally, a separate large-scale, propensity score-matched study by Wu et al 2025 evaluated the impacts of tirzepatide compared with lifestyle interventions on all-cause mortality, major adverse cardiovascular events (MACE), and major adverse kidney events (MAKE) in 42,300 individuals with OSA and obesity.[158] See Supplement Table D2.3.

Table D2.3. Summary of Included Observational RWE Studies

Author, Year	Comparators	Database	N	Outcome(s) of Interest Assessed
Semaglutide				
Ruseva, 2025	Semaglutide	Komodo	4,424	Weight loss , BMI, Cardiometabolic outcomes
Ruseva, 2025	Semaglutide	Komodo	8,857	Weight loss, Cardiometabolic outcomes
	Non-treated		35,428	
Smolderen	Semaglutide	Komodo	9,321	CV outcomes
	Non-user		18,642	
Baser, 2024	Semaglutide	Kythera Medicare	1,360	Risk of osteoarthritis
	Non-user		39,891	
Wang, 2023	Semaglutide	TriNetX	52,783	Risk of suicidal ideation
	Other AOM		52,783	
Able, 2024	Semaglutide	TriNetX	3,094	Risk of erectile dysfunction
	Non-user		3,094	
Gleason, 2024	Injectable Semaglutide	Integrated medical and pharmacy claims	419	Adherence and Persistence
	Oral Semaglutide		285	
Tirzepatide				
Hankosky, 2023	Tirzepatide	Optum's Market Clarity	20,998	Persistence and Weight loss
Hankosky, 2024	Tirzepatide	Healthcare Integrated Research	4,177	Persistence and Weight loss
Hunter-Gibble, 2024	Tirzepatide	Veradigm's Network EHR and claims	10,193	Adherence and Persistence
Wu, 2025	Tirzepatide	TriNetX	21,150	All-cause mortality, MACE, and MAKE
	Placebo		21,150	
Hunter-Gibble, 2025	Tirzepatide	MarketScan	15,534	Persistence
		Optum Clinformatics	6,800	
Direct Comparison (Tirzepatide vs. Semaglutide)				
Rodriguez, 2024	Tirzepatide	Truveta	4,420	Weight loss and GI side effects
	Semaglutide		4,402	
Ng, 2025	Tirzepatide	Komodo	6,794	Weight loss
	Semaglutide		3,122	
Baser, 2024	Tirzepatide	Kythera	12,854	Incidence of OA
	Semaglutide		23,933	
Anson, 2024	Tirzepatide	TriNetX	6,923	Incidence of T2D
	Semaglutide		6,923	
Huang, 2024	Tirzepatide	TriNetX	8,840	Ocular outcomes
	Semaglutide		8,840	

AOM: anti-obesity medication, BMI: body mass index, EHR: electronic health record, GI: gastrointestinal, MACE: major adverse cardiovascular events, MAKE: major adverse kidney events, OA: osteoarthritis, T2D: type 2 diabetes

Additional Clinical Benefits

Injectable Semaglutide

Additional Meta-Analyses of STEP Trials

In a pooled meta-analysis of STEP 1, STEP 3, and STEP 8 trials, participants treated with semaglutide had statistically significantly greater reductions in mean SBP (change from baseline -5.96, 95% CI: -8.96 to -2.95; I^2=70%) and mean HbA1C (change from baseline -0.31; 95% CI: -0.40 to -0.22; I^2=86%) than those treated with placebo.[23,24,27] STEP 5 and STEP 10 trials were excluded from the meta-analysis due to study design differences; however, results from these trials also showed similar reductions in these outcomes.

STEP 1

A post-hoc analysis of the STEP 1 trial reported that participants achieving greater weight loss showed greater physical functioning improvements in these two instruments.[159]

The STEP 1 trial assessed body composition using dual energy X-ray absorptiometry (DEXA) in a subset of participants. Participants in the DEXA subpopulation (N = 140) were slightly older (51 years) and had lower baseline body weight (98 kg) and BMI (35) compared to the overall study population. Baseline body compositions were comparable between injectable semaglutide and placebo. Body composition data at week 68 showed that there was greater reduction in total fat mass (7 kg, percent point change -3%), regional visceral fat mass (-0.3 kg, percent point change -2%), and total lean body mass (-3 kg, percent point change -3%) with injectable semaglutide compared with placebo.[23] See Supplement Table D2.42.

In the STEP 1 trial extension, which included 327 participants, both treatment groups experienced weight regain one year after the withdrawal of semaglutide. The semaglutide arm regained a mean of 11.6% of weight from week 68 to 120, while the placebo arm regained a mean of 1.9% from week 68 to 120. Data also showed increases in BMI and cardiometabolic risk factors including SBP, HbA1C, and LDL cholesterol, in both treatment groups from week 68 to week 120; thus returning to the baseline values. Other STEP trials also included off-treatment follow-up periods ranging from 7 to 28 weeks, but did not measure weight regain.[67]

STEP 5

Data from the STEP 5 trial suggested a statistically significant difference between injectable semaglutide 2.4 mg and placebo on percent weight change from baseline (mean difference -8.51%; 95% CI: -8.75% to -8.27%) after 104 weeks.[25]

In an exploratory analysis, the STEP 5 trial assessed the intensity and type of food cravings using the 19-item Control of Eating Questionnaire (CoEQ). This questionnaire included four domains with 17 items related to craving control, positive mood, craving for savory, and craving for sweet, each scored on a 0 to 10 scale, and two questions related to hunger and fullness. Among 174 participants completing the questionnaire, the percent mean body weight change from baseline to week 104 was -14.8% in the injectable semaglutide group compared to -2.4% in the placebo group (mean difference -12.4; 95% CI: -16.2 to -8.5). Semaglutide treatment improved all domain scores compared to placebo over the follow-up period, but only craving control and craving for savory domain scores showed statistically significant differences at week 104. Treatment with injectable semaglutide also led to improvement in scores for hunger and fullness, but were only statistically significant for short-term follow-up (week 20).[160]

STEP 4

The STEP 4 trial showed that participants who continued injectable semaglutide after the 20-week run in period lost an additional mean of 7.9% of body weight at week 68; in contrast, those who were assigned to placebo gained a mean of 6.9% from week 20 to week 68, suggesting substantial weight regain upon discontinuation of injectable semaglutide.[155] See Supplement Table D2.31.

STEP 9

The STEP 9 trial co-primary endpoints were mean body weight change from baseline and mean WOMAC pain score change from baseline to week 68. reported a -13.7% mean body weight change from baseline in the semaglutide group compared to only -3.2% changes in the placebo group (mean difference -10.5; 95% CI: -12.3 to -8.6). Injectable semaglutide demonstrated a greater reduction in the WOMAC pain score compared to the placebo group at week 68 (-41.7 points vs. -27.5 points), with a mean difference of -14.1 points (95% CI: -20 to -8.3). Secondary endpoint data also suggest a significantly greater improvement in the WOMAC physical function score in the semaglutide arm (-41.5 points) compared to the placebo arm (-26.7 points). In an exploratory analysis of STEP 9, participants with obesity and knee OA receiving injectable semaglutide achieved a greater mean improvement in six-minute walk distance from baseline to week 68 than those receiving placebo (56.8 m vs. 14.2 m, mean difference 42.6; 95% CI: 25.6 to 59.7).[28] See Supplement Table D2.30.

SELECT

In another prespecified analysis, semaglutide demonstrated a lower risk (HR 0.80; 95% CI: 0.73 to 0.87) of first MACE-5 events, defined as CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina.[161] At week 208, the mean percent body weight change from baseline for injectable semaglutide and placebo were -10.2 and -1.5, with a mean difference of -8.7 (95% CI: -9.4 to -7.9; p <0.0001).[86] The SELECT trial comparing injectable semaglutide versus placebo assessed EQ-5D-5L index score (0-1) and VAS score (0-100) for measures of HRQoL, with higher scores indicating better patient-reported health status. The mean difference for EQ-5D-5L index score was 0.01 (95% CI: 0.01 to 0.02) and for VAS score was 1.60 (95% CI: 1.16 to 2.04). Both scores were statistically significant and favored injectable semaglutide 2.4 mg over placebo in adults with obesity and preexisting CVD. Additionally, participants receiving injectable semaglutide had statistically significantly greater reductions in changes from baseline SBP (mean difference -3.31), HbA1C (mean difference -0.32), and LDL cholesterol (mean difference -2.18) at week 104 compared to placebo.[19] See Supplement Table D2.27.

STEP HFpEF

The STEP-HFpEF trial co-primary endpoints were percent body weight change from baseline and KCCQ-CSS score change from baseline to week 52. There was a greater body weight change from baseline in the injectable semaglutide arm (-13.3%) compared to placebo arm (-2.6%), with a mean difference of -10.7% (95% CI: -11.9 to -9.4; p <0.001) at week 52. Semaglutide demonstrated a greater improvement in KCCQ-CSS score from baseline at week 52 compared to placebo (16.6 vs. 8.7, mean difference 7.8; 95% CI: 4.8 to 10.9; p <0.001). Approximately 63% of the semaglutide participants achieved at least 10% increase in KCCQ-CSS score in the semaglutide group compared to 49% in the placebo group (OR 2.1; 95% CI: 1.4 to 3.1)The STEP-HFpEF trial also assessed six-minute walk test as a confirmatory secondary endpoint and semaglutide arm showed an advantage over placebo (mean difference 20.3; 95% CI: 8.6 to 32.1) at week 52.[30] See Supplement Table D2.29.

ESSENCE

The ESSENCE trial was conducted in two parts. Results related to part one coprimary endpoints were presented in the main report. At week 72, participants receiving injectable semaglutide irrespective of their diabetes status lost -10.5% of baseline body weight compared to -2% in placebo (mean difference -8.5; 95% CI: -9.6 to -7.4; p <0.001).[29] Part 2 of the trial will assess cirrhosis-free survival over 204 weeks, with results expected in 2029. See Supplement Table D2.29.

Tirzepatide

SURMOUNT 1 and SURMOUNT 3

The SURMOUNT 1 trial also reported 3-year efficacy and safety data evaluating tirzepatide in participants with prediabetes status. At week 176, the mean difference between tirzepatide 15 mg and placebo was -18.4 (95% CI: -22.2 to -14.7), similar to the percent weight loss at one-year post-titration. Additionally, around 87% of trial participants receiving tirzepatide 15 mg achieved at least a 5% weight loss from baseline compared to 30% in the placebo group.[64] SURMOUNT-1 trial showed that higher percentages of weight reductions in the tirzepatide group were associated with greater improvements in these HRQoL assessments.[59]

A total of 160 participants had body composition data from DEXA at both baseline and week 72 in the SURMOUNT 1 trial. Data were pooled for tirzepatide 5 mg, 10 mg, and 15 mg. The mean difference in percent total fat mass changes from baseline was -25.7 (95% CI: -31.4 to -20) and in percent total lean mass changes from baseline was -8.3 (95% CI: -10.6 to -6.1) at week 72. There was a notable reduction in the fat-to-lean mass ratio with tirzepatide (0.93 at baseline to 0.70 at week 72) than placebo (from 0.95 to 0.88).[162]

Both SURMOUNT 1 and SURMOUNT 3 trials reported a mean percent change in urine albumin-creatinine ratio (UACR) from baseline of -9.3% to -12.3% with tirzepatide versus -3.2% to -8.8% with placebo at week 72, indicating a potential protective effects of tirzepatide on renal function.[46,47]

SURMOUNT-5

A post-hoc analysis of SURMOUNT-5 measured change in 10-year CVD risk from baseline after 72 weeks of treatment with either injectable semaglutide or tirzepatide. Overall, there was a larger reduction in 10-year CVD risk in the tirzepatide-treated group compared with the semaglutide-treated group (-2.36% vs -1.35%). The benefit of tirzepatide over semaglutide was seen in all subgroups.163

SURPASS CVOT

An analysis reported by the manufacturer using patient-level propensity-matched data from the SURPASS-CVOT and REWIND trials reportedly calculated a 28% reduction in MACE (HR 0.72; 95% CI: 0.55 to 0.94) and 39% reduction in all-cause mortality (HR 0.61; 95% CI: 0.45 to 0.82) for tirzepatide compared with placebo[164]; however, we do not yet have sufficient data to conduct a network meta-analysis to confirm these findings.

SURMOUNT 4

In the SURMOUNT 4 trial, participants were treated with tirzepatide for 36 weeks before randomization to either continue tirzepatide or switch to placebo. At week 88, the group continuing on tirzepatide had a mean change in body weight from week 36 of -5.5% compared to a mean change of +14% in the group randomized to placebo. Key secondary endpoints showed that approximately 90% of participants treated with tirzepatide maintained ≥80% of their initial weight loss compared with only 16% in the placebo group. Additionally, the risk of returning to >95% of baseline body weight was reduced by 98% (HR 0.02; 95% CI: 0.01 to 0.06) in the tirzepatide group.[156] See Supplement Table D2.31.

SURMOUNT OSA

Around 61-72% participants in the tirzepatide group achieved at least a 50% reduction in AHI at week 52 compared to only 19-23% participants in the placebo group. Around -17.7% to -19.6% changes in body weight from baseline were observed with semaglutide compared to -1.6% to -2.3% changes with the placebo group in both trials. Injectable semaglutide also led to reductions in SBP at week 48 compared to those with placebo.[21] See Supplement Table D2.28.

SUMMIT

The composite primary endpoint of death from cardiovascular causes or a worsening heart-failure event, stratified by diabetes status, occurred in 11% non-diabetic participants in the tirzepatide group compared to 15% participants in the placebo group (HR 0.66; 95% CI: 0.37 to 1.18). There was a significant improvement in the KCCQ-CSS score changes from baseline with tirzepatide compared to placebo at week 52 weeks (mean difference 7.5; 95% CI: 2.7 to 12.3). Although data related to the non-diabetic subgroup were not available, tirzepatide demonstrated greater weight reductions (-13.9%) compared to placebo (-2.2%) at week 52 in the overall population, with a mean difference of -11.6 (95% CI: -12.9 to -10.4; $p< 0.001$).[51] See Supplement Table D2.29.

Additional Harms

Injectable Semaglutide

A pooled meta-analysis of STEP 1, STEP 3, STEP 4, and STEP 8 trials found that statistically significantly fewer participants (14%) receiving injectable semaglutide discontinued the trial for any reason compared with those receiving placebo (19%), with an RR of 0.75 (95% CI: 0.61 to 0.91; I^2 17%). However, discontinuations due to adverse events were significantly more common in the semaglutide arm (RR 1.89; 95% CI: 1.31 to 2.74; I^2 0%) compared to placebo. The pooled findings showed a higher proportion (4%) of participants receiving injectable semaglutide experienced severe GI side effects; although this was not statistically significant compared with placebo (1%).[23,24,27,155]

There were higher rates of serious adverse events in the placebo arm (12%) versus the semaglutide arm (8%) in the STEP 5 trial, thought to be due to chance events (e.g., COVID-19 infection, jaw and rib fractures, cancer) felt to be unrelated to the intervention.[25] In total, there were four deaths in the semaglutide arms compared to only one death in the placebo arms across STEP 1, STEP 5, and STEP 10 trials, with no deaths reported in STEP 3 and STEP 8 trials. Except for STEP 8, gallbladder-related disorders were more frequent in the semaglutide group compared to placebo. Rates of CV disorders were higher in the placebo arm than in the semaglutide arm across trials. Acute pancreatitis and acute renal failure rates were rarely observed in either arm.[23,24,26,27] See Supplement Table D2.32.

Harms data from the STEP 4, STEP 9, STEP-HFpEF, SELECT, and ESSENCE trials showed similar patterns to other STEP trials mentioned in the main section of this report. See Supplement Tables D2.34 and D2.36-38. In all these trials, around 49-86% of participants treated with injectable semaglutide and 48-80% of the participants treated with placebo experienced at least one treatment-emergent adverse event. Serious adverse events were generally comparable between injectable semaglutide (8-33%) and placebo (6-36%), except in the STEP-HFpEF trial, where participants in the semaglutide group reported fewer serious events (13% vs. 27%). Rates of gastrointestinal side effects were more common with those who continued injectable semaglutide than those switched to placebo in the STEP 4 trial; other trials did not report comprehensive GI side effects. There were more cardiovascular side effects in those who switched to placebo (11%) compared to those who continued semaglutide (5%).[28-30,155,165] See Supplement Tables D2.36, D2.38, and D2.39.

Tirzepatide

Harms data from SURMOUNT 1 and SURMOUNT 3 trials are mostly presented in the main section of this report. Additionally, four deaths occurred in the placebo group compared to one in the tirzepatide group in the SURMOUNT 1 trial, whereas SURMOUNT 3 reported one death in each arm.

The harms profile in SURMOUNT 4, SURMOUNT OSA, and SUMMIT trials aligned with previous tirzepatide studies.[21,51,156] The SURMOUNT 4 trial reported two deaths and none of them were deemed related to the treatment.[156] No deaths occurred in the two SURMOUNT OSA trials.[21] The SUMMIT trial reported 19 deaths (5%) in the tirzepatide group compared to 15 (4%) in the placebo group; though death from any cause was not statistically different across arms.[51] Across these trials, around 60-86% of participants treated with tirzepatide experienced at least one treatment-emergent adverse event compared to 56-77% of participants treated with placebo. Rates of serious adverse events were similar between groups (3-26%). Gastrointestinal side effects were more frequent with tirzepatide than placebo.[21,51,156] A notable difference was seen in the SUMMIT trial among participants with obesity and HFpEF, where more than double participants in the placebo group (8%) experienced cardiac failure compared to the tirzepatide group (4%).[51] See Supplement Tables D2.37, D2.38, and D2.40.

Additional Evidence from Observational Studies

Injectable Semaglutide

Ruseva et al. conducted a retrospective cohort study of 4,414 patients who were obese or overweight with ≥ 1 comorbidities and using injectable semaglutide 2.4 mg. Data were coming from a large US integrated claims and medical record database. They found a 14.8% reduction in body weight from baseline after 68 weeks of treatment. Those using semaglutide also achieved statistically significant reductions in cardiometabolic risk measures including BMI, SBP, HbA1C, and LDL cholesterol at week 52.[42] Another recent study by Ruseva et al using the same database also reported similar results at 12 months.[38] Smolderen et al 2025 reported greater reductions in multiple CV outcomes including revised MACE-3, revised MACE-5, MACE-3, MACE-5, all-cause mortality, and CV-related mortality.[39] In real-world studies, semaglutide demonstrated lower risks of suicidal ideation (HR 0.27; 95% CI: 0.20 to 0.36) and osteoarthritis (HR: 0.84; p=0.01), but had an increased risk of erectile dysfunction (RR 4.5; 95% CI: 2.3 to 9.0).[36,37,40]

Tirzepatide

The percent mean change in body weight from baseline was 11.9-12.9% at 6-month post-index period.[52,53] The proportions of patients achieving categorical weight loss thresholds of ≥5%, ≥10%, ≥15%, and ≥20% were 86-89%, 62-69%, 31-37%, and 11-15%, respectively.[52,53]

Wu et al 2025 included 21,150 patients with obesity and OSA who were prescribed tirzepatide. Against a 1:1 propensity score-matched control group, those treated with tirzepatide had a lower risk of all-cause mortality (HR 0.44; 95% CI: 0.34 to 0.58; p<0.001), MACE (HR 0.73, 0.62, 0.86; p<0.001), and major adverse kidney event (HR 0.43; 95% CI: 0.34 to 0.53; p< 0.001) compared to the control group.[158]

Direct Comparison (Tirzepatide versus Semaglutide)

Rodriguez et al 2024 conducted an observational RWE study comparing tirzepatide 5 mg with semaglutide 0.5 mg. In the one-third of the cohort that did not have diabetes, the mean percent body weight changes from baseline for tirzepatide and semaglutide were 18.1% and 10.1% at 12 months after treatment initiation, respectively, with a treatment difference of -8% (95% CI: -6.7 to -9.2). The odds of achieving ≥5%, ≥10%, and ≥15% weight loss were 2-3 times higher in the tirzepatide group than in the semaglutide group.[33] Similarly, in another recent real-world study, treatment with tirzepatide showed a greater reduction in body weight from baseline (-16.5%) than treatment with semaglutide 2.4 mg (-14.1%) after 12 months.[35] Huang et al 2024 compared 8,840 matched pairs of tirzepatide and semaglutide users from TriNetX US network data to assess ocular outcomes. Over two years of follow-up, tirzepatide users demonstrated a lower risk of cataracts (HR 0.41;, 95% CI: 0.19 to 0.85) and age-related cataracts (HR 0.34; 95% CI: 0.15 to 0.76) compared to semaglutide users.[34]

Similar rates of GI adverse events were observed between tirzepatide and semaglutide in the observational RWE study conducted by Rodriguez et al, although data specific to the non-diabetic population were not reported.[33]

Baser et al 2024 reported a lower risk of osteoarthritis with Zepbound (HR 0.57; 95% CI: 0.50 to 0.65; p <0.0001) compared with Wegovy.[32] Anson et al 2024 included both cohorts with and without pre-existing T2D, with a mean follow up close to one year. Participants receiving tirzepatide had a lower risk (HR 0.73; 95% CI: 0.58 to 0.92 ; p<0.001) of developing T2D compared to those receiving semaglutide over one year in the cohort without pre-existing T2D. There was a greater reduction in body weight changes from baseline with tirzepatide (-7.7 kg) compared to semaglutide (-4.8 kg). Similar reduction in HbA1C was also observed with tirzepatide (-0.24%) compared to semaglutide (-0.1%).[31]

D2. Evidence Tables

Table D2.4. Evidence Tables

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
Semaglutide					
STEP 1 NCT03548935	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=1961 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Semaglutide s.c. 2.4 mg once weekly -Placebo	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	- HbA1C ≥48 mmol/mol - Change of ≥5 kg in body weight within 90 days	Change in Body Weight (%) [week 68]
STEP 3 NCT03611582	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=611 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Semaglutide s.c. 2.4 mg once weekly -Placebo -Participant in both arms will also receive intensive behavioral therapy	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	- HbA1C ≥48 mmol/mol - Change of ≥5 kg in body weight within 90 days	Change in Body Weight (%) [week 68]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
STEP 4 NCT03548987	Phase III, randomized, double-blinded, placebo controlled, multicenter, withdrawal study N=902 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Semaglutide s.c. 2.4 mg once weekly -Placebo -For 20 week run in period all participants will receive open-label semaglutide	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	- HbA1C ≥48 mmol/mol - Change of ≥5 kg in body weight within 90 days	Change in Body Weight (%) [week 20 - week 68]
STEP 5 NCT03693430	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=304 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Semaglutide s.c. 2.4 mg once weekly -Placebo	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	- HbA1C ≥48 mmol/mol - Change of ≥5 kg in body weight within 90 days	Change in Body Weight (%) [week 104]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
STEP 8 NCT04074161	Phase III, randomized, open-label, multicenter study N=338 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Semaglutide s.c. 2.4 mg once weekly -Liraglutide s.c. 3 mg once daily -Placebo	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	- HbA1C ≥48 mmol/mol - Change of ≥5 kg in body weight within 90 days	Change in Body Weight (%) [week 68]
STEP 9 NCT05064735	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=407 Population: Adults with obesity and knee osteoarthritis	-Semaglutide s.c. 2.4 mg once weekly -Placebo	-BMI ≥30 -Clinical diagnosis of knee OA -Pain due to knee OA	-Joint replacement in target knee -Arthroscopy or injections into target knee within last 3 months prior to enrolment	Change in WOMAC pain score [week 68]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
STEP 10 NCT05040971	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=207 Population: Adults with obesity and prediabetes	-Semaglutide s.c. 2.4 mg once weekly -Placebo	-BMI ≥30 -HbA1c ≥6.0 and ≤6.4 percent OR -FPG ≥5.5 and ≤6.9 mmol/L	-History of type 1 or type 2 diabetes -Prior treatment with glucose-lowering agent -HbA1c ≥6.5 percent -FPG ≥7.0 mmol/L	Change in Body Weight (%) [week 52]
SELECT NCT03574597	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=17604 Population: Adults with obesity or overweight and preexisting cardiovascular disease	-Semaglutide s.c. 2.4 mg once weekly -Placebo	-≥45 years age -BMI ≥27 -Established cardiovascular disease	-Cardiovascular event within the past 60 days -HbA1C ≥48 mmol/mol -History of type 1 or type 2 diabetes	First occurrence of a composite outcome measure consisting of: CV death, non-fatal MI, or non-fatal stroke [240 weeks]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
ESSENCE NCT04822181	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=1205 Population: Adults with Non-cirrhotic non-alcoholic steatohepatitis	-Semaglutide s.c. 2.4 mg once weekly -Placebo	-Histological evidence of NASH -evidence of fibrosis stage 2 or stage 3 according to the NASH CRN -NAS ≥4 with a score of ≥1 in steatosis, lobular inflammation and hepatocyte ballooning	-Documented causes of chronic liver disease other than non-alcoholic fatty liver disease	Resolution of steatohepatitis and no worsening of liver fibrosis [72 weeks]
STEP HFpEF NCT04788511	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=529 Population: Adults with obesity-related heart failure with preserved ejection fraction	-Semaglutide s.c. 2.4 mg once weekly -Placebo	-BMI ≥27 -NYHA class II-IV -LVEF ≥45%	-HbA1c ≥6.5 percentage -Change of ≥5 kg in body weight within 90 days	Change in KCCQ [52 weeks]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
OASIS 4 NCT05564117	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=307 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Semaglutide oral 25mg daily -Placebo	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	-HbA1c ≥6.5 percentage -Change of ≥5 kg in body weight within 90 days	Change in Body Weight (%) [week 64]
Tirzepatide					
SURMOUNT-1 NCT04184622	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=2539 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Tirzepatide s.c. 5mg once -weekly -Tirzepatide s.c. 10mg once weekly -Tirzepatide s.c.15mg once weekly -Placebo	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	-Diabetes mellitus -Change of ≥5 kg in body weight within 3 months	Change in Body Weight (%) [week 72]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
SURMOUNT-3 NCT04657016	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=579 Population: Adults with obesity or overweight with at least one weight-related comorbidity who successfully lost ≥5% of baseline weight during a 12-week lead-in period with intensive lifestyle intervention.	-Tirzepatide s.c. maximum tolerated dose (10 or 15 mg) once weekly -Placebo	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	-Diabetes mellitus -Change of ≥5 kg in body weight within 3 months	Change in Body Weight (%) [week 72]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
SURMOUNT-4 NCT04660643	Phase III, randomized, double-blinded, placebo controlled, multicenter, withdrawal study N=783 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Tirzepatide s.c. maximum tolerated dose (10 or 15 mg) once weekly -Placebo -For 36-week run in period all participants will receive open-label tirzepatide	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	-Diabetes mellitus -Change of ≥5 kg in body weight within 3 months	Change in Body Weight (%) [week 88]
SURMOUNT-5 NCT05822830	Phase III, randomized, open-label, multicenter study N=751 Population: Adults with obesity or overweight with at least one weight-related comorbidity	-Tirzepatide s.c. maximum tolerated dose (10 or 15 mg) once weekly -Semaglutide s.c. maximum tolerated dose (1.7 or 2.4 mg) once weekly	-BMI ≥30 or ≥27 with presence of comorbidity (hypertension, dyslipidemia, sleep apnea, CVD) -History of at least one self-reported unsuccessful dietary effort to lose body weight	-Diabetes mellitus -Change of ≥5 kg in body weight within 3 months	Change in Body Weight (%) [week 72]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
SURPASS-CVOT NCT04255433	Phase III, randomized, double-blind, active comparator, multicenter study N=13299 Population: Adults with type 2 diabetes and increased cardiovascular risk	-Tirzepatide s.c. maximum tolerated dose (5, 10, or 15 mg) -Dulaglutide s.c. 1.5 mg	-BMI ≥25 -Diagnosis of type 2 diabetes -Established cardiovascular disease	-Hospitalized for congestive heart failure 2 months prior to screening -NYHA Classification IV	Time to first occurrence of death from CV causes, myocardial Infarction, or Stroke (MACE-3) [up to 54 months]
SURMOUNT-OSA NCT05412004	Phase III, randomized, double-blind, placebo controlled, multicenter study N=469 Population: Adults with obstructive sleep apnea and obesity	-Tirzepatide s.c. maximum tolerated dose (10 or 15 mg) once weekly -Placebo	-AHI ≥15 on PSG -BMI ≥30 -History of at least one self-reported unsuccessful dietary effort to lose body weight	-Have type 1 diabetes mellitus or type 2 diabetes mellitus -Change of ≥5 kg in body weight within 3 months	Change from Baseline in Apnea-Hypopnea Index [week 52]

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
SUMMIT NCT04847557	Phase III, randomized, double-blinded, placebo controlled, multicenter study N=731 Population: Adults with heart failure with preserved ejection fraction and obesity	-Tirzepatide s.c. maximum tolerated dose (10 or 15 mg) once weekly -Placebo	- NYHA class II-IV and LVEF ≥50% - BMI ≥30 - 6MWD 100-425m - KCCQ CSS ≤80	- HbA1c ≥9.5% or uncontrolled diabetes	Change from Baseline in KCCQ [week 52]

6MWD: 6 minute walk distance, AHI: apnea-hypopnea index, BMI: body mass index, CV: cardiovascular, CVD: cardiovascular disease, HbA1C: hemoglobin A1C, HFpEF: heart failure with preserved ejection fraction, KCCQ: Kansas city cardiomyopathy questionnaire, kg: kilogram, LVEF: left ventricular ejection fraction, mg: milligram, MI: myocardial infarction, NASH: non-alcoholic steatohepatitis, NYHA: New York heart association, PSG: polysomnography, s.c.: subcutaneous, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Source: www.ClinicalTrials.gov

Table D2.5. Baseline Characteristics of Key Trials of Injectable Semaglutide[23,24,26,27,125,166]

Trial		STEP-1		STEP-3		STEP-5		STEP-8		STEP-10	
Arms		SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO
Sample Size		1306	655	407	204	152	152	126	85	138	69
Mean Waist Circumference, cm ± SD		114.6±14.8	114.8±14.4	113.6±15.1	111.8±16.2	115.8±14.3	115.7±15.5	111.8±16.3	115.4±15.1	120.1±14.8	119.9±14.7
Mean Glycated Hemoglobin, % ± SD		5.7±0.3	5.7±0.3	5.7±0.3	5.8±0.3	NR	NR	NR	NR	NR	NR
Mean Diastolic Blood Pressure, mm Hg ± SD		80±10	80±10	80±10	81±10	80±9	80±10	81±9	79±9	NR	NR
Mean Pulse, beats/min ± SD		72±10	72±10	71±10	71±10	73±11	72±9	71±9	72±10	NR	NR
Mean Fasting Plasma Glucose ± SD		95.4±10.7	94.7±10.5	93.9±9.4	94.0±9.8	5.3±0.5	5.3±0.6	96.1±10.2	97.6±12.2	105.1±9.8	107.7±12.4
Mean Fasting Serum Insulin, Geometric Mean pmol/L (CV)		12.9 (58.6)	12.8 (61.2)	90.1 (59.5)	92.6 (61.0)	87.6 (51.4)	88.1 (62.6)	12.4 (60.1)	12.1 (67.0)	NR	NR
C-Reactive Protein, Geometric Mean (CV)		3.87 (151.1)	3.87 (135.5)	4.52 (142.1)	4.35 (129.9)	4.8 (129.9)	3.8 (128.8)	3.9 (124.1)	4.1 (187.1)	NR	NR
Lipid Levels, Mean mg/dl (CV)	Total Cholesterol	189.6 (20.5)	192.1 (19.4)	185.4 (19.8)	188.7 (20.6)	4.9* (20.9)	4.8* (18.3)	184.9 (21.0)	182.2 (22.8)	4.8* (19.8)	4.7* (18.7)
	HDL Cholesterol	49.4 (25.6)	49.5 (25.0)	107.7 (30.3)	111.8 (31.2)	1.2* (25.2)	1.2* (22.5)	51.9 (24.1)	50.7 (27.7)	1.2* (26·0)	1.2* (22.7)
	LDL Cholesterol	110.3 (31.6)	112.5 (29.8)	51.6 (24.0)	50.9 (22.6)	2.9* (30.1)	2.9* (25.7)	106.4 (32.5)	105.2 (32.9)	2.7* (31·6)	2.7* (32.1)
	VLDL Cholesterol	24.5 (45.8)	24.9 (46.5)	21.0 (49.7)	21.7 (44.5)	0.6* (46.5)	0.6* (47.4)	21.4 (47.2)	21.1 (49.2)	0.7* (44.4)	0.7* (43.2)
	Free Fatty Acids	12.3 (57.9)	12.7 (53.8)	11.9 (59.4)	11.1 (64.8)	0.4* (57.2)	0.4* (63.3)	10.5 (72.0)	10.6 (56.5)	NR	NR
	Triglycerides	126.2 (47.4)	127.9 (49.0)	107.9 (50.3)	110.9 (44.4)	1.3* (46.6)	1.2* (47.4)	110.1 (49.1)	108.2 (49.2)	1.6* (46.4)	1.5* (44.5)

Trial		STEP-1		STEP-3		STEP-5		STEP-8		STEP-10	
Arms		SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO
Sample Size		1306	655	407	204	152	152	126	85	138	69
Coexisting Conditions, n (%)	Dyslipidemia	499 (38.2)	226 (34.5)	145 (35.6)	67 (32.8)	58 (38.2)	49 (32.2)	60 (47.6)	36 (42.4)	63 (46%)	22 (32%)
	Hypertension	472 (36.1)	234 (35.7)	145 (35.6)	67 (32.8)	56 (36.8)	62 (40.8)	48 (38.1)	39 (45.9)	64 (46%)	32 (46%)
	Knee OA	173 (13.2)	102 (15.6)	76 (18.7)	31 (15.2)	21 (13.8)	25 (16.4)	23 (18.3)	22 (25.9)	18 (13%)	8 (12%)
	Obstructive Sleep Apnea	159 (12.2)	71 (10.8)	58 (14.3)	19 (9.3)	27 (17.8)	24 (15.8)	24 (19.0)	19 (22.4)	14 (10%)	8 (12%)
	Asthma or COPD	147 (11.3)	80 (12.2)	67 (16.5)	25 (12.3)	15 (9.9)	17 (11.2)	18 (14.3)	13 (15.3)	NR	NR
	Nonalcoholic Fatty Liver Disease	101 (7.7)	62 (9.5)	23 (5.7)	12 (5.9)	16 (10.5)	15 (9.9)	5 (4.0)	7 (8.2)	NR	NR
	Polycystic Ovarian Syndrome	62/955 (6.5)	34/498 (6.8)	17 (5.4)	10 (5.6)	10/123 (8.1)	5/113 (4.4)	5 (4.9)	1 (1.5)	NR	NR
	Coronary Artery Disease	32 (2.5)	17 (2.6)	6 (1.5)	4 (2.0)	2 (1.3)	3 (2.0)	4 (3.2)	4 (4.7)	NR	NR
No. of Coexisting Conditions at Screening, n (%)	None	328 (25.1)	163 (24.9)	99 (24.3)	49 (24.0)	NR	NR	32 (25.4)	16 (18.8)	NR	NR
	1	337 (25.8)	187 (28.5)	93 (22.9)	53 (26.0)	NR	NR	31 (24.6)	17 (20.0)	NR	NR
	2	298 (22.8)	135 (20.6)	96 (23.6)	43 (21.1)	NR	NR	25 (19.8)	21 (24.7)	NR	NR
	3	183 (14.0)	96 (14.7)	62 (15.2)	38 (18.6)	NR	NR	17 (13.5)	9 (10.6)	NR	NR
	4	96 (7.4)	43 (6.6)	31 (7.6)	14 (6.9)	NR	NR	10 (7.9)	9 (10.6)	NR	NR
	≥5	64 (4.9)	31 (4.7)	26 (6.4)	7 (3.4)	NR	NR	11 (8.7)	13 (15.3)	NR	NR

Trial		STEP-1		STEP-3		STEP-5		STEP-8		STEP-10	
Arms		SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO
Sample Size		1306	655	407	204	152	152	126	85	138	69
SF-36, Mean ± SD	Physical Functioning Score	51.0±6.9	50.8±7.9	51.9±6.7	52.1±6.8	NR	NR	NR	NR	NR	NR
	Physical Component Summary Score	51.1±7.3	51.1±7.9	51.6±6.9	51.7±7.3	NR	NR	NR	NR	NR	NR
	Mental Component Summary Score	55.4±5.7	55.5±5.9	55.7±5.3	55.4±6.1	NR	NR	NR	NR	NR	NR
IWQOL-Lite-CT, Mean ± SD	Physical Function Score	65.4±24.0	64.0±24.4	NR	NR	NR	NR	NR	NR	NR	NR
	Total Score	63.6±21.2	63.3±20.9	NR	NR	NR	NR	NR	NR	NR	NR

cm: centimeter, COPD: chronic obstructive pulmonary disease, CV: coefficient of variation, HDL: high-density lipoprotein, IWQOL-Lite-CT: The Impact of Weight on Quality of Life–Lite Clinical Trials Version, LDL: low-density lipoprotein, min: minute, mg/dl: milligrams per deciliter, mm Hg: millimeters of mercury, mmol/L: millimoles per liter, No.: number, NR: not reported, OA: osteoarthritis, PBO: placebo SEM: semaglutide, SD: standard deviation, SF-36: Short Form 36, VLDL: very low-density lipoprotein

*Units are mmol/L not mg/dl

Table D2.6. Baseline Characteristics of Oral Semaglutide[43,123]

Study Name		OASIS-4	
Arms		SEM	PBO
N		205	102
Mean Age, Years ± SD		48 ± 13	47 ± 13
Female, n (%)		155 (75.6)	87 (85.3)
Race or Ethnic Group, n (%)	White	190 (92.7)	91 (89.2)
	Asian	1 (0.5)	1 (0.5)
	Black or African American	13 (6.3)	9 (8.8)
	Other	1 (0.5)	1 (1)
	Hispanic or Latino	17 (8.3)	7 (6.9)
Mean body weight, kg ± SD		106.4 ± 23.5	104.8 ± 19.7
BMI, Mean kg/m^2 ± SD		37.5 ± 6.7	37.8 ± 6.1
Mean Waist Circumference, cm ± SD		114.0 ± 15.8	113.6 ± 14.7
Mean Blood Pressure, mm Hg	Systolic	131.3	131.0
	Diastolic	83.0	83.2
Fasting Plasma Glucose, Mean		95.4	95.7
Mean HbA1C, %		5.7	5.7
No. of coexisting conditions at screening, n (%)	1	63 (30.7)	37 (36.3)
	2	55 (26.8)	23 (22.5)
	3	47 (22.9)	24 (23.5)
	4	30 (14.6)	10 (9.8)
	≥5	7 (3.4)	6 (5.9)
Glycemic Status, %	Normoglycemia	51.2	52
	Prediabetes	47.3	46.1
	Diabetes*	1.5	2

BMI: body mass index, cm: centimeter, kg/m^2: kilogram per square meter, mmHg: millimeters of mercury, PBO: placebo SEM: semaglutide

*Participants did not have diabetes at screening but did at randomization.

Table D2.7. Baseline Characteristics of Key Trials of Tirzepatide[46,47,60]

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	287	292
Duration of Obesity, Years ± SD		14.8±10.75	14.0±10.71	15.4±11.6	14.8±10.8
Body-Mass Index category, n (%)	<30	40 (6.3)	24 (3.7)	37 (12.9)	50 (17.1)
	≥30 to <35	199 (31.6)	227 (35.3)	100 (34.8)	107 (36.6)
	≥35 to <40	179 (28.4)	180 (28.0)	95 (33.1)	79 (27.1)
	≥40	212 (33.7)	212 (33.0)	55 (19.2)	56 (19.2)
Waist Circumference, cm ± SD		114.4±15.59	114.0±14.92	109.3±15.2	109.6±15.1
Diastolic Blood Pressure, mm Hg ± SD		79.3±8.23	79.6±7.95	79.1±8.9	78.1±9.2
Pulse, Beats/min ± SD		72.5±9.95	72.9±9.27	72.0±10.8	70.4±10.3
Lipid Levels, Geometric Mean mg/dl (Coefficient of Variation, %)	Total Cholesterol	187.4 (19.9)	186.4 (20.3)	185.2 (37.2)	185.3 (38.2)
	HDL Cholesterol	47.5 (25.5)	46.5 (26.9)	48.4 (12.7)	49.3 (12.9)
	LDL Cholesterol	109.5 (30.0)	108.4 (30.5)	112.5 (32.5)	112.3 (32.3)
	Free Fatty Acid	0.46 (47.5)	0.47 (44)	NR	NR
	Triglycerides	127.9 (47.5)	130.5 (49.2)	121.4 (55.7)	118.6 (53.3)
Prediabetes, n (%)		253 (40.2)	270 (42.0)	NR	NR
Glycated hemoglobin % ± SD		5.6±0.41	5.6±0.38	5.3 (0.4)	5.4 (0.4)
Fasting Glucose, mg/dl ± SD		95.3±10.3	95.7±9.5	92.6 (11.3)	91.3 (9.4)
Fasting Insulin, mIU/liter ± SD		14.4±9.3	14.3±9.9	70.7 (59)	62.9 (44.4)
SF-36 Physical Function Score ± SD		49.6±7.8	49.7±7.7	51.7 (6.7)	51.7 (6.8)
IWQoL-Lite-CT Physical Function Composite Score ± SD		NR	NR	73.4±21.3	71.4±22
Obesity Related Complications, n (%)	Hypertension	207 (32.9)	199 (30.9)	95 (33.1)	104 (35.6)
	Dyslipidemia	182 (28.9)	186 (28.9)	71 (24.7)	81 (27.7)
	ASCVD	21 (3.3)	21 (3.3)	5 (1.7)	6 (2.1)
	PCOS	6 (1.4)	13 (3)	8 (4.4)	8 (4.4)
	OSA	46 (7.3)	59 (9.2)	25 (8.7)	34 (11.6)
	OA	77 (12.2)	76 (11.8)	43 (15)	48 (16.4)

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	287	292
	Anxiety	94 (14.9)	108 (16.8)	61 (21.3)	55 (18.8)
	Depression				
	NAFLD	48 (7.6)	46 (7.2)	9 (3.1)	16 (5.5)
	Asthma or COPD	53 (8.4)	78 (12.1)	21 (7.3)	21 (10.6)
	Gout	32 (5.1)	35 (5.4)	6 (2.1)	9 (3.1)
No. of Weight Related Complications, n (%)	0	249 (39.5)	245 (38.1)	96 (33.4)	100 (34.2)
	1	284 (45.1)	280 (43.6)	102 (35.5)	81 (27.7)
	2			48 (16.7)	54 (18.5)
	3	86 (13.7)	103 (16.1)	22 (7.7)	36 (12.3)
	4			14 (4.9)	14 (4.8)
	5+	11 (1.7)	15 (2.3)	5 (1.7)	7 (2.4)
SF36-v2, Mean Score (SD)	Mental Component Score	NR	NR	53.9 (0.4)	54 (0.5)
	Physical Component Score	NR	NR	52.7 (0.4)	52.7 (0.5)
Domain Scores, Mean (SD)	Physical Functioning	NR	NR	51.8 (0.4)	51.6 (0.5)
	Role Physical	NR	NR	53.1 (0.4)	52.8 (0.5)
	Bodily Pain	NR	NR	52.7 (0.5)	52.6 (0.6)
	General Health	NR	NR	54.3 (0.5)	54.8 (0.5)
	Vitality	NR	NR	56.2 (0.5)	56.2 (0.5)
	Social Functioning	NR	NR	53.3 (0.4)	53.4 (0.4)
	Role Emotional	NR	NR	51.7 (0.5)	51.4 (0.5)
	Mental Health	NR	NR	54.1 (0.5)	54.2 (0.5)

ASCVD: atherosclerotic cardiovascular disease, cm: centimeter, COPD: chronic obstructive pulmonary disease, HDL: high-density lipoprotein, IWQOL-Lite-CT: The Impact of Weight on Quality of Life–Lite Clinical Trials Version, LDL: low-density lipoprotein, mg/dl: milligrams per deciliter, mIU/liter: milli-international units per liter, mm Hg: millimeters of mercury, NAFLD: non-alcoholic fatty liver disease, OA: osteoarthritis, OSA: obstructive sleep apnea, PBO: placebo, PCOS: polycystic ovary syndrome, SD: standard deviation, SF-36: Short Form 36, TZP: tirzepatide

Table D2.8. Baseline Characteristics of Direct Comparison Trial (Tirzepatide vs Semaglutide)[48]

Study Name		SURMOUNT-5	
Arms		TZP	SEM
N		374	376
Age, Years ± SD		45 (12.9)	44.4 (12.7)
Female, n (%)		242 (64.7)	243 (64.6)
Race or Ethnic Group, n (%)	American Indian or Alaska Native	6 (1.6)	0
	Asian	11 (2.9)	7 (1.9)
	Black or African American	77 (20.6)	67 (17.8)
	White	276 (73.8)	295 (78.5)
	Multiple	4 (1.1)	7 (1.9)
	Hispanic or Latino	93 (24.9)	103 (27.4)
Duration of Obesity, Years ± SD		16.4 (11.6)	14.7 (11)
Body Weight, kg ± SD		112.7 (24.8)	113.4 (26.3)
Mean Body-Mass Index ± SD		39.4 (7.4)	39.4 (7.7)
Body-Mass Index Category, n (%)	<35	115 (30.7)	118 (31.4)
	≥35	259 (69.3)	258 (68.6)
Waist Circumference, cm ± SD		117.7 (16.1)	118.8 (17.6)
Blood Pressure, mm Hg ± SD	Systolic	125.6 (13.56)	125.8 (12.48)
	Diastolic	81.1 (8.48)	81.6 (8.04)
	Pulse, Beats per min	72 (9.54)	72.7 (10.02)
Lipid Levels, Geometric Mean mg/dl (Coefficient of Variation, %)	Total cholesterol	188.7 (37.4)	190.9 (35.3)
	HDL Cholesterol	49.4 (13.1)	49.9 (13.5)
	LDL Cholesterol	113.5 (31.7)	114.6 (30.7)
	Triglycerides	127 (66.2)	133.5 (105.1)
Estimated GFR, ml/min/1.73 m^2		104.6 (17.43)	106 (16.88)
Prediabetes, n (%)		215 (57.5)	210 (55.9)
Glycated Hemoglobin % ± SD		5.6 (0.35)	5.6 (0.38)
Fasting Glucose, mg/dl ± SD		94.4 (10.43)	94.9 (9.83)

Study Name		SURMOUNT-5	
Arms		TZP	SEM
N		374	376
Obesity Related Complications	Hypertension	156 (41.7)	141 (37.5)
	Dyslipidemia	86 (23)	96 (25.5)
	Impaired Glucose	77 (20.6)	66 (17.6)
	Back Pain	49 (13.1)	48 (12.8)
	Gallbladder Disease	36 (9.6)	45 (12)
	OSA	55 (14.7)	55 (14.6)
	OA	32 (8.6)	35 (9.3)
	Anxiety	70 (18.7)	67 (17.8)
	Depression	45 (12)	46 (12.2)
	NAFLD	11 (2.9)	7 (1.9)
	Asthma or COPD	42 (11.2)	31 (8.2)
	Gout	11 (2.9)	7 (1.9)
Number of Weight Related Complications	0	102 (27.3)	79 (21)
	1	85 (22.7)	108 (28.7)
	2	73 (19.5)	74 (19.7)
	3	40 (10.7)	58 (15.4)
	4	26 (7)	24 (6.4)
	5+	48 (12.8)	33 (8.8)

COPD: chronic obstructive pulmonary disease, GFR: glomerular filtration rate, HDL: high-density lipoprotein, kg: kilogram, LDL: low-density lipoprotein mg/dl: milligrams per deciliter, NAFLD: non-alcoholic fatty liver disease, OA: osteoarthritis, OSA: obstructive sleep apnea, SD: standard deviation, SEM: semaglutide, TZP: tirzepatide

Table D2.9. Baseline Characteristics of Key Cardiovascular Trials[19,50]

Study Name		SELECT		SURPASS-CVOT	
Arms		SEM	PBO	TZP	DULA
N		8803	8801	6586	6579
Age, Years ± SD		61.6 (8.9)	61.6 (8.8)	64	64.1
Female, n (%)		2448 (27.8)	2424 (27.5)	28.7%	29.3%
Race or Ethnic Group, n (%)	Asian	720 (8.2)	727 (8.3)	8.8%	9.1%
	Black or African American	348 (4)	323 (3.7)	NR	NR
	White	7387 (83.9)	7404 (84.1)	81.5%	81.4%
	Hispanic or Latino	914 (10.4)	908 (10.3)	30.2%	30.1%
Body Weight, kg ± SD		96.5 (17.5)	96.8 (17.8)	92.6	92.5
Body-mass index ± SD		33.3 (5)	33.4 (5)	32.6	32.6
BMI category, n (%)	<30	2555 (29)	2469 (28.1)	NR	NR
	≥30 to <35	3693 (42)	3781 (43)	NR	NR
	≥35 to <40	1687 (19.2)	1659 (18.9)	NR	NR
	≥40	868 (9.9)	892 (10.1)	NR	NR
Mean Waist Circumference, cm (SD)		111.3 (13.1)	111.4 (13.1)	NR	NR
Glycated Hemoglobin, % (SD)		5.78 (0.34)	5.78 (0.33)	8.4	8.4
Mean Systolic Blood Pressure, mm Hg (SD)		131 (15.6)	130.9 (15.3)	135.1	135.5
Mean Diastolic Blood Pressure, mm Hg (SD)		79.4 (10)	79.2 (9.9)	NR	NR
Mean Pulse, beats/min (SD)		68.9 (10.6)	68.6 (10.7)	NR	NR
Lipid Levels, Geometric mean mg/dl (CV)	Total Cholesterol	153 (131, 182)	153 (131, 183)	NR	NR
	HDL Cholesterol	44 (37, 52)	44 (37, 52)	NR	NR
	LDL Cholesterol	78 (61, 102)	78 (61, 102)	80.5	80.7
	Triglycerides	134 (99, 188)	135 (100, 190)	160.3	159.4
Glycemic status, n (%)	Normoglycemia	2925 (33.2)	2980 (33.9)	NA	NA
	Prediabetes	5877 (66.8)	5819 (66.1)	NA	NA
Median High-Sensitivity CRP Level (IQR), mg/liter		1.87 (0.89, 4.18)	1.80 (0.86, 4.06)	NR	NR
EQ-5D-5L Index Score		0.88 (0.15)	0.88 (0.15)	NR	NR
EQ-5D-5L VAS Score		77.15 (15.63)	77.15 (15.73)	NR	NR

BMI: body mass index, cm: centimeter, CV: coefficient of variation, DULA: dulaglutide, HDL: high-density lipoprotein, IQR: interquartile range, LDL: low-density lipoprotein, mg: milligram, PBO: placebo, SD: standard deviation, SEM: semaglutide, TZP: tirzepatide

Table D2.10. Baseline Characteristics of Tirzepatide Obstructive Sleep Apnea Trial[21]

Study Name		SURMOUNT-OSA			
Arms		TZP	PBO	TZP	PBO
N		114	120	120	115
Body-Mass Index Category, n (%)	<35	33 (28.9)	44 (36.7)	33 (27.7)	33 (28.9)
	≥35 to <40	39 (34.2)	35 (29.2)	47 (39.5)	41 (36)
	≥40	42 (36.8)	41 (34.2)	39 (32.8)	40 (35.1)
Waist Circumference, cm ± SD		122.6 (16.6)	119.8 (14.8)	120.7 (13.1)	121 (14)
Diastolic Blood Pressure, mm Hg ± SD		83.7 (8.9)	84 (8.6)	832.2 (8.2)	80.5 (8.6)
Prediabetes, n (%)		74 (64.9)	78 (65)	69 (57.5)	64 (55.7)
Glycated Hemoglobin % ± SD		5.69 (0.37)	5.64 (0.35)	5.62 (0.37)	5.65 (0.44)
Apnea-Hypopnea Index Events		52.9 (30.5)	50.1 (31.5)	46.1 (22.4)	53.1 (30.2)
OSA Severity	No Apnea	0	1 (0.8)	NR	NR
	Mild: AHI <15 Events/hr	1 (0.9)	2 (1.7)	0	2 (1.8)
	Moderate: AHI ≥15 Events	39 (34.2)	43 (36.1)	35 (29.4)	37 (32.5)
	Severe: AHI ≥30 Events/hr	74 (64.9)	73 (61.3)	84 (70.6)	75 (65.8)
	Missing Data	0	1 (0.8)	1 (0.8)	1 (0.9)
PROMIS Sleep-Related Impairment T Score		53.2 (7.5)	54.3 (8.5)	55.3 (8.4)	55 (9.5)
PROMIS Sleep-Related Disturbance T Score		53.8 (6)	53.5 (7.4)	56 (7.6)	55.7 (7.6)
ESS Score		10.3 (5.3)	10.8 (5.2)	10.8 (4.6)	9.5 (4.4)
Sleep Apnea-specific Hypoxic Burden, min/hr		153.6 (102.7)	137.8 (104.1)	132.2 (83.4)	142.1 (112.5)
hsCRP Concentration, mg/liter		3.5 (120)	3.6 (124.6)	3.0 (124.3)	2.7 (127.5)

AHI: apnea-hypopnea index, cm: centimeter, ESS: Epworth Sleepiness Scale, hsCRP: high-sensitivity C-reactive protein, mm Hg: millimeters of mercury, OSA: obstructive sleep apnea, PROMIS: Patient-Reported Outcomes Measurement Information System, SD: standard deviation

Table D2.11. Baseline Characteristics of Additional Clinical Trials[29,30,51]

Trials		ESSENCE		STEP-HFpEF		SUMMIT	
Study Arms		**SEM**	**PBO**	**SEM**	**PBO**	**TZP**	**PBO**
Sample Size		**534**	**266**	**263**	**266**	**364**	**367**
Mean Age, Years		56 (11)	55 (12)	70	69	66 (11)	65 (11)
Female, %		59%	54%	57%	56%	55%	53%
Race and Ethnicity, %	**White**	68%	67%	97%	95%	70%	70%
	Black	1%	1%	3%	5%	6%	4%
	Asian	27%	28%	NR	NR	16%	20%
	Hispanic	18%	19%	6%	8%	54%	56%
Baseline Weight, kg		95 (25)	98 (25)	105	105	103 (22)	103 (23)
Baseline BMI, kg/m^2		34 (7)	35 (7)	37	37	38 (6)	38 (7)
Mean HbA1C, %		NR	NR	NR	NR	48%	49%
Type 2 Diabetes, %		55%	57%	0%	0%	48%	49%
Mean Systolic Blood Pressure		NR	NR	133	132	128 (13)	128 (14)
Mean eGFR, mL/min/1.73m2		NR	NR	NR	NR	65 (24)	64 (24)
Median UACR, mg/g, (IQR)		NR	NR	NR	NR	NR	NR

NYHA Functional Class, n (%)	**II**	NR	NR	70%	63%	72%	73%
	III or IV	NR	NR	30%	37%	28%	27%
Comorbidities, n (%)	**Coronary Artery Disease**	NR	NR	20%	17%	31%	29%
	Hypertension	NR	NR	82%	82%	NR	NR

BMI: body mass index, eGFR: estimated glomerular filtration rate, IQR: interquartile range, NYHA: New York Heart Association, PBO: placebo, SEM: semaglutide, TZP: tirzepatide, UACR: urine albumin-to-creatinine ratio

Table D2.12. Baseline Characteristics of Semaglutide Knee Osteoarthritis Trial[28]

Study Name		STEP-9	
Arms		SEM	PBO
N		271	136
Mean Age, Years ± SD		56±10	56±10
Female, n (%)		228 (84.1)	104 (76.5)
Race or Ethnic Group, n (%)	White	168 (62.0)	80 (58.8)
	Asian	16 (5.9)	6 (4.4)
	Black or African American	18 (6.6)	13 (9.6)
	Other	32 (11.8)	26 (19.1)
Mean Body Weight, kg ± SD		108.7±24.1	108.5±24.5
BMI, Mean ± SD		40.5±7.3	40.0±7.1
BMI Category, n (%)	<30	0	1 (0.7)
	≥30 to <35	67 (24.7)	32 (23.5)
	≥35 to <40	84 (31.0)	56 (41.2)
	≥40	120 (44.3)	47 (34.6)
Mean Waist Circumference, cm ± SD		118.3±15.8	119.7±15.9
Mean Blood Pressure, mm Hg ± SD	Systolic	132±14	131±15
	Diastolic	82±10	82±10
Coexisting Conditions at the Time of Screening, n (%)	Dyslipidemia	80 (29.5)	44 (32.4)
	Hypertension	128 (47.2)	68 (50.0)
	Asthma or COPD	19 (7.0)	19 (14.0)
	Gastroesophageal Reflux Disease	31 (11.4)	15 (11.0)
	Cardiovascular Disease	13 (4.8)	8 (5.9)
WOMAC Pain Score, Mean (SD)		72.8±15.6	67.2±16.0

BMI: body mass index, COPD: Chronic obstructive pulmonary disease, kg: kilogram PBO: placebo, SEM: semaglutide, SD: standard deviation, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table D2.13. Baseline Characteristics of Treatment Withdrawal Trials[155,156]

Study Name		STEP-4		SURMOUNT-4	
Arms		SEM	PBO	TZP	PBO
N		535	268	335	335
Mean Age, Years (SD)		47 (12)	46 (12)	49 (13)	48 (12)
Female, n (%)		429 (80.2)	205 (76.5)	236 (70.4)	237 (70.7)
Race or ethnic group, n (%)	White	446 (83.4)	226(84.3)	264 (78.8)	273 (81.5)
	Asian	15(2.8)	4(1.5)	26 (7.8)	22 (6.6)
	Black or African American	69(12.9)	35(13.1)	39 (11.6)	36 (10.7)
	Hispanic or Latino	42(7.9)	21(7.8)	141 (42.1)	155 (46.3)
Mean Body Weight, kg (SD)		96.5 (22.5)	95.4 (22.7)	84.6 (19.8)	85.8 (22.3)
BMI, Mean (SD)		34.5 (6.9)	34.1 (7.1)	30.3 (6)	30.7 (6.8)
BMI, n (%)	<25	7(1.3)	9(3.4)	NR	NR
	≥25 to <30	153(28.6)	69(25.7)	NR	NR
	<30	NR	NR	181 (54)	183 (54.6)
	≥30 to <35	166(31.0)	97(36.2)	88 (26.3)	75 (22.4)
	≥35 to <40	116(21.7)	52(19.4)	41 (12.2)	43 (12.8)
	≥40	93(17.4)	41(15.3)	25 (7.5)	34 (10.1)
Mean Waist Circumference, cm (SD)		105.5 (15.9)	104.7 (16.9)	96.8 (14.1)	98.2 (16)
Glycated Hemoglobin, % (SD)		5.4 (0.3)	5.4 (0.3)	5.07 (0.30)	5.04 (0.31)
Mean Blood Pressure, mm Hg (SD)	Systolic	121 (13)	121 (13)	115 (12)	115 (12)
	Diastolic	78 (9)	78 (9)	75 (9)	76 (9)
	Pulse, beats/min	76 (9)	76 (9)	77 (9)	78 (9)
Fasting Plasma Glucose, mean (SD)		87.9 (7.7)	86.9 (7.6)	85.1 (7.4)	85 (7.8)
Lipid Levels, Geometric Mean mg/dl (Coefficient of Variation)	Total Cholesterol	177.2 (152.9-201.9)*	177.6 (156.0-198.8)*	179.9 (36.8)	180.2 (37.2)
	HDL Cholesterol	44.4(37.8-51.7)*	44.0(36.5-51.0)*	49.1 (11.6)	48.8 (11.5)
	LDL Cholesterol	110.4(91.1-130.9)*	112.5(93.6-130.9)*	111 (32.4)	113.2 (33.6)
	VLDL Cholesterol	18.5(14.3-24.7)*	17.8(13.5-24.7)*	NR	NR
	Free Fatty Acids	12.5(9.0-18.0)*	12.5(8.5-17.9)*	NR	NR
	Triglycerides	95.2(73.9-125.5)*	90.8(69.4-126.4)*	99.1 (45.1)	93 (44.3)

Study Name		STEP-4		SURMOUNT-4	
Arms		SEM	PBO	TZP	PBO
N		535	268	335	335
	Estimated GFR, ml/min/1.73 m^[2]	94.2 (81.3-106.6)*	95.9 (83.5-108.1)*	96.4 (18.8)	97.9 (17.9)
Coexisting Conditions at the Time of Screening, n (%)	Dyslipidemia	189 (35.3)	99 (36.9)	113 (33.7)	99 (29.6)
	Hypertension	199 (37.2)	99 (36.9)	119 (35.5)	117 (34.9)
	Knee osteoarthritis	72 (13.5)	27 (10.1)	NR	NR
	Obstructive sleep apnea	61 (11.4)	33 (12.3)	40 (11.9)	41 (12.2)
	Asthma or COPD	57 (10.7)	35 (13.1)	34 (10.1)	35 (10.4)
	Nonalcoholic Fatty Liver Disease	37 (6.9)	18 (6.7)	22 (6.6)	26 (7.8)
	Polycystic Ovarian Syndrome	15 (3.5)	10 (4.9)	9 (3.8)	14 (5.9)
	Coronary artery disease	4 (0.7)	3 (1.1)	NR	NR
No. of Coexisting Conditions at Screening, n (%)	None	144 (26.9)	70 (26.1)	98 (29.3)	107 (31.9)
	1	160 (29.9)	78 (29.1)	99 (29.6)	96 (28.7)
	2	103 (19.3)	68 (25.4)	59 (17.6)	53 (15.8)
	3	77 (14.4)	34 (12.7)	39 (11.6)	37 (11)
	4	38 (7.1)	15 (5.6)	26 (7.8)	26 (7.8)
	≥5	13 (2.4)	3 (1.1)	14 (4.2)	16 (4.8)
SF-36 (SD)	Physical Functioning Score	53.8 (5.7)	54.1 (5.0)	53.4 (5.8)	53.2 (6.5)

BMI: body mass index, cm: centimeter, COPD: chronic obstructive pulmonary disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein, mm Hg: millimeters of mercury, kg: kilogram, SD: standard deviation, VLDL: very low-density lipoprotein

*(interquartile range)

Table D2.14. Additional Results of Key Weight Loss Trials of Injectable Semaglutide[23,24,26,27,125]

Study Name	Arm	N	Body Weight Change from Baseline		% Unadjusted Weight Loss from Baseline to One Year	≥5% Body-Weight Reduction	
			% (SE)	Difference vs Placebo (95% CI; p value)	Mean (SE)	% of Particip-ants	Odds Ratio (95% CI; p value)
STEP-1	**SEM**	**1306**	-14.85	-12.44 (-13.37, -11.51; <0.001)	-15.6	86.4	11.2 (8.9, 14.2; <0.001)
	PBO	**655**	-2.41		-2.8	31.5	
STEP-3	**SEM**	**407**	–16.0	–10.3 (–12.0, –8.6; <0.001)	-16.5	86.6	6.1 (4.0, 9.3; <0.001)
	PBO	**204**	–5.7		-5.8	47.6	
STEP-5	**SEM**	**152**	–15.2 (0.9)	–12.6 (–15.3, –9.8; <0.0001)	-17.4	77.1	5.0 (3.0, 8.4; <0.0001)
	PBO	**152**	–2.6 (1.1)		-2.7	34.4	
STEP-8	**SEM**	**126**	–15.8 (–17.6, –13.9)*	–13.9 (–16.7, –11.0)	-16.4	87.2	NR
	PBO	**85**	–1.9 (–4.0, 0.2)*		-1.6	29.5	
STEP-10	**SEM**	**138**	–13.9 (0.7)†	–11.2 (–13.0, –9.4; <0.0001)	NR	86	15.9 (7.5, 33.6; <0.0001)
	PBO	**69**	–2.7 (0.6)†		NR	26	

CI: confidence interval, NR: not reported, PBO: placebo, SE: standard error, SEM: semaglutide

*(95% CI)

†Standard deviation

Table D2.15. Additional Results of Key Weight Loss Trials of Injectable Semaglutide Continued[23,24,26,27,125]

Study Name	Arm	N	≥10% Body-Weight Reduction		≥15% Body-Weight Reduction		≥20% Body-Weight Reduction	
			% of Participants	Odds ratio (95% CI; p value)	% of Participants	Odds Ratio (95% CI; p value)	% of Participants	Odds Ratio (95% CI; p value)
STEP-1	**SEM**	**1306**	69.1	14.7 (11.1, 19.4; <0.001)	50.5	19.3 (12.9, 28.8: <0.001)	32	26.9 (14.2, 51)
	PBO	**655**	12		4.9		1.7	
STEP-3	**SEM**	**407**	75.3	7.4 (4.9, 11.0; <0.001)	55.8	7.9 (4.9, 12.6; <0.001)	35.7	13.7 (6.2, 30.3; <0.001)
	PBO	**204**	27.0		13.2		3.7	
STEP-5	**SEM**	**152**	61.8	7.2 (4.0, 13.2; <0.0001)	52.1	9.4 (4.4, 20.0; <0.0001)	36.1	12.8 (3.9, 41.9)
	PBO	**152**	13.3		7.0		2.3	
STEP-8	**SEM**	**126**	70.9	NR	55.6	NR	38.5	NR
	PBO	**85**	15.4	NR	6.4	NR	2.6	NR
STEP-10	**SEM**	**138**	74	32.7 (12.0, 89.1; <0.0001)	48	52.2 (7.1, 383.1; 0.0001)	25	39.6 (2.4, 641.2; 0.0097)
	PBO	**69**	8		2		0	

CI: confidence interval, NR: not reported, PBO: placebo, SEM: semaglutide

Table D2.16. Secondary Outcomes of Key Weight Loss Trials of Injectable Semaglutide [23,24,26,27,125]

Study Name	Arm	N	Waist Circumference, cm		Systolic Blood Pressure, mm Hg	
			Mean Change from Baseline (95% CI)	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline	Difference vs Placebo (95% CI; p value)
STEP-1	**SEM**	**1306**	-13.54	–9.42 (–10.30, –8.53; <0.001)	-6.16	-5.10 (–6.34, –3.87; <0.001)
	PBO	**655**	-4.13		-1.06	
STEP-3	**SEM**	**407**	–14.6	–8.3 (–10.1, –6.6; <0.001)	–5.6	–3.9 (–6.4, –1.5; 0.001
	PBO	**204**	–6.3		–1.6	
STEP-5	**SEM**	**152**	–14.4 (0.9)*	–9.2 (–12.2 to –6.2; <0.0001)	–5.7 (1.1)*	–4.2 (–7.3 to –1.0; 0.0102)
	PBO	**152**	–5.2 (1.2)*		–1.6 (1.2)*	
STEP-8	**SEM**	**126**	–13.2 (–15.0, –11.5)	NR	–5.7 (–8.1, –3.3)	NR
	PBO	**85**	–2.0 (–4.0, 0.1)	NR	3.2 (0.3, 6.1)	NR
STEP-10	**SEM**	**138**	–11.1 (0.8)†	–8.3 (–10.4, 6.2; <0.0001	–8·8 (1.1)†	–7.8 (–11.3, –4.3; <0.0001
	PBO	**69**	–2.8 (0.7)†		–1·0 (1.4)†	

CI: confidence interval, cm: centimeter, mm Hg: millimeters of mercury, NR: not reported, PBO: placebo, SEM: semaglutide

*Standard error

†Standard deviation

Table D2.17. Secondary Outcomes of Key Weight Loss Trials of Injectable Semaglutide Continued[23,24,26,27,125]

Study Name	Arm	N	Body Weight, kg		Body-Mass Index		Glycated Hemoglobin, Percentage Points	
			Mean Change from Baseline	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline	Difference vs Placebo (95% CI; p value)
STEP-1	**SEM**	**1306**	-15.3	–12.7 (–13.7, –11.7)	-5.54	–4.61 (–4.96, –4.27)	-0.45	–0.29 (–0.32, –0.26)
	PBO	**655**	-2.6		-0.92		-0.15	
STEP-3	**SEM**	**407**	–16.8	–10.6 (–12.5, –8.8; <0.001)	–6.0	–3.8 (–4.4, –3.1; <0.001)	–0.51	–0.24 (–0.29, –0.19; <0.001)
	PBO	**204**	–6.2		–2.2		–0.27	
STEP-5	**SEM**	**152**	–16.1 (1.0)*	–12.9 (–16.1, –9.8)	–5.9 (0.4)*	–4.3 (–5.7, –2.9)	NR	NR
	PBO	**152**	–3.2 (1.2)*		–1.6 (0.6)*		NR	
STEP-8	**SEM**	**126**	–15.3(–17.3, –13.4)	–13.8 (–16.8, –10.7)	NR	NR	NR	NR
	PBO	**85**	–1.6 (–3.9, 0.8)		NR		NR	
STEP-10	**SEM**	**138**	–15·2 (0.8)†	–12.4 (–14.4, –10.3)	NR	NR	NR	NR
	PBO	**69**	–2·8 (0.6)†		NR		NR	

CI: confidence interval, kg: kilogram, NR: not reported, PBO: placebo, SEM: semaglutide

*Standard error

†Standard deviation

Table D2.18. Secondary Outcomes of Key Weight Loss Trials of Injectable Semaglutide Continued[23,24,26,27,125,166]

Study Name	Arm	N	Fasting Serum Insulin		Fasting Plasma Glucose, mg/dl	
			% Change from Baseline	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline (SE)	Difference vs Placebo (95% CI; p value)
STEP-1	**SEM**	**1306**	-26	-21 (-26, -17; <0.0001)	-8.53	–7.87 (–9.04, –6.70; <0.0001)
	PBO	**655**	-7		-0.48	
STEP-3	**SEM**	**407**	–32.3	–20.3 (–30.4, –8.7; 0.001)	–6.73	–6.09 (–8.13, –4.04; <0.001)
	PBO	**204**	–15.0		–0.65	
STEP-5	**SEM**	**152**	–32.7	–27.4 (–39.3, –13.3)	–0.4 (0.05)	–0.5 (–0.7, –0.4)
	PBO	**152**	–7.2		0.1 (0.06)	
STEP-8	**SEM**	**126**	–27.8	NR	–8.3	NR
	PBO	**85**	–3.5		3.3	
STEP-10	**SEM**	**138**	NR	NR	–0.8 (0.1)*	–0.6 (–0.8, –0.4; <0.0001)
	PBO	**69**	NR		–0.2 (0.1)*	

CI: confidence interval, mg/dl: milligrams per deciliter, NR: not reported, PBO: placebo, SE: standard error, SEM: semaglutide

*mmol/L (standard deviation)

Table D2.19. Secondary Outcomes of Key Weight Loss Trials of Injectable Semaglutide Continued [23,24,26,27,125,166]

Study Name	Arm	N	Diastolic Blood Pressure, mmHg		Total Cholesterol		HDL Cholesterol	
			Mean Change from Baseline (95% CI; p value)	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline (95% CI; p value)	Difference vs Placebo (95% CI; p value)	Ratio to Baseline	Difference vs Placebo (95% CI; p value)
STEP-1	**SEM**	**1306**	-2.83	–2.41 (–3.25, –1.57; <0.0001)	0.97†	0.97 (0.95, 0.98)	1.05†	1.04 (1.02, 1.05)
	PBO	**655**	-0.42		1†		1.01†	
STEP-3	**SEM**	**407**	–3.0	–2.2 (–3.9, –0.6; 0.008)	–3.8	–5.8 (–8.4, –3.2; <0.001)	6.5	1.5 (–1.8, 4.9; 0.39)
	PBO	**204**	–0.8		2.1		5.0	
STEP-5	**SEM**	**152**	–4.4 (0.9)*	–3.7 (–6.1, –1.2)	–3.3	–4.6 (–8.4, –0.6)	9.6	1.3 (–3.9, 6.9)
	PBO	**152**	–0.8 (0.9)*		1.4		8.1	
STEP-8	**SEM**	**126**	–5.0 (–7.0, –3.1)	NR	–7.1 (–10.7, –3.3)	NR	–0.3(–3.6, 3.0)	NR
	PBO	**85**	0.7 (–1.5, 2.9)	NR	–3.3 (–7.9, 1.5)	NR	–0.9 (–4.5, 2.9)	NR
STEP-10	**SEM**	**138**	NR	NR	0.9†	0.9 (0.9, 1.0; 0.017)	0.8†	0.9 (0.8, 1.0; 0.0024)
	PBO	**69**	NR	NR	1.0†		1.0†	

CI: confidence interval, HDL: high-density lipoprotein, mm Hg: millimeters of mercury, NR: not reported, PBO: placebo, SE: standard error, SEM: semaglutide

*Standard error

†Ratio to baseline

Table D2.20. Secondary Outcomes of Key Weight Loss Trials of Injectable Semaglutide Continued[23,24,26,27,125,166]

Study Name	Arm	N	LDL Cholesterol		VLDL Cholesterol		Free Fatty Acids	
			Mean Change from Baseline (95% CI; p value)	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline (95% CI; p value)	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline (95% CI; p value)	Difference vs Placebo (95% CI; p value)
STEP-1	**SEM**	**1306**	0.97*	0.96 (0.94, 0.98; 0.0011)	0.78*	0.84 (0.81, 0.87)	0.83*	0.89 (0.83, 0.94)
	PBO	**655**	1.01*		0.93*		0.93*	
STEP-3	**SEM**	**407**	–4.7	–7.1 (–10.9, –3.2; <0.001)	–22.5	–17.0 (–22.8, –10.9; <0.001)	–11.9	–15.3 (–25.0, –4.3; 0.008)
	PBO	**204**	2.6		–6.6		4.0	
STEP-5	**SEM**	**152**	–6.1	-3.4 (–9.1, 2.6)	–18.9	–21.5 (–29.6, –12.4)	0.3	–6.2 (–21.2, 11.6)
	PBO	**152**	–2.7		3.3		7.0	
STEP-8	**SEM**	**126**	–6.5 (–12.4, –0.1)	NR	–20.7(–25.1, –16.0)	NR	–12.6 (–22.1, –2.0)	NR
	PBO	**85**	–1.1 (–11.4, 10.4)		–4.1 (–12.1, 4.6)		2.6 (–10.5, 17.5)	
STEP-10	**SEM**	**138**	0.8*	0.9 (0.8, 1.0; 0.0018)	1*	1.0 (1.0, 1.1; 0.14)	0.9*	0.9 (0.9, 1.01; 0.072)
	PBO	**69**	1*		1*		1*	

CI: confidence interval, LDL: low-density lipoprotein, NR: not reported, PBO: placebo, SE: standard error, SEM: semaglutide, VLDL: very low-density lipoprotein
*Ratio to baseline

Table D2.21. Secondary Outcomes of Key Weight Loss Trials of Injectable Semaglutide Continued[23,24,26,27,125,166]

Study Name	Arm	N	Triglycerides		C-reactive Protein	
			Mean Change from Baseline (95% CI; p value)	Difference vs Placebo (95% CI; p value)	Mean Change from Baseline (95% CI; p value)	Difference vs Placebo (95% CI; p value)
STEP-1	**SEM**	**1306**	0.78*	0.84 (0.81, 0.87; <0.0001)	0.47*	0.56 (0.51, 0.61; <0.0001)
	PBO	**655**	0.93*		0.85*	
STEP-3	**SEM**	**407**	–22.5	–17.0 (–22.8, –10.8; <0.001)	–59.6	–47.6 (–55.0, –39.0; <0.001)
	PBO	**204**	–6.5		–22.9	
STEP-5	**SEM**	**152**	–19.0	–21.9 (–29.8, –13.2)	–56.7	–53.1 (–63.2, –40.0)
	PBO	**152**	3.7		–7.8	
STEP-8	**SEM**	**126**	–20.7 (–25.6, –15.6)	NR	–52.6 (–61.3, –42.0)	NR
	PBO	**85**	–3.2 (–11.4, 5.8)		–20.1 (–34.7, –2.3)	
STEP-10	**SEM**	**138**	NR	NR	NR	NR
	PBO	**69**	NR		NR	

CI: confidence interval, NR: not reported, PBO: placebo, SEM: semaglutide

*Ratio to baseline

Table D2.22. Patient Reported Outcomes of Injectable Semaglutide Trials[23,24,167,168]

Study Name		STEP-1		STEP-3	
Arm		SEM	PBO	SEM	PBO
N		1306	655	407	204
SF-36 Physical Functioning Score	Mean Change from Baseline	2.21	0.41	2.4	1.6
	Difference vs Placebo (95% CI; p value)	1.80 (1.18, 2.42; <0.001)		0.8 (–0.2, 1.9; 0.12)	
Clinically Meaningful SF-36 Physical Functioning Score Improvement (≥3.7 points)	% of Participants	39.8	24.1	36.3	25.5
	Estimated Treatment Difference (95% CI; p value)	15.6 (10.4, 20.8; <0.0001)		10.8 (0.9, 20.7; 0.0318)	
SF-36 Physical Component Summary Score	Mean Change from Baseline	NR	NR	3.0	2.3
	Difference vs Placebo (95% CI; p value)	NR		0.7 (–0.5, 1.9; 0.27)	
SF-36 Mental Component summary Score	Mean change from baseline	NR	NR	–0.8	–2.9
	Difference vs Placebo (95% CI; p value)	NR		2.1 (0.5, 3.6; 0.011)	
SF-36 Bodily Pain Score	Mean Change from Baseline	NR	NR	0.9	-0.5
	Difference vs Placebo (95% CI; p value)	NR		1.3 (0, 2.7; 0.05)	
SF-36 Role-physical	Estimated Treatment Difference (95% CI; p value)	1.4 (0.7, 2.0; <0.0001)		NR	
SF-36 General Health	Estimated Treatment Difference (95% CI; p value)	2.2 (1.5, 2.9; <0.0001)		NR	
SF-36 Vitality	Estimated Treatment Difference (95% CI; p value)	1.9 (1.1, 2.7; <0.0001)		NR	
SF-36 Social Functioning	Estimated Treatment Difference (95% CI; p value)	1.3 (0.6, 2.0; 0.0002)		NR	
SF-36 Role-emotional	Estimated Treatment Difference (95% CI; p value)	0.7 (-0.1, 1.5; 0.0979)		NR	
SF-36 Mental Health	Estimated Treatment Difference (95% CI; p value)	1.1 (0.4, 1.9; 0.0026)		NR	
IWQOL-Lite-CT Physical Function Score	Mean Change from Baseline	14.67	5.25	NR	NR

Study Name		STEP-1		STEP-3	
Arm		SEM	PBO	SEM	PBO
N		1306	655	407	204
	Difference vs Placebo (95% CI; p value)	9.43 (7.50, 11.35; <0.001)		NR	
Clinically Meaningful IWQOL-Lite-CT Physical Function Score Improvement (≥14.6 points)	% of Participants	51.2	32.9	NR	NR
	Odds Ratio (95% CI; p value)	2.72 (2.14, 3.47)		NR	

CI: confidence interval, IWQOL-Lite-CT: The Impact of Weight on Quality of Life–Lite Clinical Trials Version, PBO: placebo, SF-36: Short Form 36, SEM: semaglutide

Table D2.23. Additional Results of Oral Semaglutide Trial[43,123]

Study Name		OASIS-4	
Arms		SEM	PBO
N		205	102
Body Weight Change from Baseline	% (95% CI)	-13.6	-2.2
	Difference vs Placebo (95% CI; p value)	-11.4 (-13.9, -9.0; <0.0001)	
≥5% Body-weight Reduction	% of participants	79.2	31.1
	Odds ratio (95% CI; p value)	7.3 (4.2, 12.8; <0.0001)	
≥10% Body-weight Reduction	% of participants	63	14.4
	Odds ratio (95% CI; p value)	9.1 (4.7, 17.3; <0.0001)	
≥15% Body-weight Reduction	% of participants	50	5.6
	Odds ratio (95% CI; p value)	15.7 (6.2, 40.2; <0.0001)	
≥20% Body-weight Reduction	% of participants	29.7	3.3
	Odds ratio (95% CI; p value)	12.2 (3.7, 40.3; <0.0001)	
Body-mass Index	Mean change from baseline	-5.1	-0.8
	Difference vs Placebo (95% CI)	-4.3 (-5.2, -3.4)	
Waist Circumference, cm	Mean change from baseline (95% CI)	-12.2	-2.8
	Difference vs Placebo (95% CI; p value)	-9.5 (-12.4, -6.6; <0.0001)	
Systolic Blood Pressure, mm Hg	Mean change from baseline	-6.8	-5.4
	Difference vs Placebo (95% CI; p value)	-1.4 (-4.6, 1.8; 0.3960)	
IWQOL-Lite-CT Physical Function Score	Mean change from baseline	16.2	8.4
	Difference vs Placebo (95% CI; p value)	7.7 (3.3, 12.2; 0.0006)	
Fasting Plasma Glucose, mg/dl	Mean change from baseline	-6.6	0.4
	Difference vs Placebo (95% CI; p value)	-7 (-11.2, -2.8; 0.0012)	
Diastolic Blood Pressure, mm Hg	Mean change from baseline	-2.7	-2.1
	Difference vs Placebo (95% CI; p value)	-0.65 (-2.8, 1.5; 0.5500)	
HDL Cholesterol	Ratio to baseline	3.1	-0.4
	Difference vs Placebo (95% CI; p value)	3.5 (-0.7, 7.9; 0.0999)	
LDL Cholesterol	Ratio to baseline	-4.4	0.2
	Difference vs Placebo (95% CI; p value)	-4.6 (-10.6, 1.7; 0.1511)	

Study Name		OASIS-4	
Arms		SEM	PBO
N		205	102
VLDL Cholesterol	Ratio to baseline	-18.2	-8.3
	Difference vs Placebo (95% CI; p value)	-10.8 (-19.2, -1.4; 0.0249)	
Triglycerides	Ratio to baseline	-18.4	-7.5
	Difference vs Placebo (95% CI; p value)	-11.8 (-20.2, -2.5; 0.0140)	
C-Reactive Protein	Ratio to baseline	-46.4	-4.2
	Difference vs Placebo (95% CI; p value)	-44.0 (-57.8, -25.7; <0.0001)	
HbA1c, %	Mean change from baseline	-0.29	-0.06
	Difference vs Placebo (95% CI; p value)	-0.23 (-0.31, -0.15; <0.0001)	

CI: confidence interval, cm: centimeter, HDL: high-density lipoprotein, IWQOL-Lite-CT: The Impact of Weight on Quality of Life–Lite Clinical Trials Version, LDL: low-density lipoprotein, mm Hg: millimeters of mercury, PBO: placebo, SEM: semaglutide

Table D2.24. Additional Results of Key Trials of Tirzepatide[46,47,162]

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	287	292
Body Weight Change from Baseline	% (95% CI or SE)	-20.9 (-21.8, -19.9)	-3.1 (-4.3, -1.9)	-18.4 (0.7)	2.5 (1)
	Difference vs Placebo (95% CI; p value)	-17.8 (-19.3, -16.3; <0.001)		-20.8 (-23.2, -18.5)	
≥5% Body-Weight Reduction	%	90.9 (88, 93.8)	34.5 (29.8, 39.2)	87.5 (2.2)	16.5 (3)
	Odds ratio (95% CI; p value)	NR		34.6 (19.2, 62.6)	
≥10% Body-Weight Reduction	%	83.5 (80, 86.9)	18.8 (14.9, 22.7)	76.7 (2.7)	8.9 (2.4)
	Odds ratio (95% CI; p value)			34.7 (17.6, 68.3)	
≥15% Body-weight Reduction	%	70.6 (66.7, 74.5)	8.8 (5.9, 11.7)	65. 4 (3)	4.2 (1.8)
	Odds ratio (95% CI; p value)			48.2 (19.2, 121)	
≥20% Body-weight Reduction	%	56.7 (52.6, 60.8)	3.1 (1.1, 5.1)	44.7 (3)	2.2 (1.3)
	Odds ratio (95% CI; p value)			40.4 (12.2, 133.8)	
≥25% Body-weight Reduction	%	36.2 (32.3, 40.1)	1.5 (0.1, 2.9)	28.7 (2.7)	1.2 (0.9)
	Odds ratio (95% CI; p value)	NR		33.70 (8.84, 128.52)	
≥30% Body-weight Reduction	%	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	NR		NR	
Proportion of Patients achieving waist circumference ≤88 cm	%	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	18.5 (11.6, 29.5)		NR	
Waist Circumference, cm	Mean change from baseline	-18.5 (-19.3, -17.6)	-4.0 (-5.1, -2.8)	NR	NR
	Difference vs Placebo (95% CI; p value)	-14.5 (-15.9, -13.0)		NR	
Systolic Blood Pressure, mm Hg	Mean change from baseline	-7.6 (-8.5, -6.7)	-1.2 (-2.1, -0.3)	-5.1 (0.7)	4.1 (0.7)
	Difference vs Placebo (95% CI; p value)	NR		-9.2 (-11.2, -7.2)	
Diastolic Blood Pressure, mm Hg	Mean change from baseline	-4.6 (-5.2, -4.0)	-1.0 (-1.7, -0.3)	-3.2 (0.5)	2.3 (0.5)
	Difference vs Placebo (95% CI; p value)	NR		-5.5 (-6.9, -4.1)	
Body Weight, kg	Mean change from baseline	NR	NR	-21.5 (0.7)	3.5 (0.7)
	Difference vs Placebo (95% CI; p value)	NR		-25.0 (-26.9, -23.2)	
Body-mass Index	Mean change from baseline	NR	NR	-7.7 (0.2)	1.2 (0.2)
	Difference vs Placebo (95% CI; p value)	NR		-8.9 (-9.6, -8.3)	

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	287	292
Glycated Hemoglobin, percentage points	Mean change from baseline	NR	NR	-0.5 (0)	0
	Difference vs Placebo (95% CI; p value)	NR		-0.5 (-0.5, -0.4)	
Fasting Plasma Glucose, mg/dl	Mean change from baseline	-10.6 (-11.5, -9.6)	0.9 (-0.1, 1.9)	-8.8 (0.8)	2.4 (0.9)
	Difference vs Placebo (95% CI; p value)			-11.2 (-13.5, -8.8)	
Fasting Serum Insulin	% change from baseline	-49.6 (-52.3, -46.9)	-9.7 (-14.8, -4.6)	-39.1 (2.5)	17.3 (5)
	Difference vs Placebo (95% CI; p value)			-48.1 (-53.7, 41.7)	
Triglycerides	% change from baseline	-31.4 (-33.5, -29.3)	-6.3 (-9.3, -3.3)	-25.8 (1.6)	3 (2.3)
	Difference vs Placebo (95% CI; p value)			-28.0 (-32.3, -23.4)	
Total Cholesterol	% change from baseline	-7.4 (-8.6, -6.2)	-1.1 (-2.5, 0.2)	-3.0 (1)	5.2 (1.1)
	Difference vs Placebo (95% CI; p value)			-7.8 (-10.4, -5.1)	
HDL Cholesterol	% change from baseline	8.2 (6.7, 9.7)	0.2 (-1.2, 1.7)	15.4 (1.2)	3.6 (1.1)
	Difference vs Placebo (95% CI; p value)			11.4 (8.2, 14.7)	
LDL Cholesterol	% change from baseline	-8.6 (-10.5, -6.8)	-0.9 (-3.0, 1.3)	-6.1 (1.4)	6.1 (1.7)
	Difference vs Placebo (95% CI; p value)			-11.5 (-15.3, -7.5)	
VLDL Cholesterol	% change from baseline	-31.7 (-33.8, -29.6)	-5.6 (-8.6, -2.6)	-25.6 (1.6)	3 (2.3)
	Difference vs Placebo (95% CI; p value)			-27.8 (-32.1, -23.2)	
Free Fatty Acids	Ratio to baseline	-9.8 (-14.0, -5.6)	6.1 (-0.1, 12.3)	-33.1 (2.2)	-15.0 (3)
	Difference vs Placebo (95% CI; p value)			-21.3 (-28.4, -13.6)	
HbA1c	Mean change from baseline	-0.51 (-0.53, -0.49)	-0.07 (-0.09, -0.05)	NR	NR
Fat Mass (pooled TZP)	Sample Size, N	124	36	NR	NR
	% change from baseline	-33.9	-8.2	NR	NR
	Difference vs Placebo (95% CI; p value)	-25.7 (-31.4, -20.0; p <0.001)		NR	
Lean Mass (pooled TZP)	Sample Size, N	124	36	NR	NR
	% change from baseline	-10.9	-2.6	NR	NR
	Difference vs Placebo (95% CI; p value)	-8.3 (-10.6, -6.1; p<0.001)		NR	
Visceral Fat Mass (pooled TZP)	Sample Size, N	106	29	NR	NR

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	287	292
	% change from baseline	-40.1	-7.3	NR	NR
	Difference vs Placebo (95% CI; p value)	-32.8 (-42.8, -22.8; p <0.001)		NR	

CI: confidence interval, cm: centimeter, HDL: high-density lipoprotein, kg: kilogram, LDL: low-density lipoprotein, mg/dl: milligrams per deciliter, mm Hg: millimeters of mercury, PBO: placebo SE: standard error, TZP: tirzepatide, VLDL: very-low-density lipoprotein

Table D2.25. Patient Reported Outcomes of Key Trials of Tirzepatide[59,60]

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	231	209
SF-36	Mental component score	NR	NR	53.8 (0.5)	52.8 (0.5)
	Mean change from baseline	0.71 (0.29)	-0.47 (0.30)	NR	NR
	Difference vs Placebo (95% CI; p value)	1.19 (0.37, 2.00); p<0.01		0.9 (-0.4, 2.3); p = 0.182	
	Physical component score	NR	NR	55.8 (0.4)	51.8 (0.4)
	Mean change from baseline	4.18 (0.23)	1.62 (0.25)	NR	NR
	Difference vs Placebo (95% CI; p value)	2.56 (1.89, 3.23); p<0.001		4.0 (2.8, 5.1): p<0.001	
Domain Scores	Physical functioning	4.14 (0.25)	1.76 (0.26)	3.3 (0.4)	-0.6 (0.4)
	Difference vs Placebo (95% CI; p value)	2.38 (1.67, 3.09); p<0.001		3.9 (2.8, 4.9)	
	Role Physical	2.76 (0.25)	1.42 (0.26)	54.8 (0.4)	52.3 (0.4)
	Difference vs Placebo (95% CI; p value)	1.34 (0.62, 2.05); p<0.001		2.5 (1.4, 3.6); p<0.001	
	Bodily Pain	2.85 (0.32)	0.44 (0.34)	54.9 (0.5)	51.5 (0.5)
	Difference vs Placebo (95% CI; p value)	2.41 (1.50, 3.32); p<0.001		3.3 (1.9, 4.8); p<0.001	
	General Health	4.20 (0.28)	1.03 (0.29)	56.9 (0.4)	52.8 (0.5)
	Difference vs Placebo (95% CI; p value)	3.16 (2.38, 3.95); p<0.001		4.1 (2.8, 5.3); p<0.001	
	Vitality	3.19 (0.30)	0.21 (0.32)	57.5 (0.5)	55.1 (0.5)
	Difference vs Placebo (95% CI; p value)	2.99 (2.12, 3.86); p<0.001		2.4 (1.0, 3.8); p<0.001	
	Social Functioning	1.15 (0.26)	0.29 (0.28)	54.1 (0.4)	52.5 (0.4)

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	231	209
	Difference vs Placebo (95% CI; p value)	0.86 (0.11, 1.60); p<0.05		1.6 (0.5, 2.7); p=0.005	
	Role Emotional	1.79 (0.30)	0.32 (0.32)	52.5 (0.5)	50.6 (0.5)
	Difference vs Placebo (95% CI; p value)	1.48 (0.62, 2.33); p<0.001		1.9 (0.5, 3.3); p=0.008	
	Mental Health	1.05 (0.30)	-0.23 (0.32)	54.4 (0.5)	53 (0.5)
	Difference vs Placebo (95% CI; p value)	1.28 (0.42, 2.15); p<0.01		1.5 (0.1, 2.8); p=0.036	
IWQOL-Lite-CT Total Score	Mean change from baseline	22.6 (0.6)	10.5 (0.7)	18	2.8
	Difference vs Placebo (95% CI; p value)	12.1 (10.3, 13.9); p<0.001		15.2 (12.5, 17.9)	
IWQOL-Lite-CT Physical Function score	Mean change from baseline	21.8 (0.7)	10.1 (0.8)	13.9 (1.1)	1.1 (1.2)
	Difference vs Placebo (95% CI; p value)	11.7 (9.6, 13.8); p<0.001		12.8 (9.7, 16)	
IWQOL-Lite-CT Physical Composite score	Mean change from baseline	20.8 (0.7)	9.7 (0.7)	14.5	0.9
	Difference vs Placebo (95% CI; p value)	11.1 (9.1, 13.1); p<0.001		13.6 (10.6, 16.6)	
IWQOL-Lite-CT Psychosocial Composite Score	Mean change from baseline	23.6 (0.7)	11 (0.7)	19.9	3.8
	Difference vs Placebo (95% CI; p value)	12.7 (10.7, 14.6); p<0.001		16 (13.1, 19)	
EQ-5D-5L Index Score	Mean changes from baseline	0.06 (0.01)	0.02 (0.01)	NR	NR
	Estimated treatment difference (95% CI; p value)	0.05 (0.03, 0.06); p<0.001		NR	
EQ-5D-5L VAS Score	Mean changes from baseline	8.6 (0.5)	2.4 (0.5)	NR	NR
	Estimated treatment difference (95% CI; p value)	6.2 (4.8, 7.6); p<0.001		NR	

CI: confidence interval, IWQOL-Lite-CT: The Impact of Weight on Quality of Life–Lite Clinical Trials Version, NR: not reported, PBO: placebo, SF-36: Short Form 36, TZP: tirzepatide

Table D2.26. Additional Results of Tirzepatide vs Semaglutide Direct Comparison Trial[48]

Study Name		SURMOUNT-5	
Arms		TZP	SEM
N		374	376
Body Weight Change from Baseline	% (95% CI or SE)	-20.2 (-21.4, -19.1)	-13.7 (-14.9, -12.6)
	Difference vs Semaglutide (95% CI; p value)	-6.5 (-8.1, -4.9)	
≥10% Body-weight Reduction	%	304 (81.6)	227 (60.5)
	Odds ratio (95% CI; p value)	1.3 (1.2, 1.5)	
≥15% Body-weight Reduction	%	241 (64.6)	151 (40.1)
	Odds ratio (95% CI; p value)	1.6 (1.4, 1.9)	
≥20% Body-weight Reduction	%	181 (48.4)	103 (27.3)
	Odds ratio (95% CI; p value)	1.8 (1.5, 2.2)	
≥25% body-weight reduction	%	118 (31.6)	60 (16.1)
	Odds ratio (95% CI; p value)	2.0 (1.5, 2.6)	
≥30% Body-weight Reduction	%	74 (19.7)	26 (6.9)
	Odds ratio (95% CI; p value)	2.8 (1.9, 4.3)	
Waist Circumference, cm	Mean change from baseline	-18.4 (-19.6, -17.2)	-13.0 (-14.3, -11.7)
	Difference vs Semaglutide (95% CI; p value)	-5.4 (-7.1, -3.6)	
Body Weight, kg	Mean change from baseline	-22.8 (-24.1, -21.5)	-15 (-16.3, -13.7)
	Difference vs Semaglutide (95% CI; p value)	-7.9 (-9.7, -6.0)	
Body-Mass Index	Mean change from baseline	-8.0 (-8.5, -7.5)	-5.3 (-5.8, -4.8)
	Difference vs Semaglutide (95% CI; p value)	-2.7 (-3.3, -2.0)	

CI: confidence interval, cm: centimeter, IWQOL-Lite-CT: The Impact of Weight on Quality of Life–Lite Clinical Trials Version, kg: kilogram, SE: standard error, SEM: semaglutide, TZP: tirzepatide

Table D2.27. Additional Results of Cardiovascular Trials (SELECT, SURPASS-CVOT)[19,20,50,161]

Study Name		SELECT		SURPASS-CVOT	
Arms		SEM	PBO	TZP	DULA
N		8803	8801	6586	6579
Body Weight Change from Baseline	% (95% CI)	-9.39 (0.09)	-0.88 (0.08)	-12.1	-5
	Difference vs Placebo (95% CI; p value)	-8.51 (-8.75, -8.27)		-7.1 (-7.4, -6.8; <0.001)	
Waist Circumference, cm	Mean change from baseline (95% CI)	-7.56 (0.09)	-1.03 (0.09)	NR	NR
	Difference vs Placebo (95% CI; p value)	-6.53 (-6.79, -6.27)		NR	
Systolic Blood Pressure, mm Hg	Mean change from baseline	-3.82 (0.16)	-0.51 (0.16)	NR	NR
	Difference vs Placebo (95% CI; p value)	-3.31 (-3.75, -2.88)		NR	
Diastolic Blood Pressure, mm Hg	Mean change from baseline	-1.02 (0.10)	-0.47 (0.10)	NR	NR
	Difference vs Placebo (95% CI; p value)	-0.55 (-0.83, -0.27)		NR	
Total Cholesterol	Ratio to baseline	-4.63%	-1.92%	NR	NR
	Difference vs Placebo (95% CI; p value)	-2.77 (-3.37, -2.16)		NR	
HDL Cholesterol	Ratio to baseline	4.86%	0.59%	NR	NR
	Difference vs Placebo (95% CI; p value)	4.24 (3.70, 4.79)		NR	
LDL Cholesterol	Ratio to baseline	-5.25%	-3.14%	NR	NR
	Difference vs Placebo (95% CI; p value)	-2.18 (-3.22, -1.12)		NR	
Triglycerides	Ratio to baseline	-18.34%	-3.20%	NR	NR
	Difference vs Placebo (95% CI; p value)	-15.64 (-16.68, -14.58)		NR	
Primary Cardiovascular Composite End Point	% of participants	569 (6.5)	701 (8)	NR	NR
	Odds ratio (95% CI; p value)	0.80 (0.72, 0.90); p<0.001		NR	
Cardiovascular death, MI, or Stroke	Hazard ratio (95% CI; p value)	NR		0.92 (0.83, 1.01; 0.086)	
Death from Cardiovascular	% of participants	223 (2.5)	262 (3)	5.6	6.2

Study Name		SELECT		SURPASS-CVOT	
Arms		SEM	PBO	TZP	DULA
N		8803	8801	6586	6579
	Odds ratio (95% CI; p value)	0.85 (0.71, 1.01); p=0.07		0.89 (0.77-1.02)	
Heart Failure Composite	% of participants	300 (3.4)	361 (4.1)	NR	NR
	Odds ratio (95% CI; p value)	0.82 (0.71, 0.96)		NR	
Death from any Cause	% of participants	375 (4.3)	458 (5.2)	8.6	10.2
	Odds ratio (95% CI; p value)	0.81 (0.71, 0.93)		0.84 (0.75, 0.94)	
Cardiovascular Expanded Composite Endpoint	% of participants	873 (9.9)	1074 (12.2)	NR	NR
	Odds ratio (95% CI; p value)	0.80 (0.73, 0.87)		NR	
Cardiovascular Expanded Composite plus Death from any Cause	% of participants	710 (8.1)	877 (10)	NR	NR
	Odds ratio (95% CI; p value)	0.80 (0.72, 0.88)		NR	
CV Death, MI, stroke, Coronary Revascularization	% of participants	NR	NR	16.5	18.5
	Hazard ratio (95% CI; p value)	NR		0.88 (0.81, 0.96)	
CV Death, or Hospitalization or Urgent Visits for HF	% of participants	NR	NR	7.8	8.5
	Hazard ratio (95% CI; p value)	NR		0.91 (0.81, 1.03)	
Nonfatal MI	% of participants	234 (2.7)	322 (3.7)	NR	NR
	Odds ratio (95% CI; p value)	0.72 (0.61, 0.85)		NR	
MI	% of participants	NR		4.7	5.4
	Hazard ratio (95% CI; p value)	NR		0.86 (0.74, 1.00)	
Nonfatal Stroke	% of participants	154 (1.7)	165 (1.9)	NR	NR
	Odds ratio (95% CI; p value)	0.93 (0.74, 1.15)		NR	
Stroke	% of participants	NR	NR	3.5	3.8
	Hazard ratio (95% CI; p value)	NR		0.91 (0.76, 1.09)	
Hospitalization or Urgent Visit for HF	% of participants	97 (1.1)	122 (1.4)	NR	NR
	Odds ratio (95% CI; p value)	0.79 (0.60, 1.03)		NR	
Coronary Revascularization	% of participants	473 (5.4)	608 (6.9)	NR	NR
	Odds ratio (95% CI; p value)	0.77 (0.68, 0.87)		NR	
	% of participants	109 (1.2)	124 (1.4)	NR	NR

Study Name		SELECT		SURPASS-CVOT	
Arms		SEM	PBO	TZP	DULA
N		8803	8801	6586	6579
Unstable Angina Leading to Hospitalization	Odds ratio (95% CI; p value)	0.87 (0.67, 1.13)		NR	
Glycated Hemoglobin Level at Least 6.5%	% of participants	306 (3.5)	1059 (12)	NR	NR
	Odds ratio (95% CI; p value)	0.27 (0.24, 0.31)		NR	
Nephropathy Composite Endpoint	% of participants	155 (1.8)	198 (2.2)	NR	NR
	Odds ratio (95% CI; p value)	0.78 (0.63, 0.96)		NR	
Heart Rate, beats/min	Mean changes from baseline	3.79 (0.11)	0.69 (0.11)	NR	NR
	Estimated treatment difference (95% CI; p value)	3.10 (2.80, 3.39)		NR	
High Sensitivity CRP Level	Mean changes from baseline	-39.12%	-2.08%	NR	NR
	Estimated treatment difference (95% CI; p value)	-37.82 (-39.70, -35.90)		NR	
EQ-5D-5L Index Score	Mean changes from baseline	0.01 (0)	-0.1 (0)	NR	NR
	Estimated treatment difference (95% CI; p value)	0.01 (0.01, 0.02)		NR	
EQ-5D-5L VAS Score	Mean changes from baseline	2.52 (0.16)	0.92 (0.16)	NR	NR
	Estimated treatment difference (95% CI; p value)	1.60 (1.16, 2.04)		NR	
First MACE-5 Events	Hazard ratio (95% CI; p value)	0.8 (0.73, 0.87; <0.001)		NR	
Total MACE-5 Events	Mean ratio (95% CI; p value)	0.78 (0.70, 0.86; <0.001)		NR	
Non-fatal MIs	Mean ratio (95% CI; p value)	0.69 (0.58, 0.82; <0.001)		NR	
Coronary Revascularization	Mean ratio (95% CI; p value)	0.74 (0.65, 0.84; <0.001)		NR	
Change in eGFR mL min^{-1} 1.73 m^{-2}	Mean change	-0.86	-1.61	NR	NR
	Estimated treatment difference (95% CI; p value)	0.75 (0.43, 1.06; <0.001)		NR	
Initiation of Chronic Kidney Replacement Therapy	n (%)	4 (<0.1)	6 (0.1)	NR	NR
	Hazard Ratio (95% CI; p value)	0.66 (0.17, 2.32; 0.52)		NR	
	n (%)	5 (0.1)	4 (<0.1)	NR	NR

Study Name		SELECT		SURPASS-CVOT	
Arms		SEM	PBO	TZP	DULA
N		8803	8801	6586	6579
Onset of Persistent eGFR <15 ml min^{-1} 1.73 m^{-2}	Hazard Ratio (95% CI; p value)	1.24 (0.33, 5.02; 0.74)		NR	

CI: confidence interval, CM: centimeter, CRP: c-reactive protein, eGFR: estimated glomerular filtration rate, HF: heart failure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, MACE: Major Adverse Cardiovascular Events, MI: Myocardial infarction, mm Hg: millimeters of mercury

Table D2.28. Additional Results from Tirzepatide Obstructive Sleep Apnea Trial[21,169]

Study Name		SURMOUNT-OSA			
Arms		TZP	PBO	TZP	PBO
N		114	120	120	115
Body-weight Change from Baseline	% (95% CI)	-17.7 (-19.0, -16.3)	-1.6 (-2.9, -0.2)	-19.6 (-21.0, -18.2)	-2.3 (-3.8, -0.9)
	Difference vs Placebo (95% CI; p value)	-16.1 (-18.0, -14.2)		-17.3 (-19.3, -15.3)	
Systolic Blood Pressure, mm Hg	Mean change from baseline	-9.5 (-11.5, -7.5)	-1.8 (-3.9, 0.2)	-7.6 (-9.7, -5.6)	-3.9 (-6.3, -1.6)
	Difference vs Placebo (95% CI; p value)	-7.6 (-10.5, -4.8)		-3.7 (-6.8, -0.7)	
Diastolic Blood Pressure, mm Hg	Mean change from baseline	-4.9 (-6.4, -3.5)	-2.1 (-3.6, -0.6)	-3.3 (-4.7, -1.9)	-2.2 (-3.8, -0.6)
	Difference vs Placebo (95% CI; p value)	-2.8 (-5.0, -0.7)		-1.1 (-3.2, 1.0)	
Change in Apnea Hypopnea Index	Mean change from baseline	-25.3 (-29.3, -21.2)	-5.3 (-9.4, -1.1)	-29.3 (-332, -25.4)	-5.5 (-9.9, -1.2)
	Difference vs Placebo (95% CI; p value)	-20.0 (-25.8, -14.2)		-23.8 (-29.6, -17.9)	
Change in Apnea Hypopnea Index	% change from baseline	-50.7 (-62.3, -39.1)	-3.0 (-16.9, 10.9)	-58.7 (-69.1, -48.4)	-2.5 (-16.2, 11.2)
	Difference vs Placebo (95% CI; p value)	-47.7 (-65.8, -29.6)		-56.2 (-73.7, -38.7)	
Reduction of ≥50% in AHI Events	n (%)	70 (61.2)	23 (19)	86 (72.4)	27 (23.3)
	Odds ratio (95% CI; p value)	3.3 (2.1, 5.1)		3.1 (2.1, 4.5)	
	Mean change from baseline	-1.4 (-1.7, -1.1)	-0.7 (-1.1, -0.3)	-1.4 (-1.6, -1.1)	-0.3 (-0.8, 0.1)

Study Name		SURMOUNT-OSA			
Arms		TZP	PBO	TZP	PBO
N		114	120	120	115
Change in hsCRP Concentration	Difference vs Placebo (95% CI; p value)	-0.7 (-1.2, -0.2)		-1.0 (-1.6, -0.5)	
Change in Sleep Apnea Specific Hypoxic Burden	Mean change from baseline	-95.2 (-103.2, -87.2)	-25.1 (-44.3, -5.9)	-103.0 (-110.3, -95.6)	-41.7 (-63.9, -19.5)
	Difference vs Placebo (95% CI; p value)	-70.1 (-90.9, -49.3)		-61.3 (-84.7, -37.9)	
Change in PROMIS Sleep-related Impairment T Score	Mean change from baseline	-6.6 (-8.2, -4.9)	-3.1 (-4.7, -1.6)	-8.2 (-10.0, -6.3)	-3.9 (-5.9, -1.9)
	Difference vs Placebo (95% CI; p value)	-3.4 (-5.7, -1.2)		-4.3 (-7, -1.6)	
Change in PROMIS Sleep Disturbance T Score	Mean change from baseline	-4.5 (-5.8, -3.1)	-2.4 (-3.8, -1.1)	-7.0 (-8.6, -5.4)	-3.1 (-4.8, -1.4)
	Difference vs Placebo (95% CI; p value)	-2.0 (-4.0, -0.1)		-3.9 (-6.2, -1.6)	
SF-36v2 Mental Component Score	LSM change difference (95% CI; p value)	1.9	0.2	2.7	0.1
	Estimated treatment difference (95% CI; p value)	1.7 (-0.5, 3.9)		2.6 (0.4, 4.9; < 0.05)	
SF-36v2 Physical Component Score	LSM change difference (95% CI; p value)	5.7	3.3	7.6	2.5
	Estimated treatment difference (95% CI; p value)	3.6 (1.7, 5.4; < 0.01)		5 (3.3, 6.8; <0.01)	
EQ-5D-5L Index Score	Mean changes from baseline	0.06	0.01	0.06	0.01
	Estimated treatment difference (95% CI; p value)	0.04 (0, 0.08; < 0.05)		0.05 (0.01, 0.09; < 0.01)	
EQ-5D-5L VAS Score	Mean changes from baseline	6.86	1.71	9.51	-0.4
	Estimated treatment difference (95% CI; p value)	5.2 (1, 9.3; < 0.05)		9.9 (5.9, 14; < 0.01)	

CI: confidence interval, hsCRP: high-sensitivity C-reactive protein, OSA: obstructive sleep apnea, PBO: placebo, PROMIS: Patient-Reported Outcomes Measurement Information System, TZP: tirzepatide

Table D2.29. Results of Additional Trials[29,30,51]

Study Name		STEP-HFpEF		ESSENCE		SUMMIT	
Arms		SEM	PBO	SEM	PBO	TZP	PBO
N		263	266	534	266	364	367
Body Weight Change from Baseline	% (95% CI)	–13.3	–2.6	-10.5	-2	-13.9 (0.4)	-2.2 (0.5)
	Difference vs Placebo (95% CI; p value)	–10.7 (–11.9, –9.4; <0.001)		-8.5 (-9.6, -7.4; <0.001)		-11.6 (-12.9, -10.4); p < 0.001	
≥10% body-weight Reduction	% of participants	65.9	9.5	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	15.5 (9.4, 25.4)		NR	NR	NR	NR
≥15% body-weight Reduction	% of participants	43.9	2.1	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	30.6 (12.2, 76.6)		NR	NR	NR	NR
≥20% body-weight Reduction	% of participants	23.6	0.4	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	56.0 (7.8, 400.8)		NR	NR	NR	NR
Waist Circumference, cm	Mean change from baseline (95% CI)	–11.7	–2.7	NR	NR	NR	NR
	Difference vs Placebo (95% CI; p value)	–9.1 (–10.6, –7.5)		NR	NR	NR	NR
Systolic Blood Pressure, mm Hg	Mean change from baseline	–4.9	–2.0	−5.39	−1.39	-4.6 (0.8)	0.1 (0.8)
	Difference vs Placebo (95% CI; p value)	–2.9 (–5.8, 0.1)		−4.00 (−5.93, −2.07)		-4.7 (-6.8, -2.5)	
Diastolic Blood Pressure, mm Hg	Mean change from baseline	NR	NR	−1.90	0.24	-1.2	-0.3
	Difference vs Placebo (95% CI; p value)	NR	NR	−2.14 (−3.43, −0.85)		-0.9 (-2.3, 0.5)	
Total Cholesterol	Ratio to baseline	NR	NR	−6.03	−3.19	NR	NR
	Difference vs Placebo (95% CI; p value)	NR	NR	−2.93 (−5.60, −0.19)		NR	NR
HDL Cholesterol	Ratio to baseline	NR	NR	2.62	−1.95	NR	NR
	Difference vs Placebo (95% CI; p value)	NR	NR	4.66 (2.12, 7.26)		NR	NR
LDL Cholesterol	Ratio to baseline	NR	NR	−6.07	−4.11	NR	NR
	Difference vs Placebo (95% CI; p value)	NR	NR	−2.04 (−6.35, 2.46)		NR	NR
Triglycerides	Ratio to baseline	NR	NR	−16.77	−0.27	NR	NR

Study Name		STEP-HFpEF		ESSENCE		SUMMIT	
Arms		SEM	PBO	SEM	PBO	TZP	PBO
N		263	266	534	266	364	367
	Difference vs Placebo (95% CI; p value)	NR	NR	−16.54 (−21.02, −11.81)		NR	NR
C-reactive Protein	Ratio to baseline	–43.5	–7.3	−53.83	−19.83	-38.8 (4.5)	-5.9 (5.3)
	Difference vs Placebo (95% CI; p value)	0.61 (0.51, 0.72; <0.001)*		−42.41 (−49.75, −33.98)		-34.9 (-45.6, -22.2); p < 0.001	
6 -Minute Walk Distance	Mean change, meters	21.5	1.2	NR	NR	26 (3.8)	10.1 (3.9)
	Estimated treatment difference (95% CI)	20.3 (8.6, 32.1; <0.001)		NR	NR	18.3 (9.9, 26.7); p < 0.001	
KCCQ-CSS, Points	Mean change	16.6	8.7	NR	NR	19.5 (1.2)	12.7 (1.3)
	Estimated Difference (95% CI; p value)	7.8 (4.8, 10.9; <0.001)		NR	NR	6.9 (3.3, 10.6)	
Hierarchical Composite End Point	Crude percentage of wins	60.1	34.9	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	1.72 (1.37, 2.15; <0.001)		NR	NR	NR	NR
Mean Change in KCCQ-OSS	Points	16.6	9.1	NR	NR	NR	NR
	Estimated Difference (95% CI; p value)	7.5 (4.4, 10.6)		NR	NR	NR	NR
≥5-point Increase in KCCQ-CSS	% of participants	75.3	63.7	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	1.9 (1.3, 2.8)		NR	NR	NR	NR
≥10-pointlincrease in KCCQ-CSS	% of participants	63.4	48.5	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	2.1 (1.4, 3.1)		NR	NR	NR	NR
≥15-point Increase in KCCQ-CSS	% of participants	123 (50.6)	85 (35.9)	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	2.2 (1.5, 3.2)		NR	NR	NR	NR
Attainment of Anchor-based Threshold for Change in 6MWT	% of participants	42.5	28	NR	NR	NR	NR
	Odds ratio (95% CI; p value)	2.0 (1.4 to 3.0)		NR	NR	NR	NR
Reduction in NT-proBNP Level	Percentage	–20.9	–5.3	NR	NR	NR	NR
	Estimated Treatment Ratio (95% CI; p value)	0.84 (0.71, 0.98)		NR	NR	NR	NR
Adjudicated Heart Failure Event, Time-to-event Analysis	Number of events	1	12	NR	NR	NR	NR
	Hazard Ratio (95% CI; p value)	0.08 (0.00 to 0.42)		NR	NR	NR	NR
	% of participants	NR	NR	62.9	34.3	NR	NR

Study Name		STEP-HFpEF		ESSENCE		SUMMIT	
Arms		SEM	PBO	SEM	PBO	TZP	PBO
N		263	266	534	266	364	367
Resolution of Steatohepatitis with No Worsening of Liver Fibrosis	Estimated treatment difference (95% CI; p value)	NR	NR	28.7 (21.1, 36.2; <0.001)		NR	NR
Reduction in Liver Fibrosis with No Worsening of Steatohepatitis	% of participants	NR	NR	36.8	22.4	NR	NR
	Estimated treatment difference (95% CI; p value)	NR	NR	14.4 (7.5, 21.3; <0.001)		NR	NR
Resolution of Steatohepatitis with Improvement in Liver Fibrosis	% of participants	NR	NR	32.7	16.1	NR	NR
	Estimated treatment difference (95% CI; p value)	NR	NR	16.5 (10.2, 22.8)		NR	NR
Proportion of Participants Achieving Decrease in Enhanced Liver Fibrosis Score of ≥5	% of participants	NR	NR	55.8	25.5	NR	NR
	Estimated treatment difference (95% CI; p value)	NR	NR	30.3 (23.3, 37.4)		NR	NR
Proportion of Participants Achieving Improvement in Liver Fibrosis	% of participants	NR	NR	40	26.9	NR	NR
	Estimated treatment difference (95% CI; p value)	NR	NR	13.1 (5.9, 20.3)		NR	NR
Proportion of Participants Achieving ≥25% Decrease in Liver Stiffness	% of participants	NR	NR	59.5	35.6	NR	NR
	Estimated treatment difference (95% CI; p value)	NR	NR	23.9 (15.5, 32.3)		NR	NR
Proportion of Participants Achieving ≥30% Decrease in Liver Stiffness	% of participants	NR	NR	52	30.3	NR	NR
	Estimated treatment difference (95% CI; p value)	NR	NR	21.7 (13.4, 29.9)		NR	NR
Decrease in Enhanced Liver Fibrosis Score of ≥0.5	% of participants	NR	NR	55.8	25.5		NR
eGFR Change	Mean change from baseline	NR	NR	NR	NR	2.6	-0.3
	Difference vs Placebo (95% CI; p value)	NR	NR	NR	NR	2.9 (0.9, 4.9); p = 0.004	
UACR Change	Mean change from baseline	NR	NR	NR	NR	-14.7	0.4
	Difference vs Placebo (95% CI; p value)	NR	NR	NR	NR	-15.1 (-28, 0.1); p = 0.051	

Study Name		STEP-HFpEF		ESSENCE		SUMMIT	
Arms		SEM	PBO	SEM	PBO	TZP	PBO
N		263	266	534	266	364	367
Adjudicated Worsening Heart-failure Event Resulting in Hospitalization, Intravenous Drugs in an Urgent Care Setting, or Intensification of oral Diuretic Therapy — no. (%)	**Mean change from baseline**	NR	NR	NR	NR	29 (8)	52 (14.2)
	Difference vs Placebo (95% CI; p value)	NR	NR	NR	NR	0.54 (0.34, 0.85)	
Adjudicated Worsening Heart-failure Event Resulting in Hospitalization, no. (%)	**Mean change from baseline**	NR	NR	NR	NR	12 (3.3)	26 (7.1)
	Difference vs Placebo (95% CI; p value)	NR	NR	NR	NR	0.44 (0.22, 0.87)	
Adjudicated Worsening Heart-failure Event Resulting in Intravenous Diuretic Therapy in an Urgent Care Setting, no. (%)	**Mean change from baseline**	NR	NR	NR	NR	5 (1.4)	12 (3.3)
	Difference vs Placebo (95% CI; p value)	NR	NR	NR	NR	0.41 (0.14, 1.16)	
Adjudicated Worsening Heart-failure Event Resulting in Intravenous Diuretic Therapy in an Outpatient Setting, no. (%)	**Mean change from baseline**	NR	NR	NR	NR	17 (4.7)	21 (5.7)
	Difference vs Placebo (95% CI; p value)	NR	NR	NR	NR	0.80 (0.42, 1.52)	

6MWT: 6 minute walk test, CI: confidence interval, eGFR: Estimated glomerular filtration rate, HDL: high-density lipoprotein, KCCQ: Kansas City Cardiomyopathy Questionnaire, LDL: low-density lipoprotein, no.: number, NT-proBNP: N-terminal pro B-type natriuretic peptide, UACR: Urine albumin-to-creatinine ratio

*Estimated treatment ratio

†The hierarchical composite end point included death from any cause, the number and timing of heart failure events, differences of at least 15, at least 10, and at least 5 points in the change in the KCCQ-CSS, and a difference of at least 30 m in the change in the 6-minute walk distance.

Table D2.30. Results of STEP 9 Knee Osteoarthritis Trial[28]

Study Name		STEP-9	
Arms		SEM	PBO
N		271	136
Body Weight Change from Baseline	Percent change	-13.7	-3.2
	Difference vs Placebo (95% CI; p value)	-10.5 (-12.3, -8.6; <0.001)	
≥5% body-weight Reduction	% of participants	85.2	33.6
	Odds ratio (95% CI; p value)	51.6 (41.6, 61.6; <0.001)	
≥10% body-weight Reduction	% of participants	68.1	12.9
	Odds ratio (95% CI; p value)	55.2 (46.1, 64.3; <0.001)	
≥15% body-weight Reduction	% of participants	45.6	4.5
	Odds ratio (95% CI; p value)	41.1 (33.3, 48.8)	
≥20% body-weight Reduction	% of participants	22.3	1.3
	Odds ratio (95% CI; p value)	21.0 (15.2, 26.8)	
Waist Circumference, cm	Mean change from baseline	-13	-6.1
	Difference vs Placebo (95% CI; p value)	-6.9 (-9.1, -4.7; <0.001)	
SF-36 Physical Functioning score	Mean change from baseline	12	6.5
	Difference vs Placebo (95% CI; p value)	5.6 (3.1, 8.0; <0.001)	
Clinically Meaningful SF-36 Physical Functioning Score Improvement (≥3.7 points)	% of participants	58	29.4
	Estimated treatment difference (95% CI; p value)	28.7 (18, 39.3)	
WOMAC Pain Score	Change from baseline	-41.7	-27.5
	Estimated treatment difference (95% CI)	-14.1 (-20, -8.3; <0.001)	
≥30% Reduction in WOMAC Pain Score	% of participants	77.6	57.8
	Estimated treatment difference (95% CI)	19.8 (9.3, 30.4)	
≥50% Reduction in WOMAC Pain Score	% of participants	65.2	35.3
	Estimated treatment difference (95% CI)	29.9 (19.1, 40.6)	
WOMAC Physical Function Score	Change from baseline	-41.5	-26.7
	Estimated treatment difference (95% CI)	14.9 (-20.4, -9.3; <0.001)	

Study Name		STEP-9	
Arms		SEM	PBO
N		271	136
Meaningful Improvement in WOMAC Physical Function Score (≥41.2 point reduction)	Proportion of participants (%)	50.4	29
	Estimated treatment difference (95% CI)	21.4 (10.6, 32.2)	
6 -Minute Walk Distance	Mean change, meters	56.8	14.2
	Estimated treatment difference (95% CI)	42.6 (25.6, 59.7)	

CI: confidence interval, SF-36: Short Form 36, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table D2.31. Results of Treatment Withdrawal Trials[155,156,170]

Study Name		STEP-4		SURMOUNT-4	
Arms		SEM	PBO	TZP	PBO
N		535	268	335	335
Follow-up Period		Weeks 20-68		Weeks 36-88	
Body-weight Change from Baseline	% (95% CI)	−7.9 (−8.6, −7.2)	6.9 (5.8, 7.9)	-5.5 (-6.8, -4.2)	14 (12.8, 15.2)
	Difference vs Placebo (95% CI; p value)	−14.8 (−16.0, −13.5; <0.001)		-19.4 (-21.2, -17.7)	
≥5% Body-weight Reduction	n (%)	NR	NR	326 (97.3)	235 (70.5)
	Odds ratio (95% CI; p value)	NR		20.3 (7.7, 53.3)	
≥10% Body-weight Reduction	n (%)	NR	NR	309 (92.1)	155 (46.2)
	Odds ratio (95% CI; p value)	NR		26.1 (12.6, 54.1)	
≥15% Body-weight Reduction	n (%)	NR	NR	282 (84.1)	87 (25.9)
	Odds ratio (95% CI; p value)	NR		32.6 (16.4, 64.8)	
≥20% Body-weight Reduction	% of participants	NR	NR	233 (69.5)	42 (12.6)
	Odds ratio (95% CI; p value)	NR		46.1 (20.7, 102.9)	
≥25% Body-weight Reduction	n (%)	NR	NR	183 (54.5)	17 (5)
	Odds ratio (95% CI; p value)	NR		61.5 (25.9, 146.1)	
Waist Circumference, cm	Mean change from baseline (95% CI)	–6.4 (–7.1, –5.7)	3.3 (2.3, 4.3)	-4.7 (-5.7, -3.6)	7.8 (6.9, 8.8)

Study Name		STEP-4		SURMOUNT-4	
Arms		SEM	PBO	TZP	PBO
N		535	268	335	335
Follow-up Period		Weeks 20-68		Weeks 36-88	
	Difference vs Placebo (95% CI; p value)	–9.7 (–10.9, –8.5; <0.001)		-12.1 (-13.5, -10.6)	
Systolic Blood Pressure, mm Hg	Mean change from baseline	0.5 (-0.6, 1.6)	4.4 (2.9, 6.0)	NR	NR
	Difference vs Placebo (95% CI; p value)	–3.9 (–5.8, –2.0; < 0.001)		NR	
SF-36v2 Mental Component Score	LSM change difference (95% CI; p value)	NR	NR	0.1	-1.6
	Estimated treatment difference (95% CI; p value)	NR		1.7 (0.7, 2.8; < 0.01)	
SF-36v2 Physical Component Score	LSM change difference (95% CI; p value)	NR	NR	0.4	-1.4
	Estimated treatment difference (95% CI; p value)	NR		1.8 (1.0, 2.6; < 0.001)	
Clinically Meaningful SF-36 Physical Functioning Score Improvement (≥3.7 points)	% of participants	18	6.6	NR	NR
	Estimated treatment difference (95% CI; p value)	11.4 (6.5, 16.4; <0.0001)		NR	
IWQOL-Lite-CT Score	LSM change difference (95% CI; p value)	NR	NR	4.7	-6.4
	Estimated treatment difference (95% CI; p value)	NR		NR	
IWQOL-Lite-CT Physical Function Score Improvement	LSM change difference (95% CI; p value)	NR	NR	4.3	-5.1
	Estimated treatment difference (95% CI; p value)	NR		9.4 (6.9, 12.0; < 0.001)	
EQ-5D-5L Index Score	Mean changes from baseline	NR	NR	0.003	-0.029
	Estimated treatment difference (95% CI; p value)	NR		0.032 (0.008, 0.057; <0.05)	
EQ-5D-5L VAS Score	Mean changes from baseline	NR	NR	1.3	-3.6
	Estimated treatment difference (95% CI; p value)	NR		4.9 (3.1, 6.6; <0.001)	
Body Weight, kg	Mean change from baseline (95% CI)	−7.1 (−7.8, −6.5)	6.1 (5.1, 7.0)	-4.7 (-5.7, -3.6)	11.1 (10.1, 12.2)
	Difference vs Placebo (95% CI; p value)	−13.2 (−14.3. −12.0; <0.001)		-15.8 (-17.3, -14.3)	
Body-mass Index	Mean change from baseline	−2.6 (−2.8, −2.4)	2.2 (1.8, 2.5)	NR	NR

Study Name		STEP-4		SURMOUNT-4	
Arms		SEM	PBO	TZP	PBO
N		535	268	335	335
Follow-up Period		Weeks 20-68		Weeks 36-88	
	Difference vs Placebo (95% CI; p value)	−4.7 (−5.2, −4.3; <0.001)		NR	
Participants Maintaining ≥80% of Lead-in Body Weight Lost at Week 72	n (%)	NR	NR	300 (89.5)	55 (16.6)
	Odds ratio (95% CI; p value)	NR		44 (24.9, 77.5)	
Fasting Plasma Glucose, mg/dl	Mean change from baseline	-0.8 (-1.7, 0.1)	6.7 (4.9, 8.6)	NR	NR
	Difference vs Placebo (95% CI; p value)	-7.5 (-9.6, -5.4; <0.001)		NR	
Fasting Serum Insulin	% change from baseline	-20 (-20, -10)	0 (-10, 10)	NR	NR
	Difference vs Placebo (95% CI; p value)	-18 (-27, -8; <0.001)		NR	
Diastolic Blood Pressure, mm Hg	Mean change from baseline	0.3 (-0.4, 1.1)	0.9 (-0.4, 2.1)	NR	NR
	Difference vs Placebo (95% CI; p value)	-0.6 (-2.0, 0.9; 0.46)		NR	
Participants who Gained Weight	n (%)	79 (15.2)	206 (82.4)	NR	NR
	Odds ratio (95% CI; p value)	0.0 (0.0, 0.1; <0.001)		NR	

CI: confidence interval, cm: centimeter, IWQOL-Lite-CF: The Impact of Weight on Quality of Life–Lite Clinical Trials Version, kg: kilogram, LSM: least squares mean, mg/dl: milligrams per deciliter, mm Hg: millimeters of mercury, NR: not reported, SF-36: Short Form 36

Table D2.32. Safety of Key Trials of Injectable Semaglutide[19,23,24,26,125]

Study Name		STEP-1		STEP-3		STEP-5		STEP-8		STEP-10	
Arms		SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO	SEM	PBO
N		1306	655	407	204	152	152	126	85	138	69
Any Adverse Event, n (%)		1171 (89.7)	566 (86.4)	390 (95.8)	196 (96.1)	146 (96.1)	136 (89.5)	120 (95.2)	81 (95.3)	NR	NR
Serious AE, n (%)		128 (9.8)	42 (6.4)	37 (9.1)	6 (2.9)	12 (7.9)	18 (11.8)	10 (7.9)	6 (7.1)	12 (9%)	6 (9%)
Serious GI Disorders, n (%)		(1.4)	(0)	NR	NR	NR	NR	1 (0.8)	1 (1.2)	NR	NR
Discontinuation due to AE, n (%)	Any	92 (7.0)	20 (3.1)	24 (5.9)	6 (2.9)	9 (5.9)	7 (4.6)	4 (3.2)	3 (3.5)	4 (3%)	0
	GI	59 (4.5)	5 (0.8)	14 (3.4)	0	6 (3.9)	1 (0.7)	NR	NR	NR	NR
Fatal Events, n (%)		1 (0.1)	1 (0.2)	NR	NR	1 (0.7)	0 (0)	0	0	2 (1%)	0
Most Common Adverse Events, n (%)											
Nausea		577 (44.2)	114 (17.4)	237 (58.2)	45 (22.1)	81 (53.3)	33 (21.7)	77 (61.1)	19 (22.4)	NR	NR
Diarrhea		412 (31.5)	104 (15.9)	147 (36.1)	45 (22.1)	53 (34.9)	36 (23.7)	35 (27.8)	22 (25.9)	NR	NR
Vomiting		324 (24.8)	43 (6.6)	111 (27.3)	22 (10.8)	53 (34.9)	36 (23.7)	32 (25.4)	5 (5.9)	NR	NR
Constipation		306 (23.4)	62 (9.5)	150 (36.9)	50 (24.5)	47 (30.9)	17 (11.2)	49 (38.9)	20 (23.5)	NR	NR
Nasopharyngitis		281 (21.5)	133 (20.3)	90 (22.1)	49 (24.0)	24 (15.8)	23 (15.1)	10 (7.9)	9 (10.6)	NR	NR
Headache		198 (15.2)	80 (12.2)	78 (19.2)	20 (9.8)	16 (10.5)	16 (10.5)	20 (15.9)	10 (11.8)	NR	NR
Dyspepsia		135 (10.3)	23 (3.5)	NR	NR	20 (13.2)	7 (4.6)	11 (8.7)	5 (5.9)	NR	NR
Abdominal Pain		130 (10.0)	36 (5.5)	54 (13.3)	10 (4.9)	20 (13.2)	4 (2.6)	NR	NR	NR	NR
Abdominal Pain Upper		NR	NR	NR	NR	22 (14.5)	10 (6.6)	NR	NR	NR	NR
Upper Respiratory Tract Infection		114 (8.7)	80 (12.2)	85 (20.9)	44 (21.6)	20 (13.2)	23 (15.1)	9 (7.1)	18 (21.2)	NR	NR
Backpain		NR	NR	54 (13.3)	22 (10.8)	15 (9.9)	19 (12.5)	6 (4.8)	9 (10.6)	NR	NR
Dizziness		NR	NR	52 (12.8)	11 (5.4)	NR	NR	NR	NR	NR	NR
Fatigue		NR	NR	52 (12.8)	15 (7.4)	NR	NR	12 (9.5)	4 (4.7)	NR	NR
Flatulence		NR	NR	47 (11.5)	23 (11.3)	20 (13.2)	10 (6.6)	NR	NR	NR	NR
Gastroenteritis Viral		NR	NR	42 (10.3)	13 (6.4)	20 (13.2)	4 (2.6)	NR	NR	NR	NR
Urinary Tract Infection		NR	NR	42 (10.3)	10 (4.9)	NR	NR	NR	NR	NR	NR
Abdominal Distention		NR	NR	41 (10.1)	20 (9.8)	NR	NR	NR	NR	NR	NR
Sinusitis		NR	NR	39 (9.6)	26 (12.7)	NR	NR	8 (6.3)	13 (15.3)	NR	NR

Study Name	STEP-1		STEP-3		STEP-5		STEP-8		STEP-10	
Arms	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**	**SEM**	**PBO**
N	**1306**	**655**	**407**	**204**	**152**	**152**	**126**	**85**	**138**	**69**
Arthralgia	NR	NR	NR	NR	NR	NR	8 (6.3)	7 (8.2)	NR	NR
Influenza	NR	NR	NR	NR	20 (13.2)	16 (10.5)	5 (4.0)	6 (7.1)	NR	NR
Decreased Appetite	NR	NR	NR	NR	17 (11.2)	6 (3.9)	15(11.9)	3 (3.5)	NR	NR
Eructation	NR	NR	NR	NR	17 (11.2)	1 (0.7)	17 (13.5)	4 (4.7)	NR	NR

AE: adverse event, GI: gastrointestinal, NR: not reported, PBO: placebo, SEM: semaglutide,

Table D2.33. Safety of Oral Semaglutide Trial[43,140]

Study Name		OASIS-4	
Arms		SEM	PBO
N		205	102
Any Adverse Event, %		93.1%	85.3%
Serious Adverse Events, %		3.9%	8.8%
Serious Gastrointestinal Disorders, %		0	1%
Adverse Events Leading to Discontinuation, %	Any	6.9%	5.9%
	Gastrointestinal Disorders	3.4%	2.0%
Fatal Events, n (%)		0	0
Most Common Adverse Events, n (%)			
Nausea		95 (46.6)	19 (18.6)
Diarrhea		36 (17.6)	9 (8.8)
Vomiting		63 (30.9)	6 (5.9)
Constipation		41 (20.1)	10 (9.8)
Nasopharyngitis		43 (21.1)	27 (26.5)
Headache		24 (11.8)	9 (8.8)
Dyspepsia		37 (18.1)	9 (8.8)
Eructation		21 (10.3)	2 (2.0)
Nervous System Disorder		51 (25)	15 (14.7)
Metabolism and Nutritional Disorders		30 (14.7)	9 (8.8)
Musculoskeletal and Connective Tissue Disorders		30 (14.7)	21 (20.6)
Skin and Subcutaneous Tissue Disorders		27 (13.2)	10 (9.8)
General Disorders and Administration Site Conditions		36 (17.6)	6 (5.9)
Respiratory, Thoracic and Mediastinal Disorders		24 (11.8)	11 (10.8)
Injury, Poisoning and Procedural Complications		23 (11.3)	14 (13.7)
Psychiatric Disorders		18 (8.8)	13 (12.7)
Vascular Disorders		13 (6.4)	6 (5.9)
Cardiac Disorders		3 (1.5)	6 (5.9)
Reproductive System and Breast Disorders		11 (5.4)	2 (2)

Study Name	OASIS-4	
Arms	**SEM**	**PBO**
N	**205**	**102**
Gastrointestinal Disorders	151 (74)	43 (42.2)

PBO: placebo, SEM: semaglutide

Table D2.34. Safety of Key Trials of Tirzepatide[46,47]

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		**TZP**	**PBO**	**TZP**	**PBO**
N		**630**	**643**	**287**	**292**
Any Adverse Event, n (%)		497 (78.9)	463 (72.0)	250 (87.1)	224 (76.7)
Serious Adverse Events, n (%)		32 (5.1)	44 (6.8)	17 (5.9)	14 (4.8)
Serious Gastrointestinal Disorders, n (%)		21 (3.3)	7 (1.1)	16 (5.6)	5 (1.7)
Adverse Events Leading to Discontinuation, n (%)	**Any**	39 (6.2)	17 (2.6)	30 (10.5)	6 (2.1)
	Nausea	12 (1.9)	2 (0.3)	24 (8.4)	4 (1.4)
	Diarrhea	3 (0.5)	0	3 (1)	0
	Abdominal Pain	3 (0.5)	0	NR	NR
	Dyspepsia	NR	NR	3 (1)	0
	Vomiting	0	0	6 (2.1)	0
	Constipation	NR	NR	2 (0.7)	0
Fatal Events/Death, n (%)		1 (0.2)	4 (0.6)	1 (0.3)	1 (0.3)
Safety Focus Areas, n (%)	**Nausea**	195 (31)	61 (9.5)	114 (39.7)	41 (14)
	Diarrhea	145 (23)	47 (7.3)	89 (31)	27 (9.2)
	Vomiting	77 (12.2)	11 (1.7)	52 (18.1)	4 (1.4)
	Constipation	74 (11.7)	37 (5.8)	66 (23)	20 (6.8)
	Nasopharyngitis	NR	NR	NR	NR
	Headache	41 (6.5)	42 (6.5)	27 (9.4)	22 (7.5)
	Dyspepsia	71 (11.3)	27 (4.2)	27 (9.4)	9 (3.1)

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	287	292
	Abdominal Pain	31 (4.9)	21 (3.3)	30 (10.5)	7 (2.4)
	Upper Respiratory Tract Infection	NR	NR	25 (8.7)	21 (7.2)
	Backpain	NR	NR	17 (5.9)	15 (5.1)
	Dizziness	NR	NR	20 (7.0)	6 (2.1)
	Fatigue	NR	NR	20 (7.0)	9 (3.1)
	Flatulence	NR	NR	19 (6.6)	8 (2.7)
	Urinary Tract Infection	NR	NR	11 (3.8)	15 (5.1)
	Sinusitis	NR	NR	6 (2.1)	16 (5.5)
	Arthralgia	NR	NR	7 (2.4)	15 (5.1)
	Influenza	NR	NR	12 (4.2)	25 (8.6)
	Decreased Appetite	54 (8.6)	21 (3.3)	27 (9.4)	12 (4.1)
	Alopecia	36 (5.7)	6 (0.9)	20 (7)	4 (1.4)
	Eructation	35 (5.6)	4 (0.6)	16 (5.6)	3 (1)
	Gallbladder-related Disorders	6 (1)	5 (0.8)	2 (0.7)	0
	Hepatic Disorders	0	0	NR	NR
	Acute Pancreatitis	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
	MACE	0	5 (0.8)	1 (0.3)	1 (0.3)
	Cardiac Disorders	2 (0.3)	1 (0.2)	0	1 (0.3)
	Allergic Reactions or Hypersensitivity	1 (0.2)	0	NR	NR
	Injection-site Reactions	29 (4.6)	2 (0.3)	32 (11.1)	3 (1)
	Malignant Neoplasms/Cancers	5 (0.8)	7 (1.1)	5 (1.7)	3 (1)
	Anxiety	NR	NR	9 (3.1)	19 (6.5)
	Major Depressive Disorder or Suicidal Ideation	2 (0.3)	0	1 (0.3)	0

Study Name		SURMOUNT-1		SURMOUNT-3	
Arms		TZP	PBO	TZP	PBO
N		630	643	287	292
	Hypoglycemia	10 (1.6)	1 (0.2)	NR	NR
Serious Hepatobiliary Disorders Reported in >1% of participants, n (%)	Cholelithiasis	4 (0.6)	6 (0.9)	NR	NR
	Acute Cholecystitis	1 (0.2)	0	NR	NR
	Cholecystitis	0	0	NR	NR
	Chronic Cholecystitis	3 (0.5)	3 (0.5)	NR	NR

MACE: Major Adverse Cardiovascular Events, PBO: placebo, TZP: tirzepatide

Table D2.35. Safety of Direct Comparison Trial[48]

Study Name		SURMOUNT-5	
Arms		TZP	SEM
N		374	376
Any Adverse Event, n (%)		287 (76.7)	297 (79)
Serious Adverse Events, n (%)		18 (4.8)	13 (3.5)
Serious Gastrointestinal Disorders, n (%)		17 (4.5)	14 (3.7)
Adverse Events Leading to Discontinuation, n (%)	Any	23 (6.1)	30 (8)
	GI related	10 (2.7)	21 (5.6)
	Nausea	5 (1.3)	7 (1.9)
	Diarrhea	1 (0.3)	2 (0.5)
	Vomiting	3 (0.8)	4 (1.1)
	Fatigue	1 (0.3)	1 (0.3)
	Cholelithiasis	0	2 (0.5)
	Constipation	1 (0.3)	2 (0.5)
Fatal Events/Death, n (%)		0	0

Study Name		SURMOUNT-5	
Arms		TZP	SEM
N		374	376
Safety Focus Areas, n (%)	Nausea	163 (43.6)	167 (44.4)
	Diarrhea	88 (23.5)	88 (23.4)
	Vomiting	56 (15)	80 (21.3)
	Constipation	101 (27)	107 (28.5)
	Nasopharyngitis	17 (4.5)	23 (6.1)
	Headache	27 (7.2)	27 (7.2)
	Dyspepsia	22 (5.9)	28 (7.4)
	Abdominal pain	24 (6.4)	26 (6.9)
	Upper Respiratory Tract Infection	32 (8.6)	43 (11.4)
	Dizziness	24 (6.4)	18 (4.8)
	Fatigue	39 (10.4)	46 (12.2)
	Abdominal Distention	27 (7.2)	24 (6.4)
	Sinusitis	11 (2.9)	21 (5.6)
	Decreased Appetite	17 (4.5)	19 (5.1)
	Alopecia	31 (8.3)	23 (6.1)
	Eructation	37 (9.9)	29 (7.7)
	GERD	23 (6.1)	40 (10.6)
	Gallbladder-related Disorders	4 (1.1)	5 (1.3)
	Hepatic Disorders	1 (0.3)	0
	Acute Pancreatitis	0	1 (0.3)
	MACE	0	0
	Cardiac Disorders	3 (0.8)	1 (0.3)
	Allergic Reactions or Hypersensitivity	0	0
	Injection-site Reactions	32 (8.6)	1 (0.3)
	Major Depressive Disorder or Suicidal Ideation	0	0
	Acute renal failure	1 (0.3)	0
	Hypoglycemia	0	1 (0.3)

Study Name	SURMOUNT-5	
Arms	**TZP**	**SEM**
N	**374**	**376**
Renal events, n (%)	1 (0.3)	0
COVID-19, n (%)	51 (13.6)	47 (12.5)

GERD: Gastroesophageal Reflux Disease, GI: Gastrointestinal, MACE: Major Adverse Cardiovascular Events, SEM: semaglutide, TZP: tirzepatide

Table D2.36. Safety of Cardiovascular Trials[19,50,165,171]

Study Name		SELECT		SURPASS-CVOT	
Arms		**SEM**	**PBO**	**TZP**	**DULA**
N		**8803**	**8801**	**6586**	**6579**
Any adverse event, n (%)		NR	NR	89.6%	88.7%
Serious adverse events, n (%)		2941 (33.4)	3204 (36.4)	31.8%	31.9%
Serious gastrointestinal disorders, n (%)		342 (3.9)	323 (3.7)	NR	NR
AE leading to discontinuation, n (%)	**Any**	1461 (16.6)	718 (8.2)	18.7%	16.7%
	Gastrointestinal disorders	880 (10)	172 (2)	NR	NR
Fatal events, n (%)		375 (4.3)	458 (5.2)	NR	NR
Safety Focus Areas, n (%)	**Gallbladder-related Disorders**	246 (2.8)	203 (2.3)	NR	NR
	Acute Pancreatitis	17 (0.2)	24 (0.3)	NR	NR
	Malignant Neoplasms	422 (4.8)	418 (4.7)	NR	NR
	Acute Renal Failure	171 (1.9)	200 (2.3)	NR	NR
	COVID-19	2108 (23.9)	2150 (24.4)	NR	NR
TEAEs ≥5% of Participants	**Nausea**	NR	NR	25.10%	22.40%
	Diarrhea	NR	NR	24.80%	19.10%
	Vomiting	NR	NR	11.60%	9.70%
	Constipation	NR	NR	12.70%	11.60%
	Nasopharyngitis	NR	NR	5.70%	5.70%
	Dyspepsia	NR	NR	9.90%	8.20%
	Gastrointestinal Disorders	342 (3.9)	323 (3.7)	NR	NR
	Infections and Infestations	624 (7.1)	738 (8.4)	NR	NR

Study Name		SELECT		SURPASS-CVOT	
Arms		SEM	PBO	TZP	DULA
N		8803	8801	6586	6579
Any adverse event, n (%)		NR	NR	89.6%	88.7%
Serious AEs by System Organ Class, n (%)	Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	405 (4.6)	402 (4.6)	NR	NR
	Cardiac Disorders	1008 (11.5)	11184 (13.5)	NR	NR
	Injury, Poisoning, and Procedural Complications	305 (3.5)	313 (3.6)	NR	NR
	Reproductive System and Breast Disorders	65 (0.7)	43 (0.5)	NR	NR
	Eye Disorders	41 (0.5)	41 (0.5)	NR	NR
	General Disorders and Administration Site Conditions	273 (3.1)	316 (3.6)	NR	NR
	Hepatobiliary Disorders	126 (1.4)	105 (1.2)	NR	NR
	Musculoskeletal and Tissue Disorders	236 (2.7)	254 (2.9)	NR	NR
	Product Issues	11 (0.1)	16 (0.2)	NR	NR
	Nervous System Disorder	444 (5)	496 (5.6)	NR	NR
	Vascular Disorders	231 (0.6)	259 (2.9)	NR	NR
	Medical Procedures	433 (4.9)	548 (6.2)	NR	NR
Serious GI Disorders, %	Inguinal Hernia	0.4	0.3	NR	NR
	Diarrhea	0.3	0.2	NR	NR
	Gastrointestinal Hemorrhage	0.3	0.2	NR	NR
	Vomiting	0.2	0.1	NR	NR
Events Adjudication Committee Confirmed Deaths		375 (4.3)	458 (5.2)	NR	NR
Cardiovascular Death, n (%)		223 (2.5)	262 (3)	NR	NR
Non-cardiovascular Death, n (%)		152 (1.7)	196 (2.2)	NR	NR
Common Causes of CV Death, n (%)	Acute MI	12 (0.1)	15 (0.2)	NR	NR
	Heart Failure	14 (0.2)	16 (0.2)	NR	NR
	Sudden Cardiac Death	98 (1.1)	109 (1.2)	NR	NR
	Stroke	15 (0.2)	21 (0.2)	NR	NR
Gastrointestinal Death, n (%)		3 (<0.1)	5 (<0.1)	NR	NR

AE: adverse event, CV: cardiovascular, GI: gastrointestinal, MI: myocardial infarction, PBO: placebo, SEM: semaglutide

Table D2.37. Safety of Obstructive Sleep Apnea Trial[21]

Study Name		SURMOUNT-OSA			
Arm		TZP	PBO	TZP	PBO
N		114	120	120	115
Any Adverse Event, n (%)		91 (79.8)	92 (76.7)	99 (83.2)	83 (72.8)
Serious Adverse Events, n (%)		9 (7.9)	7 (5.8)	7 (5.9)	12 (10.5)
Serious Gastrointestinal Disorders, n (%)		4 (3.5)	0	4 (3.4)	0
Adverse Events Leading to Discontinuation, n (%)		5 (4.4)	2 (1.7)	4 (3.4)	8 (7)
Fatal Events/Death, n (%)		0	0	0	0
Safety Focus Areas, n (%)	Nausea	29 (25.4)	12 (10)	26 (21.8)	6 (5.3)
	Diarrhea	30 (26.3)	15 (12.5)	26 (21.8)	10 (8.8)
	Vomiting	20 (17.5)	5 (4.2)	11 (9.2)	1 (0.9)
	Constipation	18 (15.8)	3 (2.5)	18 (15.1)	5 (4.4)
	Nasopharyngitis	3 (2.6)	8 (6.7)	15 (12.6)	12 (10.5)
	Dyspepsia	5 (4.4)	2 (1.7)	11 (9.2)	1 (0.9)
	Abdominal Pain	7 (6.1)	4 (3.3)	5 (4.2)	2 (1.8)
	Upper Respiratory Tract Infection	7 (6.1)	10 (8.3)	5 (4.2)	8 (7)
	Gastroenteritis Viral	3 (2.6)	4 (3.3)	8 (6.7)	11 (9.6)
	Arthralgia	3 (2.6)	6 (5)	4 (3.4)	5 (4.4)
	Influenza	4 (3.5)	8 (6.7)	3 (2.5)	3 (2.6)
	Eructation	9 (7.9)	0	10 (8.4)	1 (0.9)
	GERD	9 (7.9)	1 (0.8)	6 (5)	0
	Hepatic Disorders	0	0	0	0
	Acute Pancreatitis	0	0	2 (1.7)	0
	MACE	0	0	0	1 (0.9)
	Cardiac Disorders	7 (6.1)	9 (7.5)	6 (5.0)	2 (1.8)
	Allergic Reactions or Hypersensitivity	0	0	0	0
	Injection-site Reactions	8 (7)	1 (0.8)	6 (5)	0
	Major Depressive Disorder or Suicidal Ideation	2 (1.8)	1 (0.8)	0	2 (1.8)
	Hypoglycemia	0	0	0	0

Study Name	SURMOUNT-OSA			
Arm	**TZP**	**PBO**	**TZP**	**PBO**
N	**114**	**120**	**120**	**115**
Renal Events, n (%)	0	0	1 (0.8)	0
COVID-19, n (%)	6 (5.3)	10 (8.3)	8 (6.7)	11 (9.6)
Bronchitis	0	0	3 (2.5)	7 (6.1)
Hypertension	1 (0.9)	8 (6.7)	2 (1.7)	2 (1.8)
Upper Abdominal Pain	4 (3.5)	2 (1.7)	7 (5.9)	2 (1.8)

GERD: Gastroesophageal Reflux Disease, MACE: Major Adverse Cardiovascular Events, PBO: placebo TZP: tirzepatide

Table D2.38. Safety of Additional Clinical Trials[29,30,51]

Study Name		STEP-HFpEF		ESSENCE		SUMMIT	
Arms		**SEM**	**PBO**	**SEM**	**PBO**	**TZP**	**PBO**
N		**263**	**266**	**800**	**395**	**364**	**367**
Any Adverse Event, n (%)		NR	NR	690 (86.2)	315 (79.7)	313 (86)	279 (76)
Serious Adverse Events, n (%)		35 (13.3)	71 (26.7)	107 (13.4)	53 (13.4)	96 (26.4)	94 (25.6)
AEs Leading to Discontinuation, n (%)	**Any**	35 (13.3)	14 (5.3)	21 (2.6)	13 (3.3)	23 (6.3)	5 (1.4)
	Gastrointestinal Disorders	25 (9.5)	7 (2.6)	NR	NR	NR	NR
Fatal Events, n (%)		3 (1.1)	4 (1.5)	3 (0.4)	6 (1.5)	NR	NR
Common AEs Reported, n (%)	**Nausea**	NR	NR	290 (36.2)	52 (13.2)	62 (17)	24 (6.5)
	Diarrhea	NR	NR	215 (26.9)	48 (12.2)	67 (18.4)	23 (6.3)
	Vomiting	NR	NR	149 (18.6)	22 (5.6)	38 (10.4)	8 (2.2)
	Constipation	NR	NR	178 (22.2)	33 (8.4)	54 (14.8)	22 (6)
	Decreased Appetite	NR	NR	112 (14.0)	11 (2.8)	38 (10.4)	6 (1.6)
	Nervous System Disorder	8 (3.0)	7 (2.6)	NR	NR	NR	NR
	Metabolism and Nutrition Disorders	3 (1.1)	4 (1.5)	NR	NR	NR	NR
	Musculoskeletal and Connective Tissue Disorders	4 (1.5)	4 (1.5)	NR	NR	NR	NR

Study Name		STEP-HFpEF		ESSENCE		SUMMIT	
Arms		SEM	PBO	SEM	PBO	TZP	PBO
N		263	266	800	395	364	367
	General Disorders and Administration Site Conditions	1 (0.4)	3 (1.1)	NR	NR	NR	NR
	Respiratory, Thoracic and Mediastinal Disorders	0	10 (3.8)	NR	NR	NR	NR
	Injury, Poisoning and Procedural Complications	4 (1.5)	4 (1.5)	NR	NR	NR	NR
	Cardiac Disorders	7 (2.7)	30 (11.3)	NR	NR	NR	NR
	Renal or Urinary Disorder	6 (2.3)	4 (1.5)	NR	NR	NR	NR
	Coronavirus Disease 2019	NR	NR	134 (16.8)	74 (18.7)	NR	NR
	Gastrointestinal Disorders	7 (2.7)	7 (2.6)	NR	NR	NR	NR
Safety Focus Areas, n (%)	Gastrointestinal Disorders	7 (2.7)	7 (2.6)	NR	NR	NR	NR
	Gallbladder-related Disorders	NR	NR	20 (2.5)	6 (1.5)	NR	NR
	Hepatobiliary Disorders	3 (1.1)	2 (0.8)	NR	NR	NR	NR
	Acute Pancreatitis	0	1 (0.4)	3 (0.4)	2 (0.5)	NR	NR
	Cardiovascular Disorders	18 (6.8)	41 (15.4)	NR	NR	NR	NR
	Malignant Neoplasms	1 (0.4)	3 (1.1)	13 (1.6)	9 (2.3)	NR	NR
	Neoplasms	2 (0.8)	6 (2.3)	NR	NR	NR	NR
	Acute Renal Failure	5 (1.9)	1 (0.4)	NR	NR	5 (1.4)	3 (0.8)
	Infections and Infestations	4 (1.5)	17 (6.4)	NR	NR	NR	NR
	Misuse and Abuse	0	0	NR	NR	NR	NR
	Medical Errors	0	0	NR	NR	NR	NR
	Gallstone Disease	3 (1.1)	3 (1.1)	NR	NR	NR	NR
	COVID-19	39 (14.8)	45 (16.9)	NR	NR	NR	NR
	Dyspepsia	NR	NR	NR	NR	23 (6.3)	8 (2.2)
	Dizziness	NR	NR	NR	NR	34 (9.3)	18 (4.9)
	Urinary Tract Infection	NR	NR	NR	NR	36 (9.9)	22 (6)
Serious Cardiac Disorders Reported in >1% of Participants, n (%)	Cardiac Failure	NR	NR	NR	NR	15 (4.1)	30 (8.2)
	Atrial Fibrillation	NR	NR	NR	NR	7 (1.9)	3 (0.8)
	Acute MI	NR	NR	NR	NR	6 (1.6)	2 (0.5)
	Unstable Angina	NR	NR	NR	NR	3 (0.8)	5 (1.4)

AE: adverse event, NR: not reported, PBO: placebo, SEM: semaglutide

Table D2.39. Safety of Knee Osteoarthritis Trial[28]

Study Name		STEP-9	
Arms		SEM	PBO
N		269	135
Serious Adverse Events, n (%)		27 (10.0)	11 (8.1)
AE Leading to Discontinuation, n (%)	Any	18 (6.7)	4 (3.0)
	GI Disorders	6 (2.2)	0
Fatal Events, n (%)		0	0
Safety Focus Areas, n (%)	Gastrointestinal Disorders	4 (1.5)	1 (0.7)
	Gallbladder-related Disorders	3 (1.1)	1 (0.7)
	Acute Pancreatitis	0	0
	Cardiovascular Disorders	3 (1.1)	2 (1.5)
	Malignant Neoplasms	8 (3.0)	2 (1.5)
	Neoplasms	10 (3.7)	6 (4.4)
	Psychiatric Disorders	0	1 (0.7)
	Acute Renal Failure	0	1 (0.7)
	Medical Errors	2 (0.7)	4 (3.0)
	Joint Replacement	2 (0.7)	0
	COVID-19	51 (19.0)	32 (23.7)

AE: adverse event, GI: gastrointestinal

Table D2.40. Safety of Treatment Withdrawal Trials[155,156]

Study Name		STEP-4		SURMOUNT-4	
Arms		SEM	PBO	TZP	PBO
N		535	268	335	335
Any Adverse Event, n (%)		435(81.3)	201(75.0)	202 (60.3)	187 (55.8)
Serious Adverse Events, n (%)		41(7.7)	15(5.6)	10 (3)	10 (3)
Serious Gastrointestinal Disorders, n (%)		NR	NR	6 (1.8)	1 (0.3)
AE Leading to Discontinuation, n (%)		13(2.4)	6(2.2)	6 (1.8)	3 (0.9)
Fatal Events, n (%)		1(0.2)	1(0.4)	1 (0.3)	1 (0.3)
Adverse Events Reported in ≥10% of Participants, n (%)	Nausea	75(14.0)	13(4.9)	27 (8.1)	9 (2.7)
	Diarrhea	77(14.4)	19(7.1)	36 (10.7)	16 (4.8)
	Vomiting	55(10.3)	8(3.0)	19 (5.7)	4 (1.2)
	Constipation	62(11.6)	17(6.3)	NR	NR
	Nasopharyngitis	58(10.8)	39(14.6)	NR	NR
	Headache	41(7.7)	10(3.7)	NR	NR
	Abdominal Pain	35(6.5)	8(3.0)	NR	NR
	Upper Respiratory Tract Infection	NR	NR	8 (2.4)	18 (5.4)
	Backpain	28(5.2)	18(6.7)	NR	NR
	Arthralgia	25(4.7)	14(5.2)	NR	NR
	Influenza	39(7.3)	19(7.1)	NR	NR
	Cardiac Disorders	NR	NR	0	0
Safety Focus Areas, n (%)	Gastrointestinal Disorders	224(41.9)	70(26.1)	NR	NR
	Gallbladder-related Disorders	15(2.8)	10(3.7)	0	3 (0.9)
	Hepatic Disorders	11(2.1)	4(1.5)	0	0
	Acute Pancreatitis	0	0	NR	NR
	Cardiovascular Disorders	26(4.9)	30(11.2)	NR	NR
	Allergic Reactions	26(4.9)	11(4.1)	NR	NR
	Injection-site Reactions	14(2.6)	6(2.2)	NR	NR
	Malignant Neoplasms	6(1.1)	1(0.4)	0	3 (0.9)

Study Name		STEP-4		SURMOUNT-4	
Arms		SEM	PBO	TZP	PBO
N		535	268	335	335
	Psychiatric Disorders	46(8.6)	35(13.1)	NR	NR
	Acute Renal Failure	1(0.2)	1(0.4)	NR	NR
	Hypoglycemia	3(0.6)	3(1.1)	2 (0.6)	0

AE: adverse event, NR: not reported

Table D2.41. Treatment Withdrawal Subgroup[67]

STEP-1							
	Arm	Outcome	Weight Loss from Baseline to Week 68				
			<5% Subgroup	≥5 – <10% Subgroup	≥10 – <15% Subgroup	≥15 – <20% Subgroup	≥20% Subgroup
Change in Body Weight from Week 68 to Week 120	SEM	N	12	35	37	45	68
		Change, % points ± SD	4.8 ± 6.7	7.3 ± 6.0	10.7 ± 5.1	11.9 ± 7.1	15.4 ± 8.1
	PBO	N	69	16	5	2	1
		Change, % points ± SD	0.8 ± 4.6	4.4 ± 3.1	4.1 ± 4.2	9.8 ± 0.2	10.8 ± NA

NA: not applicable, SD: standard deviation

Table D2.42. Body Composition Subgroup[23]

Study Name		STEP-1	
Arm		SEM	PBO
N		95	45
Total Fat Mass, kg	Change from baseline	-10.4	-1.17
	Estimated treatment difference (95% CI)	-9.23 (-12.72, -5.74)	
Total Fat Mass, percentage	Change from baseline	-4.19	-0.19
	Estimated treatment difference (95% CI)	-4.00 (-6.27, -1.73)	
Regional Cisceral Fat Mass, kg	Change from baseline	-0.47	-0.03
	Estimated treatment difference (95% CI)	-0.45 (-0.60, -0.30)	
Regional Visceral Fat Mass, percentage	Change from baseline	-2.65	0.58
	Estimated treatment difference (95% CI)	-3.23 (-5.35, -1.10)	
Total Lean Body Mass, kg	Change from baseline	-6.92	-1.48
	Estimated treatment difference (95% CI)	-5.44 (-7.07, -3.81)	
Total Lean Body Mass, percentage	Change from baseline	3.61	0.11
	Estimated treatment difference (95% CI)	3.50 (1.35, 5.64)	

CI: confidence interval, kg: kilogram

D3. Ongoing Studies

Table D3.1. Ongoing Studies

Trial Name/NCT	Design	Treatment Arms	Inclusion Criteria	Exclusion Criteria	Primary Outcome
SURMOUNT-MAINTAIN NCT06047548	Phase III, randomized, open-label, multicenter study N=400 Population: Adults with obesity or overweight with weight-related comorbidities	-Tirzepatide s.c. maximum tolerated dose -Placebo	-BMI ≥30 or ≥27 with presence of comorbidity -History of at least one self-reported unsuccessful dietary effort to lose body weight	-Diabetes mellitus -Change of ≥5 kg in body weight within 3 months -Prior of or planned surgical treatment for obesity	Percent maintenance of body weight reduction during the 60-week weight loss period [week 112]

BMI: body mass index, N: number

Source: www.ClinicalTrials.gov

D4. Previous Systematic Reviews and Technology Assessments

We identified 12 systematic literature reviews or meta-analyses evaluating therapies for weight-loss treatment in adults with overweight or obesity, 3 of which are summarized below.

Qin, W., et al. (2024) "Efficacy and safety of semaglutide 2.4 mg for weight loss in overweight or obese adults without diabetes: An updated systematic review and meta-analysis including the 2-year STEP 5 trial"[172]

This systematic review and meta-analysis aimed to explore the safety and efficacy of once-weekly injectable semaglutide 2.4 mg in non-diabetic patients with overweight or obesity. The primary objective was to assess efficacy, measured by the mean change in body weight and the proportion of patients achieving weight loss exceeding 5%, 10%, 15% and 20% following treatment. The authors' literature search identified six randomized controlled trials involving a total of 3,962 patients that met the inclusion criteria. For the primary outcome, the findings strongly support a significant and clinically meaningful reduction in body weight with semaglutide use. Compared to placebo, semaglutide resulted in an average body weight reduction of 11.80%, equivalent to approximately 12.2 kg. Furthermore, the semaglutide group significantly outperformed the placebo group in terms of the proportion of patients achieving weight loss thresholds of 5%, 10%, 15% and 20%. Regarding safety, both groups reported similar rates of adverse and serious events. However, the semaglutide group experienced significantly higher rates of gastrointestinal adverse events and treatment discontinuation due to adverse events. The authors acknowledge several limitations, including reliance on published study-level data rather than real-world patient data, which may overestimate the therapeutic effects of semaglutide and introduce potential reporting bias. Additionally, the trials predominantly involved White individuals from Western countries. Therefore, further research involving more racially and geographically diverse populations is warranted to confirm the generalizability of these findings.

Dutta, D., et al. (2024) "Efficacy and Safety of Novel Twincretin Tirzepatide, a Dual GIP/GLP-1 Receptor Agonist, as an Anti-obesity Medicine in Individuals Without Diabetes: A Systematic Review and Meta-analysis"[173]

This systematic review and meta-analysis aimed to evaluate the efficacy and safety of tirzepatide as an anti-obesity agent in individuals without diabetes. The primary outcome was the percentage change in weight from baseline. Secondary outcomes included absolute weight change and the proportion of participants achieving weight reductions of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25. A literature search was conducted for randomized controlled trials published up to November 2023 that assessed tirzepatide for weight loss in non-diabetic populations. Of the 281 articles identified in the search, two randomized controlled trials met the inclusion criteria and were included in the

final analysis. These studies collectively enrolled 1,852 participants and had intervention durations of 72 weeks. Participants receiving tirzepatide experienced a mean percentage weight reduction of 19.44%, corresponding to an absolute weight loss of 17.55 kg over 18 months. These outcomes were significantly greater than those observed in the placebo groups. Additionally, a significantly higher proportion of participants in the tirzepatide group achieved weight loss thresholds of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25%. In terms of safety, tirzepatide was associated with a higher incidence of any adverse events, adverse events leading to treatment discontinuation, severe or serious gastrointestinal events and hypoglycemia. The rate of serious adverse events was comparable between the tirzepatide and placebo groups. A key limitation of this review is the lack of data representing diverse ethnic populations and geographic regions, limiting the generalizability of the findings. Further long-term studies are needed to assess the durability of weight loss and to evaluate outcomes across more diverse populations.

Müllertz, A., et al. (2024) "Potent incretin-based therapy for obesity: A systematic review and meta-analysis of the efficacy of semaglutide and tirzepatide on body weight and waist circumference, and safety"[174]

This systematic review and meta-analysis evaluated the efficacy and safety of injectable semaglutide and tirzepatide at obesity-approved doses in individuals with overweight or obesity, without diabetes, treated for at least one year. Primary outcomes included changes in body weight and waist circumference, with additional consideration of body composition. Researchers searched three databases for randomized controlled trials involving semaglutide or tirzepatide in this population, identifying 744 results. Seven studies met inclusion criteria: five from the STEP trials (semaglutide) and two from the SURMOUNT program (tirzepatide). In the STEP trials, semaglutide led to a pooled mean body weight reduction of 12.9% and a waist circumference decrease of 9.7 cm compared to placebo. In the SURMOUNT trials, tirzepatide showed a mean body weight reduction of 19.2% and a waist circumference decrease of 14.6 cm. Two studies assessed body composition using dual-energy X-ray absorptiometry. In STEP-1, semaglutide reduced fat mass by 8.4 kg and lean mass by 5.3 kg, compared to 1.4 kg and 1.8 kg reductions with placebo, respectively. In SURMOUNT-1, pooled tirzepatide reduced fat mass by 33.9% and lean mass by 10.9%, versus 8.2% and 2.6% with placebo. Adverse events were common for both drugs. In STEP trials, 91.0% of semaglutide-treated participants and 88.9% of placebo participants reported at least one event, primarily gastrointestinal (nausea, diarrhea, constipation, vomiting). In the SURMOUNT trials, 81.5% of tirzepatide-treated participants and 73.5% of those on placebo reported adverse events, with gastrointestinal symptoms again being the most frequent. Limitations include the small number of tirzepatide studies, suggesting stronger evidence currently exists for semaglutide. Additionally, details on study design and adherence to lifestyle interventions were often lacking.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. 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	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	

Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[175]

Description of evLY Calculations

The equal value life year (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.[176]
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 (ΔLY 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

The population of focus for the economic evaluation included individuals with obesity or with overweight and at least one obesity-related comorbidity, excluding those with already established type 2 diabetes, who are actively seeking medical management for weight loss. As the characteristics of this real-world population may differ from those enrolled in clinical trials, baseline characteristics were drawn from real-world studies of individuals using weight-lowering medications, wherever available, assuming that real-world users of these medications represent the population pursuing medical weight management.

Table E1.2. Baseline Population Characteristics

	Value	Source
Mean Age*	46 years	Gleason, 2024; Ruseva, 2025[41,42]
Percent Female	79%	Rodriguez, 2025[84]
Mean BMI	37.6 kg/m^2	Rodriguez, 2025[84]
Mean SBP for those Without HTN	125 mmHg	Steven J Atlas, 2022[74]
Mean SBP for those With HTN	135 mmHg	Rodriguez, 2014; Mackenzie, 2022[92,93]
Percent Smoking	14.6%	CDC[122]
Percent CVD*	6.5%	Ruseva, 2025[42]
Percent OSA†	40.3%	Esmaeili, 2025; Rodriguez, 2025[84,113]

BMI: Body mass index; SBP: Systolic blood pressure; HTN: Hypertension; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea

*Although Ruseva et al. included all individuals initiating semaglutide, including those with diabetes, it was considered appropriate for our purposes since only a small proportion (5.8%) of the population had diabetes at baseline. The mean age and the percentage with CVD were cross-checked against other real-world studies, Gleason et al. and Rodriguez et al., excluding people with diabetes. [41] [84]

†Estimated by weighting the prevalence of OSA among individuals with obesity (41.4%) and those who are overweight (26.1%) according to the distribution of obesity and overweight in the real-world user population reported in Rodriguez et al.[84]

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The full list of interventions is as follows: injectable semaglutide (Wegovy®, Novo Nordisk), oral semaglutide (Novo Nordisk), and tirzepatide (Zepbound®, Eli Lilly) added on to lifestyle modification. The comparator for these interventions was lifestyle modification alone (e.g., caloric restriction and increased physical activity).

E2. Model Inputs and Assumptions

Model assumptions are listed in Table 4.1.

Clinical Inputs

Key clinical inputs to the model include transition probabilities, mortality, treatment discontinuation, and adverse events.

Transition Probabilities

The probability of moving between health states was calculated based on the estimated risks of obesity-related outcomes for each treatment group. These risk estimates incorporated multiple inputs—primarily treatment effects on BMI and metabolic risk factors and either indirect or direct treatment effects on obesity-related outcomes.

Treatment Effects on BMI

The percentage change in body weight from baseline for each treatment was derived from the ICER meta-analysis of ITT populations, as well as the ITT populations of relevant clinical trials (Table E2.1). The weight change observed at the primary endpoints of the clinical trials (68, 64, and 72 weeks for semaglutide, oral semaglutide, and tirzepatide, respectively) was assumed to represent the reduction achieved during the first year after treatment initiation, as these endpoints reflect weight loss over roughly one year following the titration period. The weight change at week 104 was assumed to represent the reduction achieved by the end of the second year after treatment initiation. From year two onward, BMI remained stable, reflecting sustained weight maintenance with continued treatment. Natural age-related weight gain from year two was explored in a sensitivity analysis, with the BMI increase per year ranging from 0% to 0.4% of baseline BMI (0.4% of baseline BMI corresponds to approximately 0.15 BMI units per year), based on the previous ICER model.[74]

Table E2.1. Treatment Effects on Body Weight

Parameter	Input	Source
Change in Weight from Baseline by Year 1 (%), LSM	-3.41%	ICER Pooled data*
Change in Weight from Baseline by Year 2 (%), LSM	-2.60%	[85]
Absolute Difference in % Weight Change by Year 1, SC Semaglutide vs. LSM	-13.14%	ICER MA; Table D1.12
Absolute Difference in % Weight Change by Year 2, SC Semaglutide vs. LSM	-14.00%	[85]
Absolute Difference in % Weight Change by Year 1, Oral Semaglutide vs. LSM	-11.40%	[43]
Absolute Difference in % Weight Change by Year 2, Oral Semaglutide vs. LSM†	-12.46%	Author's calculation [43,85]
Absolute Difference in % Weight Change by Year 1, Tirzepatide vs. LSM‡	-18.97%	[64]
Absolute Difference in % Weight Change by Year 2, Tirzepatide vs. LSM‡	-18.97%	Assumed to be the same as Year 1 data

ICER MA: ICER meta-analysis, LSM: Lifestyle modification; SC: Subcutaneous
*Pooled from STEP 1, STEP 3, STEP 5, STEP 8, OASIS 4, and SURMOUNT 1 using unadjusted data
†Due to the lack of year 2 data for oral semaglutide, the absolute difference in % weight change at Year 1 for oral semaglutide was adjusted by multiplying it by the ratio of the absolute difference in % weight change at Year 2 to that at Year 1 for injectable semaglutide.

‡The estimate was derived from individuals with obesity and prediabetes due to the lack of an unadjusted efficacy estimate for the overall population; The absolute difference in % weight change at Year 2 was assumed to be the same as at Year 1, due to the absence of Year 2–specific data and consistent with the long-term BMI trend observed in Jastreboff et al.[64]

Treatment Effects on Metabolic Risk Factors:

The metabolic factors used to estimate the risk of obesity-related outcomes included the proportion of patients treated for hypertension (HTN), systolic blood pressure (SBP) among those treated and untreated for HTN, and glycemic control. In the absence of direct treatment effects on HTN, the prevalence of treated HTN was estimated as a function of BMI, based on relationships reported in the literature and consistent with the approach used in the previous ICER model.[74,91] For SBP, an average of 125 mmHg was assumed for patients without HTN.[74] For those with (treated) HTN, an average SBP of 135 mmHg was used, based on studies of hypertensive patients receiving medication, reflecting suboptimal blood pressure control despite treatment.[92,93] SBP was held constant over time and did not differ by treatment.

Treatment effects on glycemic control were captured through the modeled risk of developing type 2 diabetes. This risk was estimated for each treatment arm using trial data from individuals with obesity and no baseline diabetes (Table E2.2). The annual probability of diabetes was determined based on multiple studies.[61,64,94-96] The primary estimate of approximately 2.3% per year was derived from Kahn et al. and Torgerson et al., both studies of individuals with obesity without baseline diabetes. However, Kahn et al. included participants with a history of CVD, while Torgerson et al., though more aligned with the modeled population, was conducted in Sweden and is dated. Therefore, to ensure consistency and validity, this estimate was compared against three additional studies: two international multicenter studies of individuals with obesity and prediabetes, and a US-based study of outpatients at a tertiary center aged 45–64 without diabetes. To address any remaining parameter uncertainty, we conducted a scenario analysis using the US-based study. Although this study is US-based, we did not use this study for the basecase due to its age, potential changes in diabetes risk over time, and its somewhat high risk estimate relative to other studies.[96] The direct diabetic impact of injectable semaglutide was derived from the SELECT trial population with obesity and a history of CVD, and that of oral semaglutide was assumed to be the same as injectable semaglutide. The direct diabetic impact of tirzepatide was obtained from the prediabetes population in the SURMOUNT-1 trial. For semaglutide, extrapolation from individuals with a history of CVD was considered reasonable because the intervention is expected to improve glycemic control through mechanisms largely independent of CVD, such as enhancing glucose-dependent insulin secretion and slowing gastric emptying. [177] Although these represent the best available evidence, differences in the source populations may bias the estimates. Therefore, we conducted a scenario analysis where the direct diabetic impacts of injectable and oral semaglutide were estimated using tirzepatide's direct diabetic impact, adjusted by the ratio of year-1 BMI effects for injectable and oral semaglutide relative to tirzepatide.

Lipid control was not explicitly modeled, as it was assumed that lipid levels are optimally managed through statin therapy, and improvements in lipid profiles associated with weight loss are implicitly captured within the modeled association between BMI and CVD risk.

Table E2.2. Treatment Effects on Glycemic Control

Input	Value	Source
Annual Probability of Type 2 Diabetes for LSM	2.3%	[61] [64,94-96]
Direct Impact of SC Semaglutide on Diabetes Risk Compared to LSM (HR)	0.27	Kahn, 2024[61]
Direct Impact of Oral Semaglutide on Diabetes Risk Compared to LSM (HR)	0.27	Assumed to be the same as injectable semaglutide
Direct Impact of Tirzepatide on Diabetes Risk Compared to LSM (HR)	0.07	Jastreboff, 2025[64]

HR: Hazard ratio; LSM: Lifestyle modification

Treatment Effects on the Obesity-Related Outcomes:

In the lifestyle modification arm, the risk of obesity-related outcomes was estimated using established risk equations or known associations with BMI and metabolic risk factors, accounting for patient demographics and the previously described metabolic profile. In the active treatment arms, direct effects of treatments on outcome risks were incorporated where available to capture mechanisms beyond those mediated by BMI or metabolic factors. When direct evidence was unavailable, outcome risks were instead estimated indirectly using established associations with BMI and/or relevant metabolic factors.

In the lifestyle modification arm, annual risk of primary CVD was estimated using the office-based, non-laboratory prediction model from the Framingham Heart Study, consistent with the previous ICER model (Table E2.3).[74 97] Estimates varied by age and BMI and were calculated for specific patient subpopulations stratified by sex, smoking status, HTN treatment status, and diabetes status. For those who developed CVD, subtypes of CVD were tracked following the approach used in the previous ICER report.[74,178] In this approach, overall CVD risk was divided into stroke (23%), MI (22%), and other CVD (55%). The annual probability of developing HF following acute or post-MI events was estimated based on data from Sulo et al.[179] Among patients who have experienced an MI, the annual probability of recurrent MI was 0.08 for males and 0.07 for females, based on Peters et al.[99] The annual probability of recurrent stroke among patients with a prior stroke was 0.12 based on Kolmos et al.[98] In the intervention arms, annual primary CVD risk or recurrent risk of MI and stroke reflected treatments' direct effects on cardiovascular risk observed in clinical trials.[45,79]

Table E2.3. Risk of CVD

Input	Value	Source
Annual Probability of Primary CVD for LSM	Estimated based on the risk function from the Framingham Heart Study	D'Agostino Sr, 2008[97]
Proportion of Incident CVD by Subtype	23% for stroke 22% for MI 55% for other CVD	Steven J Atlas, 2022; Schultz, 2021[74,178]
Probability of Developing HF from Acute MI*	[0.0374*EXP(0.0241*age)[*0.624	Sulo, 2016; Gerber, 2016;[179,180] authors' calculation
Annual Probability of Developing HF Post MI*	[0.0018*EXP(0.046*age)]*0.624	Sulo, 2016; Gerber, 2016;[179,180] authors' calculation
Annual Probability of Recurrent MI	8.1% (male) 7.2% (female)	Peters, 2021[99]
Annual Probability of Recurrent Stroke	12.0%	Kolmos, 2021[98]
Direct Impact of SC Semaglutide on Cardiovascular Risk Compared to LSM (HR)†	0.80	Lincoff, 2023[79]
Direct Impact of Oral Semaglutide on Cardiovascular Risk Compared to LSM (HR)†	0.86	[44,45]
Direct Impact of Tirzepatide on Cardiovascular Risk Compared to LSM (HR)†‡	0.80	Assumed to be the same injectable semaglutide

CVD: Cardiovascular disease; LSM: Lifestyle modification; HR: Hazard ratio; MI: Myocardial infarction; HF: Heart failure; TBD: To be determined

*Exponential functions were fitted to the age-specific heart failure risk data. Given that heart failure attributable to a history of MI is predominantly heart failure with reduced ejection fraction (HFrEF), and other types of heart failure (e.g., heart failure with preserved ejection fraction) are already included as part of the other CVD health state, the incidence of post-MI heart failure was adjusted using the proportion of HFrEF among all HF types (563/902; 62.4%) observed in patients with prior MI, as reported by Gerber et al.[180]

†The hazard ratio was applied to both primary CVD risk and the risk of recurrent MI or stroke.

‡This value may be revised once the detailed results of the SURPASS-CVOT trial become available. [49]

ESKD incidence rates for each treatment arm were estimated by applying BMI-related hazard ratios to a reference ESKD incidence rate corresponding to a specified BMI level. Age-specific ESKD incidence rates from the US general population, obtained from the United States Renal Data System (USRDS), served as the reference and were assumed to reflect the risk for individuals with a BMI of 30, given that the mean BMI in the US is approximately 30 and nearly half of the population has a BMI above this threshold.[103-105] BMI-related hazard ratios were derived from a study that examined the association between BMI categories and ESKD risk in the US general population aged 45 and older, excluding key intermediate variables such as hypertension and diabetes from adjustment to capture the full effect through relevant causal pathways.[106] Although a larger US-based study was

available, we used it in a scenario analysis rather than the base case, as it is dated and clinical experts have noted that improvements in the management of obesity-related conditions may have altered the observed associations.[124]

Table E2.4. Risk of ESKD

Input	Value	Source
Annual Incidence of ESKD in the Reference Population (a BMI of 30)*	115 per 1,000,000 (age 18-44 years) 593 per 1,000,000 (age 45-64 years) 1219 per 1,000,000 (age 65-74 years) 1581 per 1,000,000 (age 75+ years)	NIH NIDDK USRDS, 2023; Albertus, 2016; Brownstein, 2024[103-105]
Hazard Ratio of ESKD Incidence Based on BMI†	BMI 25-29.9 vs. <25: 1.08 BMI 30-34.9 vs. <25: 1.29 BMI 35-39.9 vs. <25: 1.50 BMI 40 or higher vs. <25: 1.71	Panwar 2015[181]

ESKD: End stage kidney disease; BMI: Body mass index

*The incidence of ESKD in 2021 among the US general population was used as a proxy for the annual incidence of ESKD at a BMI of 30, based on the average BMI of the US population in 2021 (30.23). Consequently, the US general incidence already reflects an elevated risk of ESKD compared with individuals with normal BMI (<25), corresponding to the BMI 30–34.9 group.

†Hazard ratios for each BMI category were estimated by fitting a linear model to digitized data on the association between BMI and hazard ratios for BMI values greater than 25.[181]

The risk of cirrhosis and knee and hip replacements was modeled similarly, using US general population incidence rates as a proxy for risk at a BMI of 30 (approximating the US average BMI), with risks adjusted based on key risk factors including BMI. The incidence of cirrhosis among the US general population was obtained from a study that reported the annual incidence of cirrhosis in 204 countries based on the Global Health Data Exchange.[107] We used the annual incidence estimated for high-income North America in 2019. This incidence rate was adjusted based on BMI categories using a UK-based study that examined the effect of BMI on cirrhosis-related hospitalizations and deaths.[108] Although the UK study may be less generalizable than a US-based study, it was chosen for its recency and more detailed BMI stratification. The reported relative risks were compared with those from a US-based study, confirming their comparability.[182]

The incidence of total hip and knee replacements among the US general population was obtained from a study that used the US National Inpatient Sample (NIS) and Census Bureau data to project the total annual counts for total hip and knee replacements in the US from 2020 to 2040.[109] The age-specific annual probabilities of undergoing knee and hip replacements were estimated by dividing the projected total annual counts in the US in 2020 by the population size of each age group in 2020.[111] The annual probabilities of knee and hip replacements were adjusted using a US-based study that estimated odds ratios stratified by sex and BMI categories.[112]

Table E2.5. Risk of Cirrhosis

Input	Value	Source
Annual Incidence of Cirrhosis in the Reference Population (a BMI of 30)*	25.6 per 100,000	Lan, 2023; Brownstein, 2024[105,107]
Relative Risk of Cirrhosis Incidence Based on BMI†	BMI 25-27.49 vs. <25: 1.05 BMI 27.5-29.9 vs. <25: 1.11 BMI 30-34.9 vs. <25: 1.49 BMI 35 or higher vs. <25: 1.77	Liu, 2010[108]

BMI: Body mass index

*The incidence of cirrhosis in high-income North America was used as a proxy for the annual incidence of cirrhosis in the US general population. The average BMI of the US general population is approximately 30 based on Rader et al.[105] Consequently, the US general incidence already reflects an elevated risk of cirrhosis compared with individuals with normal BMI (<25), corresponding to the BMI 30–34.9 group.

†The reported relative risks were compared with those from a US-based study, confirming their comparability.[182]

Table E2.6. Risk of Knee and Hip Replacements

Input	Value	Source
Annual Probability of Knee replacement in the Reference Population (a BMI of 30)*	0.01% (<45 years old) 0.44% (45-64 years old) 1.53% (65-84 years old) 0.46% (85 years or older)	Singh, 2019; Zoe Caplan, 2023; United States Census Bureau, 2023[109-111]
Annual Probability of Hip Replacement in the Reference Population (a BMI of 30)*	0.01% (<45 years old) 0.21% (45-64 years old) 0.65% (65-84 years old) 0.38% (85 years or older)	Singh, 2019; Zoe Caplan, 2023; United States Census Bureau, 2023[109-111]
Odds Ratio for Knee Replacement Risk Based on Sex and BMI	Varies by sex and BMI categories (See Table 2.9)	Wendelboe, 2003[112]
Odds Ratio for Hip Replacement Risk Based on Sex and BMI	Varies by sex and BMI categories (See Table 2.9)	Wendelboe, 2003[112]

BMI: Body mass index

*Estimated by dividing the total annual counts of knee or hip replacements in the US in 2020 by the population size of each age group in 2020

Table E2.7. Odds Ratio for the Risk of Knee and Hip Replacements Based on BMI

	Odds Ratio for Knee Replacement Risk		Odds Ratio for Hip Replacement Risk	
BMI	**Male**	**Female**	**Male**	**Female**
20-22.49	**Reference**	**Reference**	**Reference**	**Reference**
22.50-24.99	1.43	1.16	1.09	1.20
25.00-27.49	2.14	2.07	1.33	1.22
27.50-29.99	2.98	4.62	1.73	1.72
30.00-32.49	3.61	6.42	2.54	1.61
32.50-34.99	5.88	7.52	3.30	2.18
35.00-37.49	8.62	11.88	6.65	2.38
37.50-39.99	16.40	17.69*	9.37	3.32*
40.00 or Higher	17.24*	19.05	10.49*	4.47
Source	Wendelboe, 2003[112]			

BMI: Body mass index

*Instead of the odds ratios reported in Wendelboe et al., we used imputed values derived from an exponential curve fitted to the remaining data. The original odds ratios deviated from the overall trend and appeared counterintuitive, likely due to small sample sizes and the resulting wide uncertainty around the point estimates.

The proportion of patients with OSA among the modeled population at baseline BMI (37.6) was estimated at 40.3%, as described previously.[84,113] To estimate the proportion of patients with OSA in each treatment arm over time, the baseline prevalence was adjusted using odds ratios from a study that examined BMI subgroups and OSA prevalence associations via individual patient data meta-analysis.[113]

Table E2.8. Prevalence of OSA

Input	Value	Source
Prevalence of OSA in the Reference Population (a BMI of 37.6)*	40.3%	Esmaeili, 2025; Rodriguez, 2025,[84,113] authors' calculation
Odds Ratio for the Prevalence of OSA Based on BMI†	1.16 per 1 unit of BMI increase	Esmaeili, 2025;[113] authors' calculation

BMI: Body mass index; OSA: Obstructive sleep apnea
*Estimated by weighting the prevalence of OSA among individuals with obesity (41.4%) and those who are overweight (26.1%) according to the distribution of obesity and overweight in the real-world user population reported in Rodriguez 2025. The mean BMI among the real-world user population is 37.6 based on Rodriguez 2025.
†Estimated under the assumption of a log-linear relationship between BMI and odds ratio, using data reported in Esmaeli et al: odds ratio for the prevalence OSA of 1.89 (BMI 25-30 vs. <25) and 4.53 (BMI ≥30 VS. <25).[113]

Discontinuation

The discontinuation rate reflected all-cause discontinuation observed in the trials among the ITT population. Discontinuation impacted only drug costs, as treatment efficacy estimates from the ITT population already account for the effects of discontinuation. All treatment discontinuations were assumed to occur within the first two years of treatment initiation, consistent with the trial follow-up period. Year 1 all-cause discontinuation was obtained from the ICER meta-analysis of ITT populations and from ITT analyses of relevant trials (Table E2.9). All-cause discontinuation by year 2 for lifestyle modification was obtained from Garvey et al.[85] For the interventions, the percentage discontinued by year 2 was assumed equal to year 1 for the following reasons: Although year 2 discontinuation data for injectable semaglutide are available from the STEP 5 trial, the cumulative discontinuation reported at week 104 (13.2%) was lower than the year 1 estimate from the ICER meta-analysis, which is implausible. No year 2 discontinuation data are available for oral semaglutide or tirzepatide. Individuals remaining on treatment after two years are assumed to continue for life.

Table E2.9. Treatment Discontinuation*

Parameter	Input	Source
% Discontinued treatment by Year 1, LSM	19.46%	ICER MA
% Discontinued treatment by Year 2, LSM	27.00%	[85]
% Discontinued treatment by Year 1, SC Semaglutide	14.60%	ICER MA
% Discontinued treatment by Year 2, SC Semaglutide	14.60%	Assumed to be the same as Year 1
% Discontinued treatment by Year 1, Oral Semaglutide	14.21%	[123]
% Discontinued treatment by Year 2, Oral Semaglutide	14.21%	Assumed to be the same as Year 1
% Discontinued treatment by Year 1, Tirzepatide	11.09%	[46]
% Discontinued treatment by Year 2, Tirzepatide	11.09%	Assumed to be the same as Year 1

*Patients are assumed to continue lifestyle modification after discontinuing the intervention.

Mortality

The impact of weight loss on mortality was modeled through its effect on lowering the risk of obesity-related outcomes. Age- and sex-specific mortality rates from the general US population were used as a proxy for individuals with obesity who do not have any of the modeled obesity-related conditions.[114] The hazard ratio (HR) for mortality associated with each obesity-related outcome was sourced from the literature and applied to baseline mortality rates for the US general population to estimate mortality for cohorts with obesity-related outcomes. We used HRs that are adjusted for other conditions wherever possible to avoid double-counting. For health states involving multiple obesity-related outcomes, HRs were combined multiplicatively, consistent with approaches used in other economic models.[74,88,89] In addition to health state–specific mortality, acute mortality was modeled separately for acute MI and stroke. No excess mortality was assumed for OSA or hip/knee replacements, as mortality directly attributable to these conditions is expected to be low and is implicitly captured through associated comorbidities modeled separately.

Table E2.10. Mortality Inputs

Input	Value	Source
Mortality HR: Post MI	1.58	Majed, 2015; Steven J Atlas, 2022[74,183]
Mortality HR: Post Stroke	3.13	Majed, 2015; Steven J Atlas, 2022[74,183]
Mortality HR: Other CVD	1.59	Pande, 2011; Steven J Atlas, 2022[74,184]
Mortality HR: HF Post MI	2.55	Gerber, 2016[180]
Mortality HR: T2D	1.16	Raghavan, 2019[185]
Mortality HR: ESKD	5.21	Lee, 2023[186]
Mortality HR: Cirrhosis	3.79	Simon, 2021[187]
Probability of Death from Acute MI*	6.43%	OECD, 2023[188]
Probability of Death from Acute Stroke*	6.69%	OECD, 2023[188]

CVD: Cardiovascular disease; T2D: Type 2 diabetes, ESKD: End-stage kidney disease; HR: Hazard ratio; MI: myocardial infarction; HF: heart failure.
*Thirty-day mortality following hospital admission for MI or stroke in the US was estimated using the estimates from the US unlinked data, adjusted by the ratio of thirty-day mortality from unlinked versus linked data observed across the OECD28 countries.

Adverse Events

Severe gastrointestinal (GI) adverse events (AEs) were modeled in the analysis. The proportion of patients experiencing severe AEs was informed by ICER meta-analysis and relevant clinical trials (Table E2.11). Disutility associated with these events, along with one-time health care costs for their management, was applied during the first year of the model to reflect their short-term impact on quality of life and costs.

Acute pancreatitis, while potentially impactful, was not modeled separately from other GI AEs because it occurred in only a very small proportion of patients and at similar rates between treatment arms.[189]

Table E2.11. Adverse Events

Parameter	Input	Source
% Experiencing severe GI AEs, LSM	1.31%	ICER MA
% Experiencing severe GI AEs, SC Semaglutide	3.20%	ICER MA
% Experiencing severe GI AEs, Oral Semaglutide	0.66%	[123]
% Experiencing severe GI AEs, Tirzepatide	4.01%	[46]

GI: Gastrointestinal; AE: Adverse events; MA: Meta analysis

Heterogeneity and Subgroups

The cost-effectiveness of treatment may vary by baseline obesity status (e.g., overweight, obesity, and severe obesity), as individuals with higher initial BMI tend to achieve greater absolute weight loss or may experience differential treatment effects. To assess how this variation affects outcomes, we performed a scenario analysis for patient groups stratified by the following baseline BMI: BMI <30, BMI ≥30, BMI ≥35, and BMI ≥40. Based on data availability, each subgroup was characterized by the baseline characteristics listed in Table E2.12 below, as well as by different direct treatment effects on CVD risk.

Table E2.12. Subgroup-Specific Characteristics

Parameter	BMI <30	BMI ≥30	BMI ≥35	BMI ≥40	Source
Mean Age	51.9	46.1	45.4	43.5	Manufacturer's data submission (STEP1 data)
Percent Female	63.2%	74.8%	76.2%	79.4%	Manufacturer's data submission (STEP1 data)
Mean BMI	28.8	38.4	41.6	46.0	Manufacturer's data submission (STEP1 data)
Percent Smoker	12%	11.6%	11.4%	12.1%	Manufacturer's data submission (STEP1 data)
HR for CVD: Injectable Semaglutide*	0.74	0.82	0.91	0.86	Lincoff, 2023[79]
HR for CVD: Oral Semaglutide	0.74	0.82	0.91	0.86	Assume to be the same as injectable semaglutide
HR for CVD: Tirzepatide†	0.74	0.82	0.91	0.86	Assume to be the same as injectable semaglutide

BMI: Body Mass Index; HR: Hazard ratio; CVD: Cardiovascular disease; TBD: To be determined
*HRs were reported for BMI groups of 30–35, 35–40, 40–45, and 45 or higher in the SELECT trial. These HRs were combined to estimate hazard ratios for broader BMI categories—over 30, over 35, and over 40—using the approach described by Van Doorn et al.[190]
†These values may be revised once the detailed results of the SURPASS-CVOT trial become available.[49]

Health State Utilities

The impact of weight loss on quality of life was modeled in two ways: through its effect on reducing the risk of obesity-related outcomes that diminish quality of life, and through additional quality-of-life gains directly associated with reductions in BMI, independent of obesity-related outcomes.

Age-specific utility values from the US general population were used to approximate baseline utilities for individuals with normal BMI and no obesity-related conditions.[115 74] Disutilities linked to specific health states or events, along with those directly attributable to BMI changes, were applied to capture the impact of weight loss on quality of life. For health states with multiple obesity-related outcomes, disutilities were combined multiplicatively using disutility multipliers, consistent with methods used in previous economic models and NICE DSU recommendations.[74,87-90] This approach assumes that each additional chronic condition reduces remaining quality of life proportionally rather than absolutely. To estimate utility multipliers, we relied on studies that reported either utility decrements or average utility values for individuals with the condition. These values were used to derive multipliers under the assumption that the baseline utility for a healthy individual without the condition is approximately 0.85.[115] Short-term disutilities from acute events were applied additively, assuming that that their temporary impact is likely independent and occurs on top of the baseline impairment associated with chronic conditions. These approaches are consistent with methodologies used in previous economic models of obesity.[74,191]

Age-specific utility values and multipliers for CVD and T2D were derived from Sullivan et al., an 'off-the-shelf' catalogue of nationally representative EQ-5D index scores for chronic conditions, adjusted for socio-demographic factors.[115] The utility value for ESKD was obtained from a study using the EQ-5D-5L to estimate quality of life among dialysis patients with ESKD.[192] Utility multipliers for cirrhosis were derived from a previous economic evaluation in Non-Alcoholic Steatohepatitis (NASH) that reported utilities for compensated and decompensated cirrhosis.[193] To estimate overall quality of life for cirrhosis, utility values for compensated and decompensated cirrhosis were weighted according to their population-level distribution as reported by Flamm et al.[194] For OSA, the disutility associated with excessive daytime sleepiness (EDS) was obtained and applied to the proportion of individuals experiencing EDS.[77,195] For those without EDS, the utility decrement associated with OSA, adjusted for EDS, was applied. This approach was used because EDS represents the primary symptomatic manifestation of OSA that significantly impacts patients' quality of life, but not all patients with OSA are expected to experience EDS.

The utility decrement associated with BMI, independent of the modeled obesity-related outcomes, was based on a study that examined the relationship between BMI and EQ-5D–measured quality of life in the general population of England.[116] The analysis was adjusted for socio-demographic characteristics and a broad set of comorbidities, including heart and circulatory disease, diabetes, cancer, mental disorder, musculoskeletal disease, and respiratory disorders. This study was

considered the most appropriate available given the absence of studies that fully match our model design, its clear documentation of included variables, and its incorporation of a broader set of comorbidities compared to previously used studies.[74,87,196,197] However, the adjustments in the study do not perfectly align with the specific obesity-related outcomes included in our model, which may result in over- or underestimation of BMI's impact independent of the modeled obesity-related outcomes. To mitigate potential double counting between the direct BMI-related quality-of-life impact and modeled obesity-related outcomes—particularly OSA, which is highly prevalent in this population—we estimated the OSA-attributable quality-of-life decrement per BMI unit (approximately –0.001, calculated as the incremental prevalence of OSA per BMI unit multiplied by the disutility associated with OSA) and excluded it from the direct BMI effect. The uncertainty surrounding this estimate was explored across a wide range in sensitivity analyses.

Table E2.13. Quality of Life

Input	Value	Source
Age-Specific Utility	0.9442-0.0007*age	Steven J Atlas, 2022; Sullivan 2006[74,115]
Utility Decrement per 1 kg/m² Increase in BMI*	0.006	Luah, 2024[116]; author's calculation
Utility Multiplier: Post MI	0.95	Steven J Atlas, 2022; Sullivan 2006[74,115]
Utility Multiplier: Post Stroke	0.94	Steven J Atlas, 2022; Sullivan 2006[74,115]
Utility Multiplier: Other CVD	0.96	Steven J Atlas, 2022; Sullivan 2006[74,115]
Utility Multiplier: HF post MI	0.93	Steven J Atlas, 2022; Sullivan 2006[74,115]
Utility Multiplier: T2D	0.96	Steven J Atlas, 2022; Sullivan 2006[74,115]
Utility Multiplier: ESKD	0.80	Yang, 2015[192]
Utility Multiplier: Cirrhosis	0.73	ICER, 2023; Flamm, 2024[193,194]
Utility Multiplier: OSA†	0.92 (with EDS) 0.97 (without EDS)	Cambron-Mellott, 2022 ; Malhotra, 2024[77,195]

Input	Value	Source
Disutility: Acute Stroke‡	0.19	Steven J Atlas, 2022; Matza, 2015[74,198]
Disutility: Acute MI‡	0.15	Steven J Atlas, 2022; Matza, 2015[74,198]
Disutility: Knee Replacement§	0.17 (male) 0.20 (female)	NICE, 2023; NICE, 2021[88,89]
Disutility: Hip Replacement§	0.17 (male) 0.20 (female)	NICE, 2023; NICE, 2021[88,89]
Disutility: Severe GI AEs#	0.05	NICE, 2019[199]

AE: Adverse events; BMI: Body mass index; CVD: Cardiovascular disease; T2D: Type2 diabetes; ESKD: End-stage kidney disease; MI: myocardial infarction; HF: heart failure; OSA: Obstructive sleep apnea; EDS: Excessive Daytime Sleepiness

*The coefficient was derived by fitting a linear function to digitized data representing the relationship between BMI and quality of life for individuals with a BMI of 25 or higher. The OSA-attributable quality-of-life decrement per BMI unit (approximately –0.001, calculated as the incremental prevalence of OSA per BMI unit multiplied by the disutility associated with OSA) and excluded it from the direct BMI effect.

†The disutility associated with EDS was estimated as a weighted average of disutilities for mild (ESS 11–12), moderate (ESS 13–15), and severe EDS (ESS 16–24), using the severity distribution of EDS among individuals with OSA. This average disutility was applied to the proportion of patients with EDS, while a separate disutility value for OSA without EDS was applied to the remaining population. The proportion of patients with EDS and its severity distribution were derived from baseline ESS scores reported in the SURMOUNT-OSA trial, assuming a normal distribution (no EDS: 66%, mild EDS: 7%, moderate EDS: 12%, and severe EDS: 15%).

‡The disutility was applied over a 6-month period, consistent with the previous ICER model for obesity.[74] Estimated by calculating the difference in quality of life between the acute and chronic health states.

§The disutility was applied for a duration of 1.5 years to capture the disutility leading up to knee or hip replacement.

#The disutility was applied for a duration of 1 week consistent with previous models in obesity[89,199]

Drug Utilization

The following inputs were used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each regimen

Table E2.14. Treatment Regimen Recommended Dosage

Generic Name	Semaglutide (SC)	Oral Semaglutide	Tirzepatide	Lifestyle Modification*
Brand Name	Wegovy®	n/a	Zepbound®	n/a
Manufacturer	Novo Nordisk	Novo Nordisk	Eli Lilly	n/a
Route of Administration	Subcutaneous injection	Oral	Subcutaneous injection	N/A
Dosing	Initiate at 0.25 mg 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	Initiate at 3 mg once per day for the first four weeks, with dose increased every four weeks to reach the maintenance dose of 25 mg by week 16	Initiate at 2.5 mg once weekly for the first four weeks, with the dose increased every four weeks to reach a maintenance dose of 15 mg by week 20	N/A

N/A: Not applicable
*Lifestyle modification includes caloric restriction and increased physical activity.

Cost Inputs

All costs used in the model, except for drug costs, were updated to 2024 dollars using the using the consumer price index for health care via Bureau of Economic Analysis data.[121] Drug costs were based on the most recent data available as of the first quarter of 2025.

Drug Costs

The annual net prices for injectable semaglutide and tirzepatide were derived directly from SSR Health as of Q1 2025, as its estimates reflect aggregated net prices that account for the use of direct-to-patient option available through NovoCare and LillyDirect.[119] As the price of oral semaglutide is not yet available, it was assumed to be the same as that of injectable semaglutide. The annual cost of lifestyle modification was assumed to be approximately $605, based on a prior economic evaluation.[74]

Table E2.15. Drug Costs

Drug	Annual Net Price
Injectable Semaglutide (Wegovy®)	$6,829†
Oral Semaglutide	$6,829*
Tirzepatide (Zepbound®)	$7,973†

WAC: wholesale acquisition cost; N/A: Not Applicable

*Given the lack of available data, the net price of oral semaglutide was assumed to match those of injectable semaglutide.

†The annual net price already accounts for the use of direct-to-patient option available through NovoCare and LillyDirect.

Non-Drug Costs

Non-drug health care costs included both related and unrelated components. Related health care costs attributable to each obesity-related outcome were sourced from existing literature. An additive approach was used to estimate costs for health states involving multiple outcomes, consistent with the previous cost-effectiveness studies in obesity.[74,88,89] In addition, related health care costs for short-term events—such as MI, stroke, knee or hip replacements, and severe GI AEs—were applied additively to individuals who experience these events.

For individuals who experience an MI or stroke, acute care costs were applied based on a study that estimated nationally representative hospitalization costs for CVD events using the National Inpatient Sample.[200] Following the acute phase, long-term health care costs associated with MI and stroke were applied based on studies that estimated the excess direct medical costs using nationally representative data from the US Medical Expenditure Panel Survey (MEPS).[201,202] Ongoing excess direct health care costs for individuals who develop diabetes, heart failure post-MI, or other cardiovascular disease were derived from a study using MEPS data to estimate costs attributable to multiple cardiovascular risk factors and conditions.[203] Ongoing health care costs for ESKD and cirrhosis were sourced from the USRDS Annual Data Reports and a study of patients with cirrhosis based on IQVIA Ambulatory Electronic Medical Records, respectively.[204,205] Health care costs

attributable to OSA were obtained from a costing study from the American Academy of Sleep Medicine, including costs of diagnosis, testing, follow-up, non-surgical and surgical treatment.[206] One-time costs for knee and hip replacements were derived from a study that reported total costs per procedure.[207] The one-time costs of grade 3-4 nausea served as a proxy for one-time costs associated with severe 3-4 GI AE costs.[208]

Gender- and age-specific unrelated health care costs were additive to the related health care costs associated with obesity-related outcomes or events and were obtained from Jiao et al.[120]

Table E2.16. Rela**ted Health Care Costs**

Input	Value	Source
Acute MI (One-Off)	$34,151	Tajeu, 2024[200]
Post MI (Annual)	$9,248	Bishu, 2020[201]
Acute Stroke (One-Off)	$25,816	Tajeu, 2024[200]
Post Stroke (Annual)	$5,642	Girotra, 2020[202]
HF Post MI (Annual)	$19,294	Kazi, 2024[203]
Other CVD (Annual)	$8,253	Kazi, 2024[203]
T2D (Annual)	$7,825	Kazi, 2024[203]
ESKD (Annual)	$96,283	NIH NIDDK USRDS, 2022[204]
Cirrhosis (Annual)	$38,708	Younossi, 2024[205]
OSA (Annual)	$2,786	American Academy of Sleep Medicine, 2016[206]
Knee Replacement (One-Off)	$31,341	Palsis, 2018[207]
Hip Replacement (One-Off)	$23,630	Palsis, 2018[207]
Severe GI AE (One-Off)	$9,148	McGregor, 2023[208]

AE: Adverse events; CVD: Cardiovascular disease; T2D: Type2 diabetes; EDS: Excessive Daytime Sleepiness; ESKD: End-stage kidney disease; G3-4: Grade 3-4; HF: heart failure; MI: myocardial infarction; OSA: Obstructive sleep apnea

Productivity Costs

The costs of lost patient productivity associated with obesity-related outcomes were included. The model focused on chronic condition productivity costs, as these represent the primary drivers of overall productivity impact, while acute event costs including hip and knee replacement, acute stroke and MI are expected to have minimal impact on results relative to chronic condition costs and limited data availability.

Table E2.17. Annual Patient Productivity Costs

Input	Value	Source
Post MI*	$10,287	American Heart Association, 2017[209]
Post Stroke*	$4,575	American Heart Association, 2017[209]
Other CVD*	$4,773	American Heart Association, 2017[209]
HF Post MI*	$11,791	American Heart Association, 2017[209]
T2D*	$2,713	Parker, 2024[210]
ESKD†	$25,015	van Haalen, 2020; US Bureau of Labor Statistics, 2025; US Bureau of Labor Statistics, 2025[211-213]
Cirrhosis	$23,752	ICER, 2023; O'Hara, 2020[193,214]
OSA‡	$4,893	American Academy of Sleep Medicine, 2016; Malhotra, 2024[77,206]

MI: myocardial infarction; CVD: Cardiovascular disease; HF: heart failure; T2D: Type2 diabetes; ESKD: End-stage kidney disease; OSA: Obstructive sleep apnea

*Estimated using the ratio between indirect and direct costs

†Estimated based on the percentage productivity loss of 38.7%, an average working hours per week (34.3 hours), and average hourly wage ($36.24)

‡Productivity loss was applied to the proportion of patients with EDS (34%), estimated from baseline Epworth Sleepiness Scale (ESS) scores reported in the SURMOUNT-OSA trial, assuming a normal distribution.

E3. Results

Results are described in Section 4.3 of the report.

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. One way sensitivity results are displayed in Figures 4.2, 4.3, and 4.4. Probabilistic sensitivity results are presented in Tables 4.6 and 4.7 and the mean probabilistic sensitivity analysis results with 95% intervals for qualities are detailed in Tables E4.1, E4.2, and E4.3.

Table E4.1. Results of Probabilistic Sensitivity Analysis for Injectable Semaglutide Added to Lifestyle Modification versus Lifestyle Modification Alone

	Injectable Semaglutide Mean (95% CI)	Lifestyle Modification Mean (95% CI)	Incremental
Costs	$453,600 (433,575, 477,964)	$379,683 (353,954, 410,501)	$73,917
QALYs	16.73 (15.65, 17.59)	15.52 (14.26, 16.55)	1.21
evLYs	16.75 (15.69, 17.6)	15.52 (14.26, 16.55)	1.23
Incremental CE Ratio per QALY			$61,088
Incremental CE Ratio per evLY			$60,095

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year, CI: Credible Interval

Table E4.2. Results of Probabilistic Sensitivity Analysis for Oral Semaglutide Added to Lifestyle Modification versus Lifestyle Modification Alone*

	Oral Semaglutide Mean (95% CI)	Lifestyle Modification Mean (95% CI)	Incremental
Costs	$455,009 (432,627, 482,744)	$378772 (353,402, 412,725)	$76,237
QALYs	16.65 (15.63, 17.47)	15.58 (14.43, 16.57)	1.07
evLYs	16.67 (15.66, 17.49)	15.58 (14.43, 16.57)	1.09
Incremental CE Ratio per QALY			$71,250
Incremental CE Ratio per evLY			$69,942

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year, CI: Credible Interval
*Based on an assumed price of oral semaglutide

Table E4.3. Results of Probabilistic Sensitivity Analysis for Tirzepatide Added to Lifestyle Modification versus Lifestyle Modification Alone

	Tirzepatide Mean (95% CI)	Lifestyle Modification Mean (95% CI)	Incremental
Costs	$463,678 (443,756, 488,967)	$379296 (354,915, 410,789)	$84,382
QALYs	17.14 (16.17, 17.92)	15.56 (14.31, 16.6)	1.58
evLYs	17.16 (16.19, 17.94)	15.56 (14.31, 16.6)	1.60
Incremental CE Ratio per QALY			$53,406
Incremental CE Ratio per evLY			$52,739

CI: confidence interval, evLY: equal-value life year, QALY: quality-adjusted life year

E5. Scenario Analyses

Alternative plausible scenarios have been explored. Additionally, since the cost-effectiveness of treatment may vary by baseline obesity status (e.g., overweight, obesity, and severe obesity), we performed an analysis for patient groups stratified by the following baseline BMI: BMI <30, BMI ≥30, BMI ≥35, and BMI ≥40.

Scenario Analysis 1

Modified Societal Perspective

This scenario adopts a modified societal perspective, incorporating patient productivity costs associated with obesity-related outcomes.

Table E5.1. Results for Scenario 1

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$132,229	$480,212	47	16.79	16.81	20.39
Oral Semaglutide*‡	$132,475	$483,224	51	16.68	16.70	20.35
Tirzepatide*	$158,493	$487,310	45.02	17.16	17.18	20.49
Lifestyle Modification	$9,036	$417,517	69.34	15.63	15.63	20.01

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: Myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

†Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

Scenario Analysis 2

Exclusion of Unrelated Health Care Costs

Health care costs not attributable to obesity or obesity-related outcomes were excluded.

Table E5.2. Results for Scenario 2

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI Events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$132,229	$216,987	47	16.79	16.81	20.39
Oral Semaglutide*‡	$132,475	$219,631	51	16.68	16.70	20.35
Tirzepatide*	$158,493	$227,132	45.02	17.16	17.18	20.49
Lifestyle Modification	$9,036	$145,100	69.34	15.63	15.63	20.01

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: Myocardial infarction
*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.
†Undiscounted values are shown. Per 100 individuals.
‡Based on an assumed price

Scenario Analysis 3

Alternative Source for the Association between BMI and ESKD risk

In this scenario, the association between BMI and ESKD risk was derived from another US-based study that, while older, had a larger sample size.[124] However, clinical experts noted that its findings are likely outdated and that the magnitude of the association may be overestimated, given advancements in the management of obesity-related comorbidities over time.

Table E5.3. Results for Scenario 3

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI Events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$132,229	$447,925	47	16.79	16.81	20.39
Oral Semaglutide*‡	$132,475	$449,980	51	16.68	16.70	20.35
Tirzepatide*	$158,726	$456,545	45.20	17.20	17.21	20.52
Lifestyle Modification	$9,015	$375,512	68.86	15.58	15.58	19.96

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

†Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

Scenario Analysis 4

Alternative Direct Diabetic Impacts of Injectable and Oral Semaglutide

In the base case, the direct diabetic impact of injectable semaglutide was derived from the SELECT trial population with obesity and a history of CVD, and that of oral semaglutide was assumed to be the same as injectable semaglutide. The direct diabetic impact of tirzepatide was obtained from the prediabetes population in the SURMOUNT-1 trial. Although these represent the best available evidence, differences in the source populations may bias the estimates. In this scenario, therefore, the direct diabetic impacts of injectable and oral semaglutide were estimated using tirzepatide's direct diabetic impact (HR = 0.07), adjusted by the ratio of year-1 BMI effects for injectable and oral semaglutide relative to tirzepatide. The HRs for diabetes were estimated at 0.10 for injectable semaglutide and 0.11 for oral semaglutide in this scenario.

Table E5.4. Results for Scenario 4

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$132,643	$440,781	45	16.88	16.90	20.45
Oral Semaglutide*‡	$132,856	$443,541	50	16.76	16.78	20.41
Lifestyle Modification*	$9,036	$370,644	69.34	15.63	15.63	20.01

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

†Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

Scenario Analysis 5

Alternative Baseline Incidence of Diabetes

In the base case, the annual probability of diabetes was determined based on multiple studies.[61,64,94,95] Although these studies were conducted among individuals with obesity but without diabetes at baseline, their generalizability may be limited, as the populations do not perfectly match the modeled US population—three were multinational studies involving individuals with obesity and either prediabetes or a history of CVD, and one was a Swedish study of individuals with obesity. To address uncertainty around the generalizability of the basecase estimates, we conducted a scenario analysis using an alternative US-based study used in the ICER 2022 report. [96] We assumed an annual diabetes incidence of approximately 4.1% in the lifestyle modification arm, based on study findings among individuals with a BMI > 30 and high-normal HbA1c (5.6%–6.0%). A higher estimate was considered to overstate the risk based on clinical expert opinion, advances in prediabetes management, and findings from other studies.

Table E5.5. Results for Scenario 5

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI Events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$131,790	$455,638	49	16.69	16.72	20.32
Oral Semaglutide*‡	$132,027	$457,663	53	16.58	16.61	20.28
Tirzepatide*	$158,332	$461,766	45.59	17.13	17.16	20.47
Lifestyle Modification	$8,968	$389,523	74.12	15.42	15.42	19.85

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: myocardial infarction
*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.
†Undiscounted values are shown. Per 100 individuals.
‡Based on an assumed price

Scenario Analysis 6

A Subgroup with Baseline BMI <30 kg

The population subgroup with a baseline BMI < 30 was modeled. Their baseline characteristics are listed in Table E.2.12.

Table E5.6. Results for a Subgroup with Baseline BMI <30

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$120,387	$412,833	34	15.99	15.99	18.55
Oral Semaglutide*‡	$120,853	$413,701	34	15.94	15.94	18.55
Tirzepatide*	$144,079	$427,402	32.70	16.24	16.24	18.61
Lifestyle Modification	$8,228	$336,028	54.15	15.05	15.05	18.18

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

† Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

A Subgroup with Baseline BMI ≥30

The population subgroup with a baseline BMI ≥ 30 was modeled. Their baseline characteristics are listed in Table E.2.12.

Table E5.7. Results for a Subgroup with Baseline BMI ≥ 30

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI Events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$131,566	$445,648	50	16.63	16.65	20.28
Oral Semaglutide*‡	$132,079	$448,428	50	16.54	16.56	20.28
Tirzepatide*	$157,538	$460,207	47.40	16.97	16.99	20.36
Lifestyle Modification	$8,996	$368,574	70.56	15.47	15.47	19.92

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

†Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

A Subgroup with Baseline BMI ≥35

The population subgroup with a baseline BMI ≥ 35 was modeled. Their baseline characteristics are listed in Table E.2.12.

Table E5.8. Results for a Subgroup with Baseline BMI ≥35

Treatment	Intervention Acquisition Costs	Total Costs	Number of stroke or MI events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$133,268	$452,764	59	16.54	16.56	20.55
Oral Semaglutide*‡	$133,659	$459,661	59	16.40	16.42	20.53
Tirzepatide*	$159,593	$467,423	56.68	16.90	16.92	20.63
Lifestyle Modification	$9,132	$381,596	74.09	15.30	15.30	20.22

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: myocardial infarction
*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.
†Undiscounted values are shown. Per 100 individuals.
‡Based on an assumed price

A Subgroup with Baseline BMI ≥ 40

The population subgroup with a baseline BMI ≥ 40 was modeled. Their baseline characteristics are listed in Table E.2.12.

Table E5.9. Results for a Subgroup with Baseline BMI ≥ 40

Treatment	Intervention Acquisition Costs	Total Costs	Number of Stroke or MI Events (per 100)†	QALYs	evLYs	Life Years
Injectable Semaglutide*	$137,512	$470,156	61	16.59	16.63	21.21
Oral Semaglutide*‡	$138,049	$471,386	61	16.50	16.54	21.21
Tirzepatide*	$164,687	$479,348	58.08	17.04	17.08	21.29
Lifestyle Modification	$9,411	$387,194	82.42	15.34	15.34	20.85

evLYs: equal value of life years gained, QALY: quality-adjusted life year, MI: myocardial infarction

*Each treatment is added to lifestyle modification; therefore, intervention acquisition costs also include the costs of lifestyle modification.

†Undiscounted values are shown. Per 100 individuals.

‡Based on an assumed price

E6. Prior Economic Models

Several economic models evaluated the cost-effectiveness of semaglutide and tirzepatide.

ICER's 2022 obesity model found that injectable semaglutide was not cost-effective compared to lifestyle modification alone, with an incremental cost-effectiveness ratio of $237,000 per QALY gained—higher than the results observed in the current model.[74] The primary reason for this difference is the lower annual net price of injectable semaglutide used in the current model ($6,829 in the current model vs. $13,618 in the 2022 model). In addition, the current model included a broader range of obesity-related outcomes and incorporated direct treatment effects on CV outcomes, which were larger than the indirectly estimated effects used in the prior model—leading to improved clinical outcomes (incremental QALY of 1.24 vs. 0.90 in the current model vs. previous ICER model for injectable semaglutide). ICER's 2022 model also evaluated the cost-effectiveness of tirzepatide in a scenario analysis, assuming the same annual drug cost as injectable semaglutide ($13,618). Tirzepatide yielded greater incremental QALYs and evLYs compared to injectable semaglutide, resulting in a more favorable cost-effectiveness ratio ($145,000 per QALY gained)—a finding consistent with our model.

Novo Nordisk has published a cost-effectiveness analysis of injectable semaglutide in the US. [87] At an annual maintenance treatment cost of $17,597, injectable semaglutide was found to be cost-effective, with an incremental cost-effectiveness ratio of $122,549 per QALY gained. The primary reason injectable semaglutide appeared cost-effective despite the higher drug cost was the assumption in Kim et al. of a two-year maximum treatment duration in the base case analysis. This assumption also contributed to the substantially lower incremental QALYs (0.18) compared to those estimated in the ICER models. The study demonstrated that the model was highly sensitive to this assumption, with the incremental cost-effectiveness ratio rising to approximately $250,000 per QALY if the treatment duration was extended to 10 years, largely due to the high cost of the drug. The same two-year maximum treatment duration assumption was also used in the NICE technical appraisals for injectable semaglutide, contributing to a lower incremental QALY gain of 0.092.[89]

Recently, Eli Lilly published a cost-effectiveness analysis of tirzepatide compared to lifestyle modification from the perspective of the US health care system.[191] The study found that tirzepatide 15 mg was associated with an additional 0.61 QALYs and $75,839 in incremental costs, resulting in an incremental cost-effectiveness ratio of $125,053 per QALY gained. While the overall conclusion aligns with our model—that tirzepatide is cost-effective—the incremental cost-effectiveness ratio reported by Eli Lilly was higher than ours, primarily due to the higher annual cost of tirzepatide ($12,720). Additionally, the study reported lower incremental QALYs, largely due to differences in treatment discontinuation assumptions. Eli Lilly's model applied longitudinal all-cause discontinuation at an annual rate of 10.6% for tirzepatide, whereas our model assumed treatment discontinuation patterns observed in the trial ITT population. In a scenario analysis where no discontinuation occurred, the manufacturer estimated a substantially higher QALY gain and a lower incremental cost-effectiveness ratio of $120,130 per QALY gained. Another reason for the lower incremental QALYs in Eli Lilly's study may be the exclusion of direct treatment effects on obesity-related outcomes, such as cardiovascular disease.

Finally, Hwang et al. evaluated the cost-effectiveness of tirzepatide and injectable semaglutide compared to lifestyle modification and found that neither treatment was cost-effective, despite using net prices for both drugs ($6,236 for tirzepatide and $8,412 for semaglutide, annually).[80] The incremental QALYs were lower than those in the current model—0.35 for tirzepatide and 0.25 for semaglutide. This may be partly due to differences in the modeled population: the study included individuals both with and without diabetes and assumed smaller weight loss in the subgroup with diabetes. Additionally, the use of an NHANES-based cohort, with most individuals classified as overweight (BMI <30) or having Class 1 obesity (BMI 30–34.9), likely contributed to less favorable cost-effectiveness results. Although the incremental life years gained were similar to our model (0.5 for tirzepatide and 0.35 for semaglutide), the lower QALYs may reflect differences in utility estimates or other model assumptions.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

To estimate the size of the potential candidate population for treatment, we used inputs for the prevalence of adults in the US with obesity (42.4%), and the prevalence of adults in the US who are overweight (30.7%)[128] multiplied by the percentage of overweight adults in the US that have multimorbidity (39.5%).[129] From this population, we excluded those who are already receiving medication treatment for obesity (22%).[130] We also excluded the population of US adults with type 2 diabetes (approximately 9.5% of the total population)[131] multiplied by the percentage of type 2 diabetes patients who are overweight or obese (approximately 90% of the type 2 diabetes population).[132,133] Applying these sources to the total US adult population averaged over the next five years (~270,900,000)[111] results in estimates of ~92,000,000 eligible patients.

We first conducted individual budget impact analyses for each intervention of interest (Figure 7.1), assuming that 20% of the eligible population would initiate the treatment in each of the five years, or ~18,400,000 patients per year. In these individual analyses, the new uptake was comprised solely of patients starting the intervention of interest (i.e. in the injectable semaglutide analysis, the new uptake comprised only patients starting injectable semaglutide). Separately, in a blended budget impact analysis (Figure 7.2), to account for multiple interventions of interest, we assumed that the 20% uptake includes patients initiating all three interventions of interest equally (i.e., 6.7% of patients initiating injectable semaglutide, 6.7% of patients initiating oral semaglutide, and 6.7% of patients initiating injectable tirzepatide), with ~30,700,000 patients initiating each treatment over the next five years, or ~6,100,000 patients per treatment each year. For both the individual and blended budget impact analyses, we assumed that all patients are on lifestyle modification alone at baseline.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[181,215] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2024-2025, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $880 million per year for new drugs.