Pharmacologic Agents for Weight Management: Clinical Evidence and Management Strategies

Systematic Review and Policy Report

October 2023

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Executive Summary

Background

The US has both the highest rate of obesity among high-income countries and the highest per capita health expenditure related to overweight and obesity in the world. Obesity has been considered a national epidemic by the Centers for Disease Control since 1999, and the most recent data show the persistence of an upward trend of adult obesity increasing from 36% in 2020 to 41% in 2021. Obesity was recognized as a disease by the American Medical Association in 2013 and is clinically defined as a body mass index (BMI) of 30 mg/kg^2 and higher in adults (overweight defined as a BMI greater than 25 but under 30); a BMI in the 95th percentile or higher for age and sex is classified as obese in youth ages 2 to 20 years. Excess body fat and increasing weight are positively correlated with morbidity and all-cause mortality. Obesity is a complex disease caused by a variety of factors including genetic, environmental, and societal components. Prevalence of obesity is greater among low-income individuals, and racial and ethnic disparities in the US are notable. With Medicaid covering mostly low-income individuals, people covered by Medicaid are 27% more likely to be obese compared to those with commercial insurance.

Lifestyle behavioral modifications continue to be the first line of treatment for obesity, although they are mostly ineffective for long-term weight loss. Research has illuminated the biological basis for obesity, advancing medical treatments in bariatric surgery and pharmacotherapy. Currently, 6 drugs are approved by the US Food and Drug Administration (FDA) for chronic weight loss management. Cost is a major barrier to chronic weight management medications. Insurance coverage historically has been mixed for weight management drugs. Broadly, state Medicaid programs are required to cover FDA-approved outpatient drugs that have a rebate agreement on file with the US Department of Health and Human Services. Federal law explicitly excludes several drugs and drug classes from mandatory coverage by Medicaid programs, including drugs for weight loss, sexual dysfunction, cosmetic use, hair growth, and infertility.

Medicaid administrators are interested in learning about the clinical evidence for chronic weight management drugs, including longer-term effects and cost-effectiveness; the clinical criteria Medicaid programs use when determining the appropriate populations for weight management drugs; and the appropriate use of these chronic weight management drugs in the obesity treatment pathway.

PICOS and Key Questions

This report focuses on select drugs for weight management in individuals of any age with primary overweight or obesity. We identified published and ongoing randomized controlled trials (RCTs), nonrandomized studies (with greater limits), and economic studies that reported the effectiveness (e.g., changes in body weight, weight-related comorbidities, quality of life [QoL]), harms (e.g., adverse events [AEs], withdrawals due to AEs), and cost-effectiveness of FDA-approved pharmacological agents, select pipeline drugs (tirzepatide), and off-label treatments (i.e., glucagon-like peptide-1 [GLP-1] agonists) for chronic weight management. Eligible comparators included another active treatment, standard of care including lifestyle interventions, and surgery or other medical devices, and placebo.

Methods

Published and ongoing trials for the evidence and economic review were identified through searching bibliographic databases (e.g., Ovid MEDLINE) through February 3, 2023; scanning reference lists of relevant systematic reviews; and searching several other websites. Effectiveness and harms literature was limited by geography (countries assessed as very high human development according to the United Nations' Human Development Index) and study duration (at least 1 year except for setmelanotide, and for studies in pediatric and type 1 diabetes [T1DM] populations); key limitations for economic studies were US data only and published within the past 5 years. We assessed the risk of bias (RoB) of eligible studies using standard instruments adapted from national and international quality standards. We rated the certainty of evidence (CoE) for 4 outcome categories for drugs with identified evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Where appropriate, statistical tests for differences (two-tailed Mantel-Haenzel chi-square) were calculated using OpenEpi and RevMan software. We combined data for meta-analyses of major outcomes with sufficient published data using RevMan 5.4. Throughout the report, statistical significance is implied when effects are reported as significant, or significantly different.

Core policy sources (e.g., FDA) and DuckDuckGo were also searched for policy and management strategy key questions, and 4 state Medicaid officials and 3 subject matter experts were interviewed.

Key Findings

Effectiveness and Harms Findings

We identified 36 studies in 47 publications for effectiveness and harms key questions:
- Liraglutide: 13 RCTs in 17 publications, 11 in adults and 2 in youth (all are vs. placebo)
- Semaglutide: 7 RCTs in 8 publications, 6 in adults and 1 in youth (all are vs. placebo)
- Semaglutide: 1 RCT in adults (vs. liraglutide)
- Tirzepatide: 1 RCT in adults (vs. placebo)
- Exenatide: 1 RCT in adults (vs. glibenclamide) and 2 in youth (vs. placebo)
- Naltrexone-bupropion: 5 RCTs in 6 publications in adults (4 vs. placebo and 1 vs. usual care)
- Phentermine-topiramate: 3 RCTs in 6 publications, 2 in adults and 1 in youth (all vs. placebo)
- Setmelanotide: 1 RCT with single-arm extension in 2 publications (vs. placebo) and 2 single-arm studies in 3 publications

No eligible trials for effectiveness and harms were identified for dulaglutide and lixisenatide.

All included studies for all drugs were funded by industry, and most authors had important conflicts of interest. Funding industry sponsors were involved in the design, data analysis, and report writing for many of the included published studies, and some authors held patents or stock options with the company providing the medications and funding the study.

Adults

Weight
- All included drugs were effective at reducing body weight respective to studied comparators (placebo, glibenclamide, or usual care).

- Tirzepatide, semaglutide, and phentermine-topiramate achieved clinically meaningful levels of at least 5% loss of body weight compared to placebo at 15.4% (1 RCT for tirzepatide, N = 2,539; moderate CoE), 11.6% (7 RCTs for semaglutide, N = 4,997; low CoE), and 8.6% (2 RCTs for phentermine-topiramate, N = 3,513; low CoE). Compared to glibenclamide, exenatide achieved a mean of 12.7 kg weight loss (1 RCT, N = 128; moderate CoE); a calculation of percent change in body weight suggests this difference was clinically meaningful.
  - Liraglutide (7 RCTs, N = 5,864; low CoE) and naltrexone-bupropion (4 RCTs, N = 4,122; low CoE) achieved smaller, but statistically significant, reductions in percent body weight loss of less than 5%, compared to placebo.
  - In the single head-to-head trial, semaglutide resulted in a clinically meaningful difference in weight loss of 9.4% compared to liraglutide (N = 253; low CoE) and participants who received semaglutide were nearly 3 times more likely to achieve at least 10% weight loss (low CoE).
- Table ES-1 presents the probabilities that individuals exposed to the drug achieved at least 5% and 10% weight loss, compared to individuals who received placebo (as risk ratio [RR]); drugs with the highest probabilities are listed first. We did not identify any eligible studies reporting this outcome for exenatide.

Table ES-1. Risk Ratio for 5% and 10% Weight Loss in Adults Compared With Placebo

With ≥ 5% Weight Loss vs. Placebo				With ≥ 10% Weight Loss vs. Placebo			
Drug	No. RCTs	N	Risk Ratio	Drug	No. RCTs	N	Risk Ratio
PhenTop	2	3,444	3.5 (95% CI, 2.9 to 4.1)	PhenTop	2	3,444	6.1 (95% CI, 5.1 to 7.4)
Tirzepatide	1	2,539	2.6 (95% CI, 2.3 to 2.9)	Semaglutide	7	4,727	4.7 (95% CI, 3.5 to 6.3)
Semaglutide	6	4,786	2.3 (95% CI, 1.9 to 2.8)	Tirzepatide	1	2,539	4.1 (95% CI, 3.5 to 4.8)
NalBup	4	3,710	2.3 (95% CI, 1.7 to 3.2)	NalBup	4	3,035	3.1 (95% CI, 2.1 to 4.7)
Liraglutide	7	5,817	2.0 (95% CI, 1.6 to 2.6)	Liraglutide	8	6,012	2.7 (95% CI, 2.0 to 3.5)

Key. *Moderate CoE*   *Low CoE*

Abbreviations. CI: confidence interval; CoE: certainty of evidence; NalBup: naltrexone-bupropion; PhenTop: phentermine-topiramate.

Indirect Measures for Comorbidity Risk Factors

Systolic Blood Pressure
- Only tirzepatide demonstrated a clinically meaningful reduction in systolic blood pressure (SBP) of at least 5 mmHg compared to placebo (-6.2 mmHg; 1 RCT, N = 2,539; low CoE).
- In general, liraglutide (10 RCTs, N = 6,125; moderate CoE), semaglutide (7 RCTs, N = 4,997; low CoE), and phentermine-topiramate (2 RCTs, N = 3,513; moderate CoE) achieved small but statistically significant decreases in SBP compared to placebo of less than 5 mmHg; there was no difference in the head-to-head trial of semaglutide and liraglutide (N = 253; very low CoE).

- Use of naltrexone-bupropion resulted in a small but significant *increase* in SBP over 52 weeks compared to placebo; this effect was not unexpected and improved with weight loss over time (3 RCTs, N = 3,447; low CoE).
- Change in SBP was not measured in the study of exenatide in adults.

Low-Density Lipoprotein Cholesterol
- None of the drugs reduced low-density lipoprotein (LDL) cholesterol by clinically meaningful levels of at least 1 mmol/L (about 36 mg/dL) compared to placebo.
- In general, liraglutide (8 RCTs, N = 5,701; moderate CoE), semaglutide (5 RCTs, 2,221; low CoE), tirzepatide (1 RCT, N = 2,539; moderate CoE), naltrexone-bupropion (4 RCTs, N = 4,122; low CoE), and phentermine-topiramate (2 RCTs, N = 3,513; moderate CoE) achieved small, but statistically significant, decreases in LDL cholesterol compared to placebo, but not at clinically meaningful levels.
- There was no difference in change in LDL cholesterol in the head-to-head trial of semaglutide and liraglutide (N = 253; very low CoE).
- Change in LDL cholesterol was not measured in the study of exenatide in adults.

Hemoglobin A1c
- Tirzepatide demonstrated clinically meaningful improvements (by at least 0.3%) in hemoglobin A1c (HbA1c) compared to placebo in people without type 2 diabetes (T2DM) by 0.4% (1 RCT, N = 2,539; moderate CoE).
- In general, liraglutide (8 RCTs, N = 5,955; low CoE), semaglutide (7 RCTs, N = 4,997; low CoE), and naltrexone-bupropion (1 RCT, N = 424; very low CoE) reduced HbA1c levels by clinically meaningful levels, mostly in populations with elevated baseline levels and people with T2DM.
- In general, change in percent HbA1c was statistically lower with phentermine-topiramate compared with placebo (1 RCT, N = 2,487; moderate CoE), but the pooled effect did not reach a clinically meaningful difference of at least 0.3% in people with mostly normal baseline HbA1c levels; the small difference between semaglutide and liraglutide was also not at clinically meaningful levels in the single head-to-head study (N = 253; low CoE).
- There was no difference in change in percent HbA1c between exenatide and glibenclamide (N = 128; low CoE).

Quality of Life
- QoL was measured in studies of liraglutide (6 RCTs, N = 5,509; low CoE), semaglutide (5 RCTs, N = 4,481; low CoE), tirzepatide (1 RCT, N = 1,909; moderate CoE), and naltrexone-bupropion (3 RCTs, N = 4,031; low CoE) in adults; overall, these drugs statistically improved physical functioning QoL compared to placebo, but likely not at clinically meaningful levels.

Safety
Withdrawals Due to Adverse Events
- Compared with placebo, all drugs resulted in significantly greater withdrawals due to AEs:
  - Liraglutide: RR, 2.20 (11 RCTs, N = 6,480; moderate CoE)
  - Semaglutide: RR, 1.81 (7 RCTs, N = 4,995; moderate CoE)
  - Tirzepatide: RR, 2.21 (1 RCT, N = 2,539; moderate CoE)
  - Naltrexone-bupropion: RR, 1.92 (4 RCTs, N = 4,481; moderate CoE)

- Phentermine-topiramate: RR, 1.88 (2 RCTs, N = 3,713; moderate CoE)

In the single head-to-head study, liraglutide was associated with nearly 4 times the risk of withdrawal due to an AE compared with semaglutide (N = 253; very low CoE).

There was no difference in withdrawals due to AEs of exenatide compared with glibenclamide (1 RCT, N = 128; low CoE).

Very high drop-out rates in the studies of naltrexone-bupropion (range across 5 RCTs, 50% to 63%) and phentermine-topiramate (range across 3 RCTs, 54% to 62%) should also be considered when assessing safety and tolerability; explanations were mostly vague with broad categories for reasons of withdrawal (e.g., "lost to follow-up," "withdrew consent," "drug non-compliance").

Adverse and Serious Adverse Events
In general, there were more AEs compared to placebo for all drugs. All common AEs occurred more frequently with the drug than with placebo, and they included:
- Liraglutide, semaglutide, and tirzepatide: nausea, diarrhea, constipation, and vomiting
- Naltrexone-bupropion: nausea, constipation, headaches, dizziness, and dry mouth
- Phentermine-topiramate: paresthesia (i.e., tingling or burning sensation of the skin), dry mouth, constipation, disordered taste, insomnia, and dizziness
- Exenatide compared to glibenclamide: more nausea, diarrhea and vomiting with exenatide; more hypoglycemia with glibenclamide

Overall, there were few serious adverse events (SAEs) across studies, and they were generally poorly described. However, in general, SAEs, occurred slightly more often with medication compared with placebo, and those attributed to the drug were often conditions triggered by rapid weight loss, such as issues with the hepatobiliary systems (e.g., cholecystitis, cholelithiasis).

Deaths
Deaths were rare and either not further described or reported as not considered related to the study drug.

Change in Medication Use
In general, net use of oral medications prescribed to improve blood pressure, cholesterol levels, and blood glucose levels decreased in all studies measuring these outcomes. Change in insulin use was measured for liraglutide in 1 RCT in people with T2DM and in 3 RCTs in people with T1DM; total insulin units used per day was lower with liraglutide than with placebo across studies, but whether the difference was statistically significant depended on diabetes type or dose of liraglutide used.

Youth

We identified studies in youth for liraglutide (10 to 17 years), semaglutide (adolescents only), exenatide (10 to 18 years), and phentermine-topiramate (adolescents only).

Weight
All drugs were effective at reducing body weight respectively compared to placebo in youth:
- Semaglutide achieved clinically meaningful decreases in BMI z/standard deviation (SD) scores (at least 0.2 SDs) and percent BMI (at least 5%) compared to placebo:

- o BMI z/SD scores: -1.0 points (1 RCT, N = 201; moderate CoE)
- o BMI, %: -16.7% (1 RCT, N = 201; moderate CoE)
- The single study of phentermine-topiramate in adolescents did not measure BMI z/SD scores, but it measured percent BMI and found clinically meaningful improvements compared to placebo:
  - o BMI, %: -9.7% (1 RCT, N = 223; low CoE)
- Liraglutide achieved significant improvements in in BMI z/SD scores and in percent BMI in 1 study, but at borderline levels of important differences across both measures:
  - o BMI z/SD scores: -0.21 (2 RCTs, N = 386; low CoE)
  - o BMI, %: -4.64% (1 RCT, N = 251; low CoE)
- Exenatide achieved a small and significant (but not clinically meaningful) decrease in change in BMI z/SD scores (1 RCT, N = 44; very low CoE) compared to placebo in 1 study at 24 weeks, but no difference in percent BMI (1 RCT, N = 66; very low CoE) in another study at 52 weeks.

Only 1 study in adolescents reported the proportion who achieved at least 5% and 10% weight loss. The probability of adolescents who received semaglutide and achieved at least:
- 5% weight loss was 4.1 times that of those who received placebo (N = 201; moderate CoE)
- 10% weight loss was 7.7 times that of those who received placebo (N = 201; moderate CoE)

Indirect Measures for Comorbidity Risk Factors

Systolic Blood Pressure
- Only liraglutide demonstrated a reduction in SBP at the level for statistical significance in youth, compared to placebo, but not at a clinically meaningful levels of at least 5 mmHg (P = .04; 1 RCT, N = 386; moderate CoE).
- There was no difference in SBP compared to placebo in youth for semaglutide (1 RCT, N = 201; moderate CoE), exenatide (2 RCTs, N = 110; low CoE), and phentermine-topiramate (1 RCT; N = 223; low CoE).

Low-Density Lipoprotein Cholesterol
- Only semaglutide demonstrated an overall significant reduction in LDL cholesterol compared to placebo in youth, but the difference is likely not clinically meaningful (1 RCT, N = 201; moderate CoE).
- There was no difference in change in LDL cholesterol compared to placebo in youth for liraglutide (2 RCTs, N = 386; moderate CoE).
- Exenatide demonstrated a small (and not clinically meaningful), but statistically significant, reduction in change in LDL cholesterol compared to placebo over 24 weeks in 1 RCT (N = 44), while in another RCT (N = 66), there was no difference in maintenance of reduced LDL cholesterol at 52 weeks in after a weight loss of at least 5% during a 4-week run-in period.
- LDL cholesterol was not reported in the study for phentermine-topiramate.

Hemoglobin A1c
- Only semaglutide demonstrated a clinically meaningful reduction in percent HbA1c compared to placebo in adolescents with normal mean levels at baseline (4% of population with T2DM; mean difference [MD], -0.3%; 1 RCT, N = 201; low CoE).

- There was no overall difference in percent change in HbA1c from placebo for liraglutide in youth (although it may depend on diabetes status; 2 RCTs, N = 386; very low CoE), and for exenatide (1 RCT, N = 66; low CoE).
- Change in HbA1c was not measured in the study of phentermine-topiramate in youth.

Quality of Life
- In youth, QoL was measured in studies of liraglutide (1 RCT, N = 251; moderate CoE) and exenatide (1 RCT, N = 66; very low CoE); overall, there was no difference in QoL survey scores compared to placebo.

Safety
Withdrawals Due to Adverse Events
- There were no significant differences in withdrawals due to AEs compared to placebo for all drug interventions in youth. Overall, there were few AEs that led to withdrawal across the different medications (32 across all studies and groups [N = 386]). Our CoE was rated as very low for liraglutide, exenatide, and phentermine-topiramate and low CoE for semaglutide.

Adverse and Serious Adverse Events
- For liraglutide (2 RCTs, N = 386) and exenatide (2 RCTs, N = 110), more youth experienced AEs when compared with placebo.
- For semaglutide (1 RCT, N = 200), slightly fewer adolescents experienced AEs when compared with placebo.
- In general for phentermine-topiramate (1 RCT, N = 223), there was no difference in AEs compared to placebo.

There were very few SAEs reported across all studies for all drugs, and most were assessed as not related to the study drug. One individual experienced a bile duct stone within 1 week after study completion with phentermine-topiramate.

The most frequent AEs with liraglutide, semaglutide, and exenatide were nausea, diarrhea, vomiting, constipation, and abdominal pain; in the 1 RCT of phentermine-topiramate, nervous system disorders (e.g., headaches) and gastrointestinal disorders (e.g., nausea, abdominal pain) were reported as more frequent AEs, but all were relatively equally dispersed across medication and placebo groups.

Deaths
No deaths were reported in any studies in youth.

Setmelanotide for Monogenic Obesity
Setmelanotide acts on the melanocortin-4 receptors for the treatment of severe obesity caused by a mutation or deficiency of a single gene, also known as monogenic obesity.

Weight

- In monogenic obesity conditions, setmelanotide demonstrated weight loss from baseline levels in general, but it appears to be more effective for weight loss for some genetic mutations studied than others (1 RCT and 2 single-arm studies, N = 69; very low CoE):
  - In a 14-week RCT, participants with Bardet-Biedl syndrome (BBS) alone achieved statistically greater loss of percent body weight compared to placebo (MD, -3.4%; P = .002), but when the analysis included participants with Alström syndrome (an indication not included in the approval by the FDA), the result was not statistically different (P = .052).
  - In 2 single-arm studies in people with BBS, there were notable differences in percent body weight lost from baseline over 52 weeks; about 7% lost in 1 study (N = 31) and over 16% lost in the other (N = 7).
  - In 1 publication with 2 single-arm studies, people with the proopiomelanocortin (POMC) variant lost more body weight from baseline with setmelanotide than did those with the leptin receptor (LEPR) variant after 52 weeks of treatment (-25.6% with POMC [N = 9]; -12.5% with LEPR [N = 7]).

Indirect Measures for Comorbidity Risk Factors

Only single-arm data were reported for these measures; all outcomes were rated as very low CoE.

Systolic Blood Pressure

There were no differences in SBP from baseline with setmelanotide for any genetic variant studied (BBS, Alström syndrome, and POMC or LEPR variants; 3 studies, N = 69; very low CoE).

Low-Density Lipoprotein Cholesterol

In general, there was no difference in LDL cholesterol levels from baseline with setmelanotide at 1 year; however, the difference may depend on the specific genetic condition (3 studies, N = 69; very low CoE). Participants with the LEPR variant achieved statistically significant reductions in LDL cholesterol from baseline after 52 weeks of treatment with setmelanotide, but not at clinically meaningful levels (MD, −10.0, P = .04; 1 RCT, N = 11); there were no differences from baseline for people with the LEPR variant, BBS, or Alström syndrome.

Hemoglobin A1c

There were no differences in percent HbA1c from baseline with setmelanotide for people with POMC or LEPR variants (1 study, N = 21; very low CoE); no other studies measured this outcome.

Quality of Life

QoL was measured in people with BBS and the POMC or LEPR variant in single-arm studies only.

All mean scores improved from baseline with setmelanotide, and all were reported as clinically meaningful improvements (2 studies, N = 59; very low CoE); statistical tests for difference from baseline were not reported, and some individuals did not demonstrate improved QoL in these studies with very small sample sizes.

Safety

Withdrawals Due to Adverse Events

- In the 14-week RCT, there was no difference in withdrawals due to AEs from placebo in people with BBS or Alström syndrome (1 study, N = 38; very low CoE).
- There was only 1 other withdrawal due to an AE across the 2 single-arm trials; grade 1 hypereosinophilia in a participant with a LEPR genetic variant was considered as possibly related to setmelanotide and resolved following discontinuation.

Adverse and Serious Adverse Events

- In the 1 RCT, there were similar rates of AEs experienced by setmelanotide and placebo groups (94.7% each) at 14 weeks.
- Nearly all of the 69 participants who received setmelanotide in the 3 trials experienced at least 1 AE, and most were reported as generally mild and transient.
- Nine SAEs were reported across all single-arm studies for setmelanotide, and none were considered related to treatment.
- In addition to nausea and vomiting, one notable common side effect of setmelanotide is hyperpigmentation, or discoloration, of the skin; the majority of participants experienced this side effect.

Deaths

The 1 death reported across all 3 studies was considered unrelated to the study drug.

Off-Treatment Outcomes

We found only limited information on the pattern of weight change after stopping treatment with liraglutide, semaglutide, and setmelanotide; we did not identify any off-treatment information for other drugs of interest.

- More weight was regained after discontinuation of liraglutide compared to the discontinuation of the placebo in adults and adolescents, but weight did not reach baseline levels within the duration of the off-treatment phases (4 RCTs, with off-treatment phases of 12 to 26 weeks)
- Adults who stopped semaglutide regained more weight compared to those switched to placebo after 20 weeks on semaglutide and those who stopped placebo (2 RCTs, with off-treatment phases of 48 to 52 weeks); about a third of weight was regained irrespective of ongoing diet and exercise background therapy.
  - This pattern of weight regain was similar in adolescents after 7 weeks off treatment.
- Weight regain after stopping setmelanotide also was demonstrated in people with POMC or LEPR genetic variants.

Ongoing Studies

We identified 42 RCTs and 5 nonrandomized ongoing studies for liraglutide, semaglutide, tirzepatide, naltrexone-bupropion, phentermine-topiramate, and setmelanotide. Study sizes range from 12 to 17,500 and are enrolling individuals aged 2 years and older. Of the 31 studies that provide eligibility details related to diabetes status, 17 (55%) explicitly exclude individuals with T1DM or T2DM, while the remainder accept participants with diabetes; only 3 studies are exclusively enrolling individuals with T2DM. No ongoing studies for exenatide, dulaglutide, or lixisenatide were identified.

Cost-Effectiveness Findings

Eight eligible cost-effectiveness studies were identified for this report and consistently ranked phentermine-topiramate most favorably with the lowest cost per quality-adjusted life year (QALY) gained, followed by naltrexone-bupropion, tirzepatide, semaglutide (2.4 mg, weekly), and liraglutide (3 mg, daily) in terms of cost-effectiveness, respectively. The studies that evaluated cost-effectiveness of phentermine-topiramate relative to usual care indicated that it is likely a cost-effective intervention with cost-effectiveness ratios (CERs) consistently below the conventional cost-effectiveness threshold of $100,000 per QALY regardless of the time horizon and other modeling choices in these studies. The CER estimates for naltrexone-bupropion, while higher than the CERs for phentermine-topiramate in all studies that included a comparison between these two interventions, may still potentially be within the cost-effective range for higher willingness-to-pay (WTP) thresholds of $150,000 and $200,000 per QALY. The findings for cost-effectiveness of semaglutide relative to usual care were mixed, with one study indicating that it was cost-effective at $150,000 WTP threshold 82% of the time and another study suggesting that it was cost-effective at $150,000 WTP threshold only 1% of the time. Finally, the CER estimates for liraglutide were consistently greater than $400,000 per QALY, above any conventional WTP threshold for cost-effectiveness.

Although all economic studies included in our review considered costs from a health care payer perspective in the US, there were significant structural and methodological differences across these studies, particularly on model time horizon, treatment duration, post-treatment weight regain, and adjustment of costs and utilities for treatment harms and AEs and weight-related complications and comorbidities.

Policy Findings

We interviewed staff from 4 state Medicaid programs that cover weight management drugs and reviewed the coverage policies of those programs and 3 non-Medicaid payers, along with policy sources on coverage.

- Payers are taking varying approaches to coverage, with some adding coverage (notably, federal employees gaining coverage) while others are cutting coverage.
- The specific drugs covered also vary from payer to payer. Some Medicaid programs cover weight management drugs that are not the focus of this report (e.g., benzphetamine and phendimetrazine).
- Payers also are working to limit off-label use of diabetes medications such as tirzepatide (Mounjaro) for weight management.
- Even among Medicaid programs that have opted to cover weight management drugs for years, coverage decisions are shifting because of the high costs of newer weight management drugs and diabetes drugs.

Among payers who cover weight management drugs, prior authorization (PA) requirements are common, though not universal.

- Prior authorization criteria typically follow the FDA-approved indications for use of the drugs. Initial PA criteria for Saxenda (liraglutide), Wegovy (semaglutide), Contrave (bupropion and naltrexone), and Qsymia (phentermine and topiramate) usually require that the patient either has obesity or has both overweight (BMI of 27 or greater) and weight-related comorbidities.

- For patients with overweight, payers vary in the strictness of their requirements regarding comorbidities or risk factors.
- Reauthorization criteria commonly require achieving and maintaining specified weight loss and sometimes also require toleration of maintenance doses, which are typically the highest FDA-approved dosage of GLP-1s.
- Some state Medicaid programs receive supplemental rebates by adding weight management drugs to their preferred drug lists, but doing so may limit the PA criteria they can set for those drugs.

Although a full review of clinical practice guidelines and their methodologies was out of scope for this report, recommendations from 4 recent guidelines are summarized as follows:
- Guidelines on obesity treatment have evolved rapidly in light of FDA approvals of new drugs and use of weight management drugs in adolescent populations.
- The US Preventive Services Task Force is working on recommendations for weight management interventions for children and adults, which includes review of pharmacotherapy, but it is unclear when the recommendations will be published.

According to the subject matter experts we interviewed, individualized assessment should be used to formulate treatment plans for patients with obesity.
- Obesity is a complex, chronic disease, and the evidence base needed to tailor treatment options to individuals' needs has not yet developed.
- Because of individual genetic factors (which have yet to be identified), individuals may respond much more strongly to one medication than another, and the individual's history, health conditions, and preferences should factor into the care plan.

Our key informants described that, ideally, a multidisciplinary care team would treat patients with obesity.
- As with other chronic conditions, specialists would work with patients with greater complexity, and primary care would manage patients with less complexity.
- Access to obesity specialists, however, is very limited, and the population with obesity is far greater than the capacity of the limited number of providers trained to care for it.
- Medical education on obesity care would need to become standardized and widespread to fill that gap and to decrease stigmatization of people with obesity.

Costs and supply shortages of weight management drugs diminish access. Over time, costs may decline as oral forms of GLP-1s become available, new medications are approved, and older drugs become available in generic forms. However, it is unclear when that might occur.

State Considerations Overview

This is a difficult time for state Medicaid programs to make coverage decisions on weight management drugs; the evidence base is rapidly evolving and some significant questions about future costs and cost-effectiveness remain unanswerable at this time. Conflicting demands may arise between members who want to access these medications and drug makers lobbying for coverage, on the one hand, and budget conscious policymakers and managed care plans, on the other.

As state Medicaid programs navigate decisions about coverage, important considerations arise related to state plan design, utilization management tools, and value-based purchasing approaches. State Medicaid programs that carve pharmacy benefits or specific drug classes out of managed care may have a larger lever for negotiating rebates from drug makers. Programs with pharmacy benefits covered under managed care will need to work with their managed care organizations to address the effect on coverage on capitation rates.

State Medicaid programs also can use utilization management tools, including PA and reauthorization criteria, quantity limits, step therapy, and cost sharing to manage these medications. Managed care organizations may be required to align their drug coverage benefit with the state's fee-for-service program. State Medicaid agencies also can explore ways to negotiate with drug makers for rebates (including supplemental rebates for drugs on the preferred drug list), joint procurements with other state agencies (e.g., state employee health insurance), and multistate purchasing pools.

Coverage decisions about weight management drugs may be considered in conjunction with related benefits, such as obesity prevention programs that support nutrition and physical activity, particularly for children.

Conclusions

Overall, the medications reviewed in this report are associated with varying levels of weight loss; however, their effect on cardiovascular risk factors is less certain, with sometimes only small changes in outcomes. Use of the medications also appears to be commonly associated with adverse effects, such as nausea, constipation, and other symptoms, depending on the specific drug.

Cost-effectiveness varies by medication, with phentermine-topiramate consistently ranked most favorably with the lowest cost per QALY gained and CER estimates for liraglutide being consistently greater than $400,000 per QALY, above any conventional WTP threshold for cost-effectiveness.

State Medicaid agencies may need to use a range of strategies, such as state plan design, utilization management tools, and value-based purchasing agreements, when covering weight management medications. As state Medicaid programs consider coverage of weight management drugs, they may want to review related benefits at the same time. Especially for children and adolescents, there may be opportunities to promote obesity prevention through support for nutrition and physical activity. Preventive interventions will require multisector collaboration with public health, education, and housing to reduce obesogenic pressures. For people who already have overweight or obesity, coverage considerations could include improving access to intensive behavioral interventions and considering coverage of and improved access to bariatric surgery.

Background

The US has both the highest rate of obesity among high-income countries[1] and the highest per capita health expenditure on conditions related to overweight and obesity in the world.[1,2] Nearly 2 in 3 adults, and 1 in 6 children in the US are classified as being overweight or obese,[3] and nearly 10% are defined as having severe obesity.[4] Obesity has been considered a national epidemic by the Centers for Disease Control (CDC) since 1999,[5] and the most recent data show the persistence of an upward trend, with the number of US states with adult obesity rates above 30% increasing from 36% in 2020 to 41% in 2021.[6]

Obesity is a condition of excess body fat that increases risk to health,[7,8] and was declared a disease by the National Institutes of Health (NIH) in 1998[9] (the American Medical Association [AMA] recognized obesity as a disease in 2013[10]). Overweight or obesity is often clinically defined using body mass index (BMI), an index of weight in kilograms divided by height, in meters squared.[11] According to the NIH and World Health Organization (WHO), adults with a BMI of 30 kg/kg^2 and over are classified as obese, with severe obesity defined as over 40 kg/m^2.[7] Having a BMI greater than 25 but under 30 is defined as overweight. In the US, the definition for obesity in children is based on the standard growth charts developed by the CDC; in children and adolescents age 2 to 20 years old, a BMI in the 95th percentile or higher for age and sex is classified as obese, while overweight begins at the 85th percentile, to less than the 95th percentile.[11] However, an expert physician's group of the AMA recently released a statement calling attention to the potential harms of using BMI as the sole measure to diagnose obesity because it does not account for differences in body shape and composition across racial and ethnic groups, sexes and genders, and across the life-span.[12] The classification of overweight and obesity for an individual should also consider the presence of other obesity-related health conditions such as hypertension, cardiovascular disease, and type 2 diabetes (T2DM),[13] as well as other anthropometric measures including waist circumference and waist-to-height ratios,[14] which are indirect measures of body composition.

Excess body fat and increasing weight are positively correlated with morbidity and mortality.[15] Research has shown that adults with obesity are six-times[16] (or higher[17]) more likely to develop T2DM, and children are 4-times more likely,[18] compared to those with a healthy body weight. The American Heart Association released a position in 2021 stating that obesity directly contributes to cardiovascular risk factors including dyslipidemia, hypertension, and sleep disorders, and also leads to the development of cardiovascular disease and mortality independently of those risk factors, particularly in individuals with greater abdominal fat depots.[19,20] Other risks of obesity include chronic obstructive pulmonary disease (COPD), lung cancer, kidney, gallbladder and liver disease, as well as mental illnesses such as depression and anxiety.[3,11,21]. The COVID-19 pandemic also afflicted worse health outcomes in persons with overweight and obesity.[11]

Obesity is a complex disease caused by a variety of factors including genetic, environmental and societal factors, which can lead to consumption of excess, often low-nutrient, calories, and contribute to reduced levels of physical activity.[19,22,23] Low-income individuals are less likely to have access to fresh fruits, vegetables, and affordable lean proteins, and are more likely to live in an area where it is less safe to engage in physical activity outdoors.[21] Linked by social and economic conditions, racial and ethnic disparities in US obesity rates are notable.[6] Communities

of color experience greater exposure to obesogenic environments, including facing higher rates of food insecurity and living in food deserts where healthful food options are not readily available.[24,25] According to recent NHANES data, Black adults have the highest obesity rates in the US, specifically with Black women having the highest rates at nearly 60%.[6]. Obesity prevalence in Latinx adults is over 45%,[6] and over 25% among Hispanic children, compared to non-Hispanic White children with an obesity prevalence of 17%.[11] With Medicaid covering mostly low-income individuals, beneficiaries are 27% more likely to be obese compared to those with commercial insurance.[26] Black patients are less likely than White patients to receive referrals for bariatric surgery,[25] and disparities in access to weight management drugs and other interventions for overweight and obesity have also been identified.[25,27]

Genetic mutations or deficiencies can also cause obesity, but such conditions are rare and account for less than 5% of all severe obesity.[28] Also called monogenic obesity, this condition typically disrupts the energy balance, including food intake regulation, that is maintained by the hypothalamic-leptin-melanocortin system in healthy persons.[28]

Diet, exercise, and other lifestyle behavioral modifications continue to be the first line of treatment for overweight and obesity. However, studies of lifestyle interventions alone typically demonstrate notable short-term weight loss, but may be less effective for maintaining weight loss over the longer term.[29,30] Recent medical advancements in the treatment of obesity has shed more light on its biological underpinnings. Importantly, the historical denial of the biological component of weight dysregulation and obesity has led to weight stigmatization and social discrimination of people who are overweight or obese.[31] Changes in gut hormone secretion and physiologic positioning of gut and intestinal organs that result from bariatric surgery procedures are thought to be the causal factors in appetite reduction and remission of obesity-related comorbidities, including diabetes.[32] In persons with a BMI greater than 35, bariatric procedures (performed as open surgery or endoscopically) have been show to result in loss of "excess" weight of 45% to over 65% over 2 years,[33] and long-term loss of over 50% of excess weight over 10 years.[34] However, eligibility for bariatric surgery is often restricted (typically indicated for persons with severe obesity or obesity with serious comorbidities, only), and includes procedural risks and complications,[35] as do most surgical procedures.

Pharmacological treatments have been around for some time, and many have shown only modest weight loss results.[36] The first glucagon-like peptide 1 receptor agonist (GLP-1 RA) was approved by the US Food and Drug Administration (FDA) in 2005 for T2DM, and demonstrated weight loss effects in addition to improved blood glucose control.[37] Since then, this drug class has evolved to include multiple GLP-1 RA products with improved weight loss profiles. The FDA has approved 6 weight management drugs for long-term use: orlistat (Xenical, Alli), phentermine-topiramate (Qsymia), naltrexone-bupropion (Contrave), liraglutide (Saxenda), semaglutide (Wegovy), and setmelanotide (Imcivree; Table 1).[38] Furthermore, there are other weight loss drugs in the pipeline, including tirzepatide (Mounjaro; Table 1), which has recently received FDA fast-track designation for the treatment of adults with obesity, or adults who are overweight with weight-related comorbidities.[39] Most prescription chronic weight management drugs work by decreasing appetite or increasing feelings of fullness.[38] Orlistat works by interfering with fat absorption.[38] Setmelanotide (Imcivree) is limited to people diagnosed with 1 of 4 specific rare

genetic disorders (deficiencies in at least 1 of 3 proteins, or Bardet-Biedl syndrome [BBS], but not Alström syndrome; Table 1).[38]

Cost is a major barrier to chronic weight management medication.[40] Supporters of increased medical insurance coverage in this space highlight additional obstacles including weight stigma, racial and ethnic biases, and perceptions of risk related to the serious side effects associated with older medications, such as fenfluramine-phentermine (also known as fen-phen).[27,40,41]

Insurance coverage historically has been mixed for weight management drugs.[8,42] Medicare does not cover pharmacological treatments for weight management, and most commercial payers view the therapies as lifestyle medications, a category that also includes treatments for acne and hair loss, and thus typically not covered.[8,42,43] Across state Medicaid programs and state employee health plans, weight management drugs are covered less frequently than other interventions, such as screening, lifestyle behavioral counseling, and bariatric surgery.[24] Among state employee health insurance benefits, coverage for weight management drugs decreased from 23 states in 2017 to 16 in 2021.[44] A review of 4 silver plans in each of 34 state-based health insurance marketplaces found that in 2016, 9 states had one or more silver plans offering some coverage of weight management drugs, while the remaining 25 states had none.[40]

Medicaid programs typically must cover any FDA-approved outpatient drug if its manufacturer has a rebate agreement on file with the US Department of Health and Human Services, but weight management drugs are among the exceptions to this requirement.[45] Federal law permits state Medicaid programs to restrict or exclude coverage of drugs "when used for anorexia, weight loss, or weight gain"[46]; therefore, state Medicaid programs often do not cover weight management drugs.[40,47] A recent survey found that 10 state Medicaid programs broadly cover weight management drugs, and another 6 provide limited coverage.[48] That survey does not reflect the recent change in policy for Mississippi, which began covering weight management drugs on July 1, 2023.[48]

Medicaid administrators are interested in learning about the clinical evidence for chronic weight management drugs, including longer-term effects and cost-effectiveness, the clinical criteria Medicaid programs use when determining the appropriate populations for weight management drugs and the appropriate use of these chronic weight management drugs in the obesity treatment pathway.

The authors of studies included in this review, written policies and guidelines, and interviewees may refer to the drugs reviewed in this report as weight loss drugs, antiobesity medications, or other names. For consistency, we will refer to them as drugs or pharmacological agents for weight management, throughout this report.

Our research was guided by the following PICOS (population, intervention, comparator, outcome, study design) statement and key questions.

PICOS (KQs 1 to 4)

A full list of inclusion and exclusion criteria is in Appendix A.

Populations

- Adults and children with primary overweight or obesity (excluding pregnant and breastfeeding individuals)

Interventions

Table 1. Included Interventions for Chronic Weight Management

Generic Name (Brand Name)		Drug Class	Dose[a]	Route of Administration	Date of FDA Approval
FDA-approved for chronic weight management					
Liraglutide (Saxenda)		GLP-1 agonist	3.0 mg daily	Injection	December 23, 2014
Naltrexone + bupropion (Contrave)		NDRI + opioid antagonist	4 tablets (32 mg + 360 mg) daily	Oral	September 10, 2014
Phentermine + topiramate (Qsymia)		Sympathomimetic amine anorectic + antiepileptic	4 capsules (15 mg + 92 mg) daily	Oral	July 17, 2012
Semaglutide (Wegovy)		GLP-1 agonist	2.4 mg weekly	Injection	June 4, 2021
FDA-approved for obesity caused by genetic conditions					
Setmelanotide [b] (Imcivree)		Melanocortin receptor agonist	3.0 mg daily	Injection	November 25, 2020
Pipeline agents					Date of FDA approval for T2DM
Tirzepatide (Mounjaro)		GLP-1 agonist + GIP receptor agonist	2.5, 5, 7.5, 10.0, 12.5, and 15.0 mg weekly	Injection	May 13, 2022
Drug interventions used off label for weight management					Date of FDA approval for T2DM
Dulaglutide (Trulicity)		GLP-1 agonist	0.45, 1.5, 3.0, and 4.5 mg weekly	Injection	September 18, 2014
Exenatide	(Byetta)	GLP-1 agonist	5 and 10 µg, twice daily	Injection	April 28, 2005
	(Bydureon BCise)		2 mg weekly		January 27, 2012
Liraglutide (Victoza)		GLP-1 agonist	0.6, 1.2, and 1.8 mg daily	Injection	January 25, 2010
Lixisenatide (Adlyxin)		GLP-1 agonist	10 and 20 µg, daily	Injection	July 28, 2016
Semaglutide	(Ozempic)	GLP-1 agonist	0.25, 0.5, 1.0, and 2 mg weekly	Injection	December 5, 2017
	(Rybelsus)		3, 7, and 14 mg daily	Oral	September 20, 2019

Note. [a] Approved dose may differ for pediatric populations; [b] Currently approved for obesity due to suspected POMC, PCSK1, or LEPR deficiency and Bardet-Biedl syndrome, but not Alström syndrome.
Abbreviations. FDA: US Food and Drug Administration; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; NDRI: norepinephrine-dopamine reuptake inhibitor; T2DM: type 2 diabetes.

Comparators

- Other agents of interest (head-to-head)
- Standard of care, including other pharmaceutical management approaches (e.g., orlistat, metformin)
- Lifestyle interventions (e.g., diet, physical exercise, counseling)
- Surgery and other interventional procedures or devices
- Placebo

Outcomes

- Body weight (e.g., change in weight [kg, BMI, percent change], proportion with 5% weight loss)
- Changes in weight-related comorbidities (e.g., blood pressure, T2DM)
- Health-related quality of life (QoL), using validated instruments
- Cardiovascular events (e.g., stroke, myocardial infarction)
- Mortality
- Health care utilization and cost-effectiveness
- Adverse events (AEs), including discontinuation due to AEs
- Serious adverse events (SAEs)

Study Designs

- Randomized controlled trials (RCTs) with a duration of at least 12 months
  - For pediatric populations and persons with type 1 diabetes (T1DM), study duration of at least 6 months
- Nonrandomized studies (NRSs) for the effectiveness and harms of setmelanotide only, with no limitation on sample size or duration
- Prospective NRSs of at least 24 months and a minimum sample size of 100 participants for listed interventions other than setmelanotide
- Cost-effectiveness modeling studies in the US

Key Questions

KQ1. What is the evidence of effectiveness, including longer-term effectiveness, of the weight management agents of interest in people who are overweight or obese?
   a. Does effectiveness vary by patient characteristic (e.g., age, diagnosis of diabetes) or clinical situation (e.g., use before bariatric surgery)?

KQ2. What are the harms, including those over longer-term use, of the weight management agents of interest in people who are overweight or obese?
   a. Do harms vary by patient characteristic (e.g., age, diagnosis of diabetes) or clinical situation (e.g., use before bariatric surgery)?

KQ3. What is the cost-effectiveness or cost impact of the weight management agents of interest in people who are overweight or obese?
   a. Does cost-effectiveness vary by patient characteristic (e.g., age, diagnosis of diabetes) or clinical situation (e.g., use before bariatric surgery)?

KQ4. What are the characteristics of ongoing studies of the weight management agents of interest in people who are overweight or obese?

KQ5. What are public and private payer policies for managing weight management drugs including:
   a. Coverage criteria
   b. Prior authorization and reauthorization requirements, including treatment duration

KQ6. What is the appropriate place in the treatment pathway for the listed weight management agents of interest, including orlistat?

Methods

Researchers from the Center for Evidence-based Policy (Center) searched DuckDuckGo and Google Scholar, and ran literature searches using the Ovid MEDLINE ALL, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (CENTRAL) databases for any RCTs and nonrandomized studies analyzing a listed intervention. For cost and economic studies, we also searched EBM Reviews, SCOPUS, and The Lens databases. We searched reference lists of relevant systematic and narrative reviews for additional studies not captured by the database searches. For effectiveness and harms literature, we did not apply any date limitations, but limited location of studies to countries assessed as very high human development according to the United Nation's Human Development Index.[49] Additional key limitations for effectiveness and harms literature included study duration of 1 year or longer, with these exceptions:

- 6 months or longer in pediatric and T1DM populations
- No duration limit for studies of setmelanotide

For economic and cost-effectiveness literature, studies were limited to US data only and published within the past 5 years. We also searched ClinicalTrials.gov, and International Clinical Trials Registry Platform (WHO) for ongoing studies of listed interventions for pharmacologic agents for weight management.

Two independent researchers conducted risk-of-bias (RoB) assessments; conflicts were handled through discussion, and any disagreements were resolved by a third independent senior researcher. Where appropriate, we calculated statistical tests for differences (two-tailed Mantel-Haenzel chi-square test) using OpenEpi[50] and RevMan[51] software, and measures of association (e.g., odds ratios [OR]) were inverted as needed for clarity and consistency. Percentages for proportions reported (n of N) were calculated where appropriate. We combined data for meta-analyses of major outcomes that had sufficient published data from studies that were assessed for RoB and that evaluated the effectiveness and harms of pharmacologic agents for weight management, using RevMan 5.4.[51] For continuous variables, we used the group sample sizes reported as the full set (the number randomized or number who received at least 1 dose in most studies) in the meta-analyses. For dichotomous variables, we used the sample sizes reported that were used to derive the proportion in the publication. We rated the certainty of the body of evidence for major outcomes using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (we did not assess certainty of evidence [CoE] for change in medication use outcomes).[52,53] We did not assess CoE for the outcome of change in medication. Only results included in the meta-analyses were used to assess CoE for each

outcome, except for QoL outcomes and outcomes for setmelanotide. Two independent researchers assigned CoE ratings from *very low* to *high*; conflicts were handled through discussion, and any disagreements were resolved by a third independent senior researcher. Throughout the report, statistical significance is implied when effects are reported as significant, or significantly different.

Outcomes assessed using GRADE:
- Weight (change in percent body weight, kg body weight, BMI, percent BMI, BMI z or standard deviation [SD] score, percent with ≥ 5% weight loss, percent with ≥ 10% weight loss)
- Comorbidity risk factors (change in systolic blood pressure [SBP], low-density lipoprotein [LDL] cholesterol, hemoglobin A1c [HbA1c])
- QoL (change in Impact of Weight on Quality of Life-Lite [IWQoL-Lite] total and physical function scores; IWQoL-Kids total score; Short-Form Health Survey, 36 questions [SF-36] physical function score; Pediatric QoL score)
- Withdrawals due to AEs

Additional eligibility criteria were studies on human participants and publication in English.

For policy and management strategy methods (KQ5 and KQ6), we searched Ovid MEDLINE using terms such as *Medicaid and (liraglutide or semaglutide or Contrave or Qsymia or setmelanotide or tirzepatide)*. We searched DuckDuckGo with terms such *Medicaid coverage "weight management" drugs*, *obesity "treatment pathway,"* and *clinical guidelines for obesity treatment*. We searched the standard Center policy sources (e.g., FDA, IPD Analytics) applicable to these KQs. We monitored newsletters (e.g., KFF Health News) for new publications of interest. We conducted 4 interviews with state Medicaid officials from California, Mississippi, Michigan, and Wisconsin. We also interviewed 3 subject matter experts: Drs. Eduardo Grunvald, Jeremy Michel, and Fatima Cody Stanford.

A full description of our methods, including an inclusion-exclusion grid for evidence studies and key informant interviewees, can be found in Appendix A.

Findings for Effectiveness and Harms and Cost-Effectiveness

For KQs 1 through 4, our bibliographic database searches returned 8,008 citations, and we identified 21 additional publications by searching gray literature sources and reference lists of relevant systematic reviews. After removing duplicates, we screened titles and abstracts of 6,666 citations, leaving 386 for full-text review. A total of 6,280 citations were excluded, leaving 44 studies in 55 publications that met the inclusion criteria for this report. Additional details can be seen in the study flow diagram in Figure 1. A bibliography of included studies can be found in Appendix M, and a bibliography of the studies excluded after full-text review, with reasons for exclusion, can be found in Appendix N.

Figure 1. Study Flow Diagram

Identification

| Records identified through database searching N = 8,008 | Records identified other sources N = 21 | Ongoing studies identified through trial registries N = 48 |

Screening

Records after duplicates removed
N = 6,666

Records screened
N = 6,666 → Records excluded
N = 6,280

Eligibility

Full-text articles assessed for eligibility
N = 386 → Full-text articles excluded, with reasons
N = 331

Aim, n = 78
Population, n = 68
Study design, n = 50
Publication type, n = 48
Short follow-up, n = 25
Outcomes, n = 17
Intervention, n = 16
Publication date n = 12
Setting, n = 12
Comparator, n = 4
Non-English, n = 1

Included

Studies included in qualitative synthesis
N = 44
(36 trials and 8 cost-effectiveness studies in 55 publications)

Studies included in quantitative synthesis
N = 36

Studies included as ongoing
N = 48
(29 included in meta-analyses)

Note. Adapted from Moher D, et al.[54]

Of the 44 eligible studies, 36 in 47 publications are clinical trials that are included in the evidence section for effectiveness and harms, and 8 studies are included in the economic evidence for pharmacologic agents for weight loss.

Effectiveness and Harms

The number of studies identified for effectiveness and harms evidence are listed as follows for each drug of interest, in the order that they appear in the report. All but 3 studies compared the intervention to placebo. The single head-to-head trial is listed first in this summary only; the reported findings are below the findings for semaglutide and liraglutide.

- Semaglutide versus liraglutide: 1 RCT comparing semaglutide with liraglutide, and each with placebo in adults[55]
- Liraglutide: 13 RCTs in 17 publications[56-72] comparing liraglutide with placebo
  - 11 RCTs[56,57,59,62-67,70,72] in 15 publications in adults and 2 RCTs in youth[60,71]
- Semaglutide: 7 RCTs in 8 publications[73-80] comparing semaglutide with placebo
  - 6 RCTs[73-76,79,80] in 7 publications in adults and 1 RCT in youth[78]
- Tirzepatide: 1 RCT comparing 3 doses of tirzepatide with placebo in adults without diabetes[81]
- Exenatide: 3 RCTs[82-84]
  - 1 RCT comparing exenatide with glibenclamide in adults[84]
  - 2 RCTs comparing exenatide with placebo in youth[82,83]
- Naltrexone-bupropion: 5 RCTs in 6 publications[85-90]
  - 4 RCTs comparing naltrexone-bupropion with placebo in adults[85,86,88,89] and 1 RCT in 2 publications[87,90] comparing naltrexone-bupropion and lifestyle program with usual care in adults
- Phentermine-topiramate: 3 RCTs in 6 publications[91-96] comparing phentermine-topiramate with placebo
  - 2 RCTs[91,93] in 5 publications in adults and 1 RCT in youth[96]
- Setmelanotide: 1 RCT in 2 publications[97,98] comparing setmelanotide with placebo and 2 single-arm studies in 3 publications[99-101]

No eligible trials for effectiveness and harms were identified for dulaglutide and lixisenatide. Summary of included study characteristics and outcomes are reported under headers for individual drugs, or drug and comparator, findings. Full details of study characteristics and participant baseline characteristics are in Appendix B, Tables B1 and B2, respectively.

We assessed the CoE for the listed comparisons and provided subgroup assessments as needed to aid clinical perspectives (for an explanation of GRADE ratings see Appendix A). Meta-analyses for key outcomes were conducted where possible and incorporated into GRADE assessments when available.

- Liraglutide versus placebo in adults
- Liraglutide versus placebo in youth
- Semaglutide versus placebo in adults
- Semaglutide versus placebo in youth
- Semaglutide versus liraglutide in adults
- Exenatide versus glibenclamide in adults
- Exenatide versus placebo in youth
- Tirzepatide versus placebo in adults
- Naltrexone-bupropion versus placebo in adults
- Phentermine-topiramate versus placebo in adults

- Phentermine-topiramate versus placebo in youth
- Setmelanotide versus placebo

Overview of Key Outcome Measures

Table 2 summarizes the primary measures used for outcomes in the included studies, the interpretation of those measures, including categories or classes that are used clinically to determine treatment approaches, and change values determined as clinically meaningful. Minimal clinically important difference (MCID) values are defined as the smallest improvement in an outcome in response to treatment that in individual patient would identify as important, leading to a change in the patient's management[102] (also known as differences, or improvements, that are clinically meaningful). While these thresholds can offer valuable information about effectiveness beyond statistical significance for responders and nonresponders, there is controversy around methods used and lack of standardization in the derivation of MCIDs.[103] MCIDs should not be applied and interpreted in isolation, but rather with consideration of the patient population, and other clinically relevant information.[103,104]

Table 2. Summary of Key Outcomes

Measure	Description	Interpretation	MCID
Weight			
Percent change in body weight	(Baseline body weight [kg] – post-treatment body weight [kg]) / baseline body weight x 100	Assessment of proportion of weight lost over time (with intervention), appropriate for adults 18 years and older *For example*, 5% weight loss in an individual with: • Baseline body weight of 135 kg (289 lb): loss of 7 kg (15 lb) to 128 kg (282 lb) • Baseline body weight of 80 kg (176 lb): loss of 4 kg (9 lb) to 76 kg (168 lb)	• ≥ 5% weight loss[105]
Body mass index (BMI) z or standard deviation (SD) score	Measure of relative weight adjusted according to references standards for child age (2 to 20 years) and sex; scores correspond to growth chart percentiles	BMI z/SD scores quantify a measurement's distance from the mean; they are often converted to percentiles used to assess child growth: • Underweight: < 5th percentile • Healthy weight: 5th to < 85th percentile • Overweight: 85th to < 95th percentile • Obesity: ≥ 95th percentile • Severe obesity: 120% of the 95th percentile	• ≥ 0.15 to 0.25 units[106-108]
Percent change in body mass index (BMI, %)	(Baseline BMI [kg/m^2] – post treatment BMI [kg/m^2]) / baseline body BMI x 100	Assessment of proportion of weight lost over time (with intervention), more appropriate for children and adolescents under 18 years, to account for growth in height	• ≥ 5% loss of BMI[105]

Measure	Description	Interpretation	MCID
Comorbidity risk factors			
Systolic blood pressure (SBP)	Represents the peak arterial force produced by the heart when pumping out blood to the body Shown to predict cardiovascular risk better than DBP Typically has linear relationship with DBP	Measured in millimeters (mm) of mercury (Hg) • Normal: < 120 mmHg • Elevated: 120 to 129 mmHg • Hypertension, stage 1: 130 to 139 mmHg • Hypertension, stage 2: ≥ 140 mmHg	• Reduction of 5 mmHg shown to reduce major CV event by 10%[109]
Low-density lipoprotein (LDL) cholesterol	Test for blood lipoproteins that transport cholesterol and fat around the body via the blood The largest component of total blood cholesterol that can contribute to atherosclerosis if high	Measured in mg/dL or mmol/L (1 mmol/L LDL = 38.7 mg/dL) • Normal: < 100 mg/dL • Near optimal: 100 to 129 mg/dL • Borderline high: 130 to 159 mg/dL • High: 160 to 189 mg/dL • Very high: ≥ 190 mg/dL	• 1 mmol/L (38.7 mg/dL) reduction associated with 23% to 25% risk reduction of major cardiovascular events[110] • Goal of statin therapy > 50% reduction in LDL cholesterol[111]
Hemoglobin A1c (HbA1c)	• Measures blood sugar volume (glucose) attached to blood hemoglobin • Represents average blood sugar levels for prior 2- to 3-month period	Measured as percent of total hemoglobin or mmol/mol (HbA1c, % = [HbA1c, mmol/mol]/10.929] + 2.15) • Normal: < 5.7% • Prediabetes: 5.7% to 6.4% • Diabetes: ≥ 6.5%	• 0.3% to 0.4%[112]
Quality of life			
Impact of Weight on Quality of Life-Lite survey (IWQoL-Lite)	• Clinical trials version is scaled and scored similarly to regular version) • 20-item self-report survey of 20 items to assess obesity-specific QoL in adults • Consists of 5 domains (physical function, self-esteem, sexual life, public distress, work)	• Transformed scores (from raw scores) range from 0 to 100, with 100 representing the best QoL • Physical function score includes only the single domain, or component	• Increases of 7.7 to 12 points of total score[113] • No MCID for component score identified
SF-36 physical function score	• The physical functioning component of RAND's SF-36 • Includes 10 of 36 items of a self-report survey	Component scores range from 0 to 100 with higher scores indicating a more favorable QoL	• > 3.8 points for obesity health-related QoL[113]

Measure	Description	Interpretation	MCID
Pediatric Quality of Life Inventory (PedsQL)	• 23-item, self- or caregiver-reported, age-dependent assessment of QoL in children and adolescents • Includes 4 domains (physical, emotional, social, and school functioning)	Transformed scores (from raw scores) range from 0 to 100, with 100 representing the best QoL	• > 4.4 points for obesity health-related QoL[114]

Abbreviations. BMI: body mass index; DBP: diastolic blood pressure; HgA1c: hemoglobin A1c; IWQoL; Impact of weight on quality of life; LDL: low-density lipoprotein; MCID: minimal clinically important difference; QoL: quality of life; SBP: systolic blood pressure; SD: standard deviation; SF-36: Short-Form Health Survey, 36 questions.

Overview of Key Findings

We reported our findings by drug, and separated analyses and assessments by age (adults and children and adolescents [youth]). We identified more studies for liraglutide and semaglutide, and we identified only 1 eligible head-to-head study. Only 1 eligible trial was identified for semaglutide in youth, exenatide in adults, tirzepatide in adults, and phentermine-topiramate in youth. We found no studies for dulaglutide, lixisenatide, tirzepatide in youth, and naltrexone-bupropion in youth.

In general, all drugs were effective at weight loss compared to placebo, and several demonstrated weight loss at levels considered clinically meaningful. In adults, most drugs improved SBP (except for naltrexone-bupropion, which *increased* SBP) and HbA1c levels compared to placebo, but they were less effective at improving LDL cholesterol levels. Adverse events, especially conditions affecting the gastrointestinal and hepatobiliary systems, were common, but typically mild or moderate in severity; cardiovascular events were very few overall. Most outcomes were rated as having moderate or low CoE; none were rated as high CoE.

The number of studies, and the number of participants per study, were much fewer in youth, contributing, in part, to the lower CoE for more outcomes. Except for exenatide, the other 3 drugs in studies included in this report demonstrated significant weight loss; however, these drugs were less effective at improving indirect measures of risk factors for comorbidities compared to the same drugs in adults. Patterns of adverse events in youth were similar to those in adults.

Tables 3 and 4 provide a high-level summary of the CoE of findings for the included studies. See Appendices B for study and population baseline characteristics and Appendices C through J for full evidence tables.

Table 3. Outcomes Summary of Findings: Adults

Drug No. Studies	Change in Wt	≥ 5% Wt Loss	≥ 10% Wt Loss	SBP (mmHg)	LDL Chol	HbA1c (%)	QoL	W/Ds Due to AEs	SAEs
Vs. placebo									
Liraglutide 12 RCTs	-4.6%	RR, 2.04	RR, 2.66	-2.9	SMD, -0.12	-0.33	+	RR, 2.20	More with liraglutide
Semaglutide 7 RCTs	-11.6%	RR, 2.34	RR, 4.70	-4.7	SMD, -0.21	-0.43	+	RR, 1.81	Slightly more with semaglutide
Tirzepatide 1 RCT	-15.4%	RR, 2.56	RR, 4.08	-6.2	-4.1%	-0.40	+	RR, 2.21	ND
Naltrexone-Bupropion 5 RCTs	-4.3%	RR, 2.31	RR, 3.12	+1.5	SMD, -0.09	-0.50	+	RR, 1.92	ND
Phentermine-topiramate 2 RCTs	-8.6%	RR, 3.47	RR, 6.12	-3.2	-2.2%	-0.17		RR, 1.88	ND
Vs. glibenclamide									
Exenatide 1 RCT	-12.7 kg					ND		ND	
Head-to-head									
Semaglutide vs. liraglutide 1 RCT	-9.4%		RR, 2.77	ND	ND	-0.20		RR, 0.25	More with liraglutide

Notes. Moderate CoE; low CoE; very low CoE. Not measured or reported; + indicates improved.
Abbreviations. AE: adverse event; Chol: cholesterol; CoE: certainty of evidence; HgA1c: hemoglobin A1c; LDL: low-density lipoprotein; No.: number; ND: no difference; QoL: quality of life; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SBP: systolic blood pressure; SMD: standardized mean difference; W/Ds: withdrawals; wt: weight.

Table 4. Outcomes Summary of Findings: Youth

Drug No. Studies	Change in BMI	≥ 5% Wt Loss	≥ 10% Wt Loss	SBP (mmHg)	LDL Chol	HbA1c (%)	QoL	W/Ds Due to AEs	SAEs
Vs. placebo									
Liraglutide 2 RCTs	-0.21 SDs			-2.1	ND	ND	ND	Mixed; overall ND	More with liraglutide
Semaglutide 1 RCT	-1.00 SDs	RR, 4.09	RR, 7.67	ND	-6.80%	-0.30		ND	More with semaglutide
Exenatide 2 RCTs	-0.09 SDs; ND in % BMI			ND	Mixed (study design); likely ND	ND	ND	ND	ND
Phentermine-topiramate 1 RCT	-9.7%			ND				ND	More with PhenTop

Notes. Moderate CoE; low CoE; very low CoE. Not measured or reported.
Abbreviations. AE: adverse event; BMI: body mass index; Chol: cholesterol; CoE: certainty of evidence;

Liraglutide

Summary of Included Studies

We identified 14 RCTs in 16 publications[55-72] that compared liraglutide with placebo (Table 5). The STEP 8 trial was a head-to-head trial of semaglutide and liraglutide in adults, and also compared liraglutide with placebo; the trial comparison of semaglutide with liraglutide is reported in a separate section. Twelve RCTs in 16 publications were in adults,[55-59,61-70,72] and 2 RCTs were in children and adolescents.[60,71]

Across the 12 RCTs for liraglutide in adults, there were differences in population (e.g., with or without T2DM), requirements for weight loss prior to randomization, background treatments, and the dose evaluated.

- 6 RCTs excluded individuals with diabetes,[55,56,62,63,65,66] the SCALE Diabetes and SCALE Insulin trials included only those with T2DM,[57,59] and 3 RCTs (including the LIRA-1 and LIDO trials) studied individuals with T1DM.[67,69,72]
  - 2 RCTs (S-LiTE[65] and SCALE Maintenance[62]) in persons without diabetes were weight loss maintenance trials in individuals who lost at least 5% body weight after run-in periods of intensive lifestyle therapy run-in periods
    - From the S-LiTE trial,[65] we only included the liraglutide and placebo groups; we did not include the liraglutide plus exercise group because the proportion of effects would not be discernable between interventions
  - The LIDO trial[72] was of crossover design in 15 adults with T1DM
- The LOSEIT trial studied individuals with knee osteoarthritis (KOA) without T1DM, but included people with a diagnosis of T2DM if treated with diet and exercise, or metformin only[64]
- 1 RCT included nonpregnant postpartum individuals with a history of gestational diabetes within the past 12 months, and allowed the use of metformin at 2,000 mg per day and general advice on diet and exercise as background treatment to liraglutide 1.8 mg per day or placebo[66]
- A daily dose of 3.0 mg liraglutide was utilized in 7 studies[55,56,59,62-65], daily 1.8 mg was used in 4 RCTs,[66,67,69,72] and 1 RCT included both of these doses[57]

In the 2 RCTs for liraglutide in youth, there were differences in eligibility criteria, background treatment, and the dose evaluated.

- The ELIPSE RCT followed children and adolescents with T2DM and on metformin who received up to 1.8 mg liraglutide weekly, or placebo, for 1 year (26 weeks blinded followed by 25 weeks open-label)[71]
- The RCT by Kelly and colleagues followed adolescents who were overweight, with or without T2DM (about one-third were with prediabetes or T2DM) who received 3.0 mg liraglutide or placebo over 1 year[60]

Table 5. Overview of Study Characteristics: Liraglutide

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Conditions
Adults								
Elkind-Hirsch, 2020[66] RCT High RoB	Yes	84	Metformin, diet and exercise	153	• SC liraglutide 1.8 mg daily • Placebo	History GDM	BMI ≥ 25 kg/m^2	Post-partum
Ghanim, 2020[67] RCT High RoB	Yes	26	Insulin	84	• SC liraglutide 1.8 mg daily • Placebo	With T1DM	BMI ≥ 27 kg/m^2	None
LIDO[72] Dubé, 2017 RCT crossover Moderate RoB	No	24	Insulin	15	• SC liraglutide 1.8 mg daily • Placebo	With T1DM	BMI ≥ 25 kg/m^2	None
LIRA-1[69,70] Dejgaard, 2016 RCT Moderate RoB	No	24	Insulin	100	• SC liraglutide 1.8 mg daily • Placebo	With T1DM	BMI ≥ 25 kg/m^2	None
LOSEIT[64] Gudbergsen, 2021 RCT Moderate RoB	No	52	Intensive diet therapy	156	• SC liraglutide 3.0 mg daily • Placebo	NR	BMI ≥ 27 kg/m^2	Knee OA
SCALE Diabetes[57] Davies, 2015 RCT Moderate RoB	Yes	56 + 12	Diet and exercise	846	• SC liraglutide 3.0 mg daily • SC liraglutide 1.8 mg daily • Placebo	With T2DM	BMI ≥ 27 kg/m^2	None
SCALE IBT[63] Wadden, 2020 RCT Moderate RoB	Yes	56	IBT	282	• SC liraglutide 3.0 mg daily • Placebo	None	BMI ≥ 30 kg/m^2	None
SCALE Insulin[59] Garvey, 2020 RCT Moderate RoB	Yes	56	IBT, insulin	396	• SC liraglutide 3.0 mg daily • Placebo	With T2DM	BMI ≥ 27 kg/m^2	None
SCALE Maintenance[62] Wadden, 2013 RCT Moderate RoB	Yes	56 + 12	Diet and exercise	422	• SC liraglutide 3.0 mg daily • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m^2 with HTN or dyslipidemia	≥ 5% weight loss during run-in

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Conditions
SCALE Obesity and Prediabetes[56,58,61,68] Pi-Sunyer, 2015 RCT Moderate RoB	Yes	56 + 104	Diet and exercise	3,731	• SC liraglutide 3.0 mg daily • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m² with HTN or dyslipidemia	None
S-LiTE[65] Lundgren, 2021 RCT Moderate RoB	No	52	Diet therapy	195[a]	• SC liraglutide 3.0 mg daily + exercise • SC liraglutide 3.0 mg daily • Placebo • Exercise	None	BMI ≥ 32 to 43 kg/m²	≥ 5% weight loss during run-in
STEP 8[55] Rubino, 2022[b] RCT Moderate RoB	Yes	68 + 7	Diet and exercise	338	• SC semaglutide 2.4 mg weekly • SC liraglutide 3.0 mg daily • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m² with ≥ 1 comorbidity	None
Youth								
Ellipse[71] Tamborlane, 2019 RCT Moderate RoB	Yes	26 + 26 open-label	Metformin, diet and exercise	135	SC liraglutide up to 1.8 mg daily Placebo	With T2DM	BMI ≥ 85th percentile	None
Kelly, 2020[60] RCT Moderate RoB	Yes	56 + 26	Diet and exercise	251	• SC liraglutide 3.0 mg daily • Placebo	With or without T2DM; ~32% to 33%[c]	BMI ≥ 30 kg/m² and ≥ 95th percentile	None

Notes. [a] Only liraglutide and placebo groups used for evidence in this report for a total sample size of 98; [b] Head-to-head trial included under liraglutide and semaglutide drug categories; [c] Prediabetes or T2DM

Abbreviations. BMI: body mass index; GDM: gestational diabetes; HTN: hypertension; IBT: intensive behavioral therapy; F/U: follow-up; OA: osteoarthritis; RCT: randomized controlled trial; RoB: risk of bias; SC: subcutaneous; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Overall, we assessed 12 of the 14 RCTs as moderate RoB,[55-57,59,60,62-65,69,71,72] and 2 as high RoB.[66,67]

- Six of the 7 RCTs in adults without diabetes were rated as moderate RoB primarily because of serious author and funding conflicts of interest,[55,56,62,63,65] and 1 with some additional concerns around small sample size and limited reporting of results.[64] The RCT in postpartum individuals with a history of GDM was rated as high risk bias because of the high rate of

attrition (> 50% at 84 weeks) and limited reporting of results in addition to author and funding conflicts of interest.[66]

- The SCALE Diabetes and SCALE Insulin RCTs in people with T2DM were rated as having moderate RoB, primarily because of study funding and author conflicts of interest. [57,59]
- In studies of T1DM, the LIRA-1 and LIDO trials were rated as having moderate RoB because of author and funding conflicts of interest[70] and very low sample size,[72] respectively; the other study was rated as high RoB with large and disproportionate attrition in addition to author and funding conflicts of interest.[67]
- Both studies in youth were rates as moderate RoB primarily because of serious author and funding conflicts of interest.[60,71]

Adults

Weight Outcomes

Summary of Findings (GRADE)

All pooled estimates demonstrate statistical differences in favor of liraglutide (Table 6). The CoE ranged from low to moderate, depending on the outcome, indicating some levels of uncertainty for all outcomes.

Table 6. Certainty of Evidence (GRADE) for Weight Outcomes: Liraglutide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
7 RCTs[55-57,59,62,63,66] N = 5,864[a]	●●○○ Low	Participants randomized to liraglutide lost a significantly greater percentage of body weight compared to placebo, but less than what is considered clinically meaningful MD, -4.61% (95% CI, -5.44 to -3.78); $P < .001$	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision • CI crosses over clinically meaningful change of ≥ 5%
Change in body weight (kg)			
8 RCTs[55,56,62,64-67,69] N = 4,777[a]	●●●○ Moderate	Participants randomized to liraglutide lost significantly more body weight, in kg, compared to placebo MD, -5.58 kg (95% CI, -6.00 to -5.15); $P < .001$	Downgraded: 1 level for RoB • Author and funding CoI
Change in BMI (kg/m^2)			
5 RCTs[56,57,62,64,66] N = 5,129	●●○○ Low	Participants randomized to liraglutide significantly reduced their BMI compared to placebo MD, -1.82 kg/m^2 (95% CI, -1.95 to -1.68); $P < .001$	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Considerable heterogeneity

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Proportion with ≥ 5% weight loss			
7 RCTs[56,57,59,62-65] N = 5,817[a]	●●○○ Low	Participants randomized to liraglutide were more likely to lose at least 5% body weight compared to placebo RR, 2.04 (95% CI, 1.61 to 2.57); $P <$ .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Considerable heterogeneity
Proportion with ≥ 10% weight loss			
8 RCTs[55-57,59,62-65] N = 6,012[a]	●●●○ Moderate	Participants randomized to liraglutide were more likely to lose at least 10% body weight compared to placebo RR, 2.66 (95% CI, 2.00 to 3.53); $P <$ .001	Downgraded: 1 level for RoB • Author and funding CoI

Note. [a] Sample used in meta-analysis is smaller than total number randomized, although all continuous measures include full sample set according to publication.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of 7 RCTs,[55-57,59,62,63,66] individuals randomized to liraglutide lost significantly more percent body weight compared to individuals randomized to placebo (mean difference [MD], -4.61%; 95% confidence interval [CI], -5.44 to -3.78; Figure 2). The overall treatment effect does not meet the change in percent body weight considered clinically meaningful (at least 5% weight loss), although the CI suggests some may experience meaningful weight loss. There was also a substantial level of heterogeneity detected, suggesting the variation of study effects was beyond that of chance alone. No other studies measured this outcome for liraglutide in adults.

Figure 2. Change in Weight (%): Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.1.1 At least 1 year									
SCALE IBT	-7.5	7.9	142	-4	7.9	140	11.6%	-3.50 [-5.34, -1.66]	
SCALE Maintenance	-6.2	7.3	207	-0.2	7	206	15.6%	-6.00 [-7.38, -4.62]	
SCALE Ob&PreDM: 1 year	-8	6.7	2437	-2.6	5.7	1225	25.5%	-5.40 [-5.82, -4.98]	
STEP 8	-6.4	10.3	127	-1.9	9.7	85	6.9%	-4.50 [-7.23, -1.77]	
Subtotal (95% CI)			2913			1656	59.7%	-5.16 [-6.02, -4.30]	
Heterogeneity: Tau² = 0.33; Chi² = 5.15, df = 3 (P = 0.16); I² = 42%									
Test for overall effect: Z = 11.75 (P < 0.00001)									
1.1.2 With T2DM: 1 year									
SCALE Diabetes: pooled	-5.5	7.2	616	-2	7.2	211	18.2%	-3.50 [-4.63, -2.37]	
SCALE Insulin	-5.8	5.8	198	-1.5	5.8	198	18.0%	-4.30 [-5.44, -3.16]	
Subtotal (95% CI)			814			409	36.2%	-3.89 [-4.70, -3.09]	
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%									
Test for overall effect: Z = 9.52 (P < 0.00001)									
1.1.3 History of GDM: 1.5 years									
Elkind-Hirsch 2020	-7.2	7.69	35	-3.1	8.52	37	4.2%	-4.10 [-7.85, -0.35]	
Subtotal (95% CI)			35			37	4.2%	-4.10 [-7.85, -0.35]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.15 (P = 0.03)									
Total (95% CI)			3762			2102	100.0%	-4.61 [-5.44, -3.78]	
Heterogeneity: Tau² = 0.66; Chi² = 16.60, df = 6 (P = 0.01); I² = 64%									
Test for overall effect: Z = 10.87 (P < 0.00001)									
Test for subgroup differences: Chi² = 4.50, df = 2 (P = 0.11), I² = 55.6%									

Favors liraglutide   Favors placebo

Abbreviations. CI: confidence interval; GDM: gestational diabetes; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

In a pooled analysis of 8 RCTs,[55,56,62,64-67,69] individuals randomized to liraglutide lost significantly more body weight, as measured in kg, compared to individuals randomized to placebo, regardless of study duration (MD, -5.58 kg; 95% CI, -6.00 to -5.15; Figure 3). The impact of losing around 6 kg more than with placebo alone will vary depending on the baseline weight and overall height. Correlated with percent change in body weight, this effect is also likely not at clinically meaningful levels. The small crossover trial (LIDO)[72] also showed that people with T1DM randomized to liraglutide achieved a lower mean body weight than people randomized to placebo (post-treatment values, 83.4 kg with liraglutide versus 88.3 kg with placebo; treatment effect, -4.83 kg; *P* = .001).

Figure 3. Change in Weight (kg): Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean [kg]	SD [kg]	Total	Placebo Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.4.1 At least 1 year									
LOSEIT	-2.8	11.7	80	1.2	10.5	76	1.5%	-4.00 [-7.49, -0.51]	
SCALE Maintenance	-6	7.3	207	-0.1	6.9	206	9.4%	-5.90 [-7.27, -4.53]	
SCALE Ob&PreDM: 1 year	-8.4	7.3	2437	-2.8	6.5	1225	81.7%	-5.60 [-6.07, -5.13]	
S-LiTE	-0.7	8.7	49	6.1	9.05	49	1.4%	-6.80 [-10.31, -3.29]	
STEP 8	-6.8	11.4	127	-1.6	10.7	85	1.9%	-5.20 [-8.22, -2.18]	
Subtotal (95% CI)			2900			1641	95.9%	-5.61 [-6.04, -5.19]	
Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 4 (P = 0.83); I² = 0%									
Test for overall effect: Z = 25.63 (P < 0.00001)									
1.4.2 History of GDM: 1.5 years									
Elkind-Hirsch 2020	-6.4	7.8	35	-2.7	7.8	37	1.4%	-3.70 [-7.30, -0.10]	
Subtotal (95% CI)			35			37	1.4%	-3.70 [-7.30, -0.10]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.01 (P = 0.04)									
1.4.3 With T1DM: 1.8 mg at 6 months									
Ghanim 2020	-4.2	5.88	37	0.4	5.88	27	2.1%	-4.60 [-7.52, -1.68]	
LIRA-1; mc values	86.5	13.4	50	93.3	13.4	50	0.6%	-6.80 [-12.05, -1.55]	
Subtotal (95% CI)			87			77	2.7%	-5.12 [-7.67, -2.57]	
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%									
Test for overall effect: Z = 3.93 (P < 0.0001)									
Total (95% CI)			3022			1755	100.0%	-5.58 [-6.00, -5.15]	
Heterogeneity: Tau² = 0.00; Chi² = 3.22, df = 7 (P = 0.86); I² = 0%									
Test for overall effect: Z = 25.99 (P < 0.00001)									
Test for subgroup differences: Chi² = 1.20, df = 2 (P = 0.55), I² = 0%									

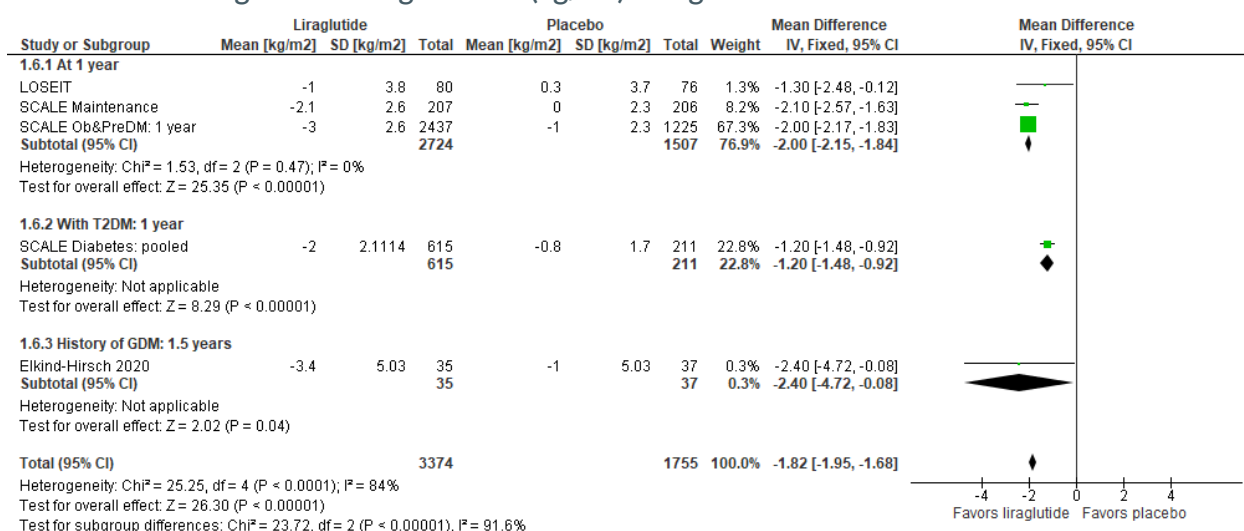-10 -5 0 5 10
Favors liraglutide   Favors placebo

Abbreviations. CI: confidence interval; df: degrees of freedom; GDM: gestational diabetes; IV: inverse variance; SD: standard deviation; T1DM: type 1 diabetes.

In a pooled analysis of 5 RCTs,[56,57,62,64,66] BMI was significantly reduced in individuals randomized to liraglutide compared to individuals randomized to placebo (MD, -1.82 kg/m^2; 95% CI, -1.95 to -1.68; Figure 4). Different populations (i.e., diabetes status) may have contributed to the considerable heterogeneity of effects across studies, but without more studies per subgroup, whether variation is due to population or chance alone remains unclear. The impact of reducing BMI further by nearly 2 kg/m^2 will vary depending on baseline BMI, and whether the change leads to a drop in class of obesity clinical severity (e.g., class 3 obesity of a BMI of 40 kg/m^2 or higher, to class 2).

The small crossover trial (LIDO)[72] also showed that people with T1DM randomized to liraglutide achieved a lower mean BMI than people randomized to placebo (post-treatment values, 28.5 kg/m^2 with liraglutide versus 30.2 kg/m^2 with placebo; treatment effect, -1.68 kg/m^2; P = .001).

Figure 4. Change in BMI (kg/m²): Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean [kg/m2]	SD [kg/m2]	Total	Placebo Mean [kg/m2]	SD [kg/m2]	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.6.1 At 1 year									
LOSEIT	-1	3.8	80	0.3	3.7	76	1.3%	-1.30 [-2.48, -0.12]	
SCALE Maintenance	-2.1	2.6	207	0	2.3	206	8.2%	-2.10 [-2.57, -1.63]	
SCALE Ob&PreDM: 1 year	-3	2.6	2437	-1	2.3	1225	67.3%	-2.00 [-2.17, -1.83]	
Subtotal (95% CI)			2724			1507	76.9%	-2.00 [-2.15, -1.84]	
Heterogeneity: Chi² = 1.53, df = 2 (P = 0.47); I² = 0%									
Test for overall effect: Z = 25.35 (P < 0.00001)									
1.6.2 With T2DM: 1 year									
SCALE Diabetes: pooled	-2	2.1114	615	-0.8	1.7	211	22.8%	-1.20 [-1.48, -0.92]	
Subtotal (95% CI)			615			211	22.8%	-1.20 [-1.48, -0.92]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 8.29 (P < 0.00001)									
1.6.3 History of GDM: 1.5 years									
Elkind-Hirsch 2020	-3.4	5.03	35	-1	5.03	37	0.3%	-2.40 [-4.72, -0.08]	
Subtotal (95% CI)			35			37	0.3%	-2.40 [-4.72, -0.08]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.02 (P = 0.04)									
Total (95% CI)			3374			1755	100.0%	-1.82 [-1.95, -1.68]	
Heterogeneity: Chi² = 25.25, df = 4 (P < 0.0001); I² = 84%									
Test for overall effect: Z = 26.30 (P < 0.00001)									
Test for subgroup differences: Chi² = 23.72, df = 2 (P < 0.00001), I² = 91.6%									

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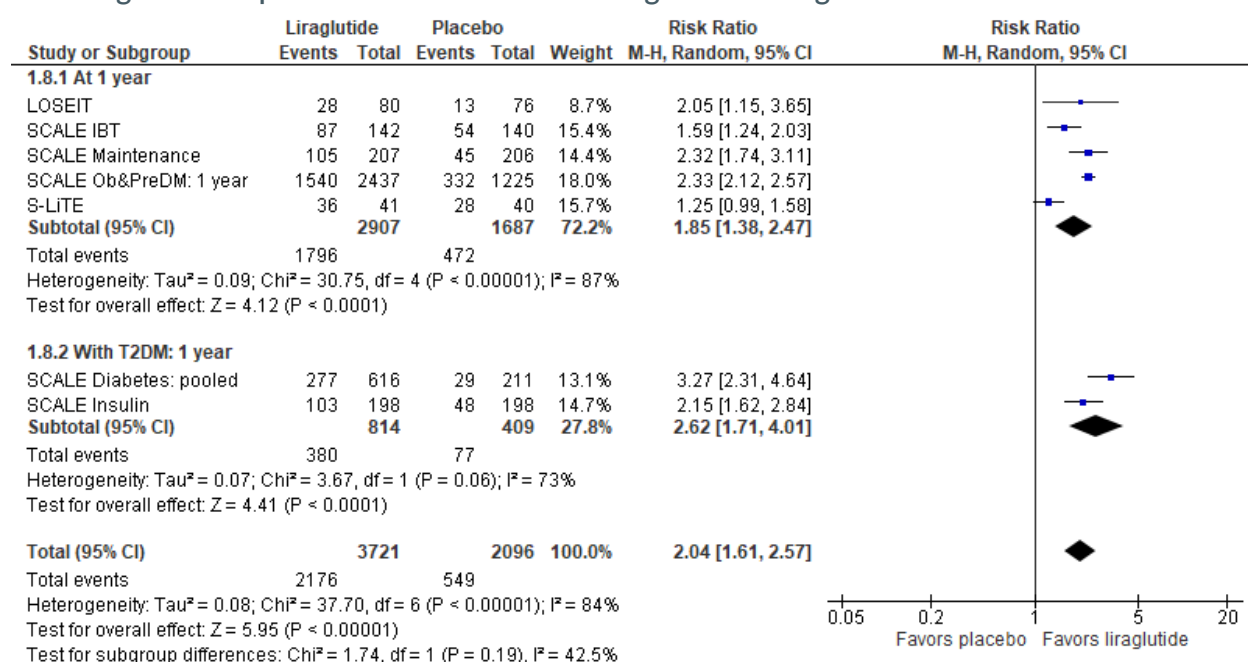Favors liraglutide   Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; df: degrees of freedom; GDM: gestational diabetes; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

In a pooled analysis of 7 RCTs,[56,57,59,62-65] individuals randomized to liraglutide were significantly more likely to lose at least 5% of their initial weight compared to individuals randomized to placebo (RR, 2.04; 95% CI, 1.61 to 2.57; Figure 5). There was also considerable heterogeneity detected overall and within population subgroups, suggesting the variation between the study effects was beyond that of chance alone. The STEP 8[55] study by Rubino and colleagues analyzed this measure as exploratory only; we did not include this data in the report.

The proportion of individuals who lost 5% or more body weight from baseline values (which is considered a clinically meaningful level of weight loss) was 58.5% with liraglutide and 26.2% with placebo across all studies included in the meta-analysis.[56,57,59,62-65]

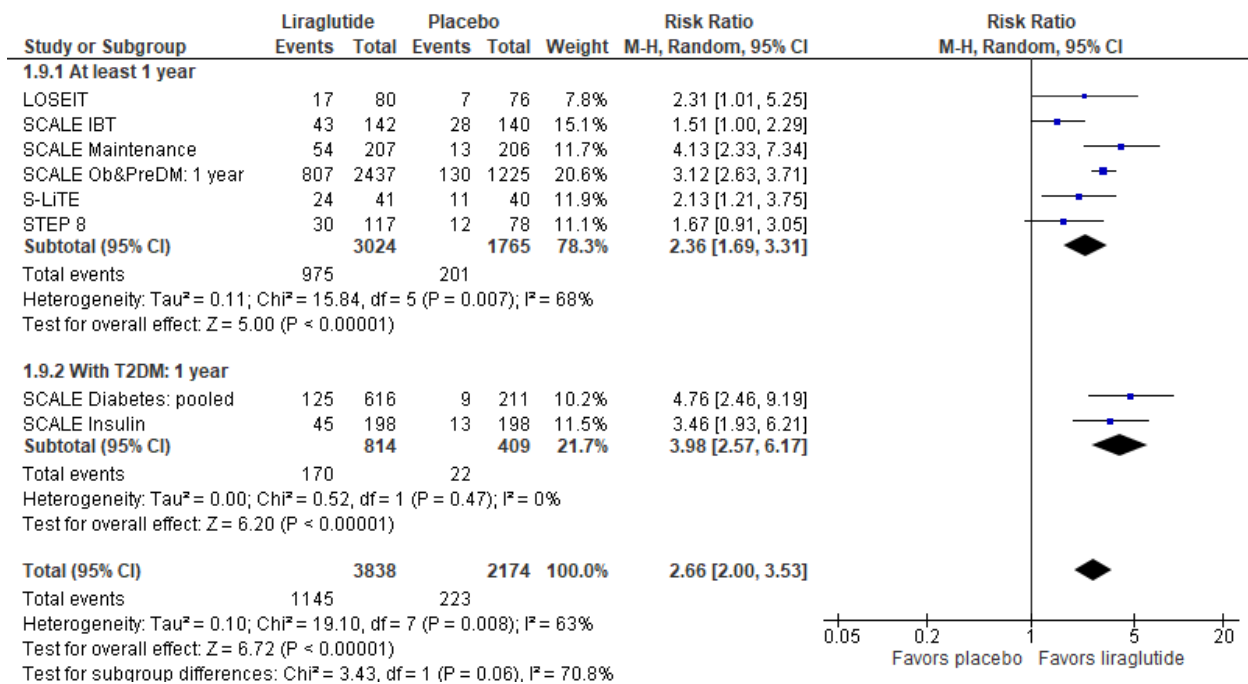## Figure 5. Proportion With at Least 5% Weight Loss: Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 At 1 year						
LOSEIT	28	80	13	76	8.7%	2.05 [1.15, 3.65]
SCALE IBT	87	142	54	140	15.4%	1.59 [1.24, 2.03]
SCALE Maintenance	105	207	45	206	14.4%	2.32 [1.74, 3.11]
SCALE Ob&PreDM: 1 year	1540	2437	332	1225	18.0%	2.33 [2.12, 2.57]
S-LiTE	36	41	28	40	15.7%	1.25 [0.99, 1.58]
Subtotal (95% CI)		2907		1687	72.2%	1.85 [1.38, 2.47]
Total events	1796		472			
Heterogeneity: Tau² = 0.09; Chi² = 30.75, df = 4 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
1.8.2 With T2DM: 1 year						
SCALE Diabetes: pooled	277	616	29	211	13.1%	3.27 [2.31, 4.64]
SCALE Insulin	103	198	48	198	14.7%	2.15 [1.62, 2.84]
Subtotal (95% CI)		814		409	27.8%	2.62 [1.71, 4.01]
Total events	380		77			
Heterogeneity: Tau² = 0.07; Chi² = 3.67, df = 1 (P = 0.06); I² = 73%						
Test for overall effect: Z = 4.41 (P < 0.0001)						
Total (95% CI)		3721		2096	100.0%	2.04 [1.61, 2.57]
Total events	2176		549			
Heterogeneity: Tau² = 0.08; Chi² = 37.70, df = 6 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 5.95 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.74, df = 1 (P = 0.19), I² = 42.5%						

Risk Ratio M-H, Random, 95% CI: scale 0.05, 0.2, 1, 5, 20. Favors placebo — Favors liraglutide.

Abbreviations. CI: confidence interval; T2DM: type 2 diabetes.

In a pooled analysis of 8 RCTs,[55-57,59,62-65] individuals randomized to liraglutide were significantly more likely to lose at least 10% of their initial weight compared to those who received placebo (RR, 2.66; 95% CI, 2.00 to 3.53; Figure 6). While the heterogeneity of effects between studies was moderate, we did not downgrade CoE for inconsistency because of the relatively large overall effect and no heterogeneity in 1 subpopulation. No other studies reported this outcome.

The proportion of individuals who lost 10% or more body weight from baseline values (more than a clinically meaningful amount of weight loss) was 29.8% with liraglutide and 10.3% with placebo across all studies included in the meta-analysis.[55-57,59,62-65]
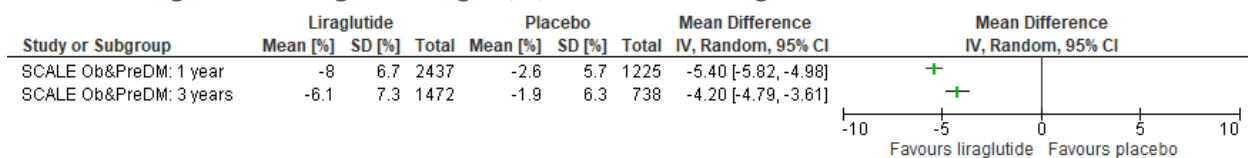
Figure 6. Proportion With at Least 10% Weight Loss: Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 At least 1 year						
LOSEIT	17	80	7	76	7.8%	2.31 [1.01, 5.25]
SCALE IBT	43	142	28	140	15.1%	1.51 [1.00, 2.29]
SCALE Maintenance	54	207	13	206	11.7%	4.13 [2.33, 7.34]
SCALE Ob&PreDM: 1 year	807	2437	130	1225	20.6%	3.12 [2.63, 3.71]
S-LiTE	24	41	11	40	11.9%	2.13 [1.21, 3.75]
STEP 8	30	117	12	78	11.1%	1.67 [0.91, 3.05]
Subtotal (95% CI)		3024		1765	78.3%	2.36 [1.69, 3.31]
Total events	975		201			

Heterogeneity: Tau² = 0.11; Chi² = 15.84, df = 5 (P = 0.007); I² = 68%
Test for overall effect: Z = 5.00 (P < 0.00001)

1.9.2 With T2DM: 1 year						
SCALE Diabetes: pooled	125	616	9	211	10.2%	4.76 [2.46, 9.19]
SCALE Insulin	45	198	13	198	11.5%	3.46 [1.93, 6.21]
Subtotal (95% CI)		814		409	21.7%	3.98 [2.57, 6.17]
Total events	170		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 6.20 (P < 0.00001)

Total (95% CI)		3838		2174	100.0%	2.66 [2.00, 3.53]
Total events	1145		223			

Heterogeneity: Tau² = 0.10; Chi² = 19.10, df = 7 (P = 0.008); I² = 63%
Test for overall effect: Z = 6.72 (P < 0.00001)
Test for subgroup differences: Chi² = 3.43, df = 1 (P = 0.06), I² = 70.8%

[Forest plot axis: 0.05 0.2 1 5 20; Favors placebo — Favors liraglutide]

Abbreviations. CI: confidence interval; T2DM: type 2 diabetes.

Only 1 RCT for liraglutide, the SCALE Obesity and Prediabetes study,[56,58] had longer-term weight change data; these results were not included in the assessment of CoE. This RCT followed a subgroup of individuals with prediabetes at baseline; participants continued to receive liraglutide or placebo through 160 weeks.[58] People did regain some weight at 3 years compared to 1 year (MD in percent change in weight declined from -5.4% at 56 weeks to -4.2% at 160 weeks),[56,58] but the difference was small and did not reach baseline values (Figure 7).

Figure 7. Change in Weight (%) Over Time: Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI
SCALE Ob&PreDM: 1 year	-8	6.7	2437	-2.6	5.7	1225	-5.40 [-5.82, -4.98]
SCALE Ob&PreDM: 3 years	-6.1	7.3	1472	-1.9	6.3	738	-4.20 [-4.79, -3.61]

[Forest plot axis: -10 -5 0 5 10; Favours liraglutide — Favours placebo]

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

The same pattern of weight changes from 1 to 3 years was reflected in the change in weight, as measured by kg, and change in BMI; people did regain weight, but on average, did not return to baseline values (Figure 8 and 9).[56,58]

Figure 8. Change in Weight (kg) Over Time: Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean [kg]	SD [kg]	Total	Placebo Mean [kg]	SD [kg]	Total	Mean Difference IV, Random, 95% CI
SCALE Ob&PreDM: 1 year	-8.4	7.3	2437	-2.8	6.5	1225	-5.60 [-6.07, -5.13]
SCALE Ob&PreDM: 3 years	-6.5	8.1	1472	-2	7.3	738	-4.50 [-5.17, -3.83]

Mean Difference IV, Random, 95% CI: scale from -10 to 10; Favors liraglutide / Favors placebo
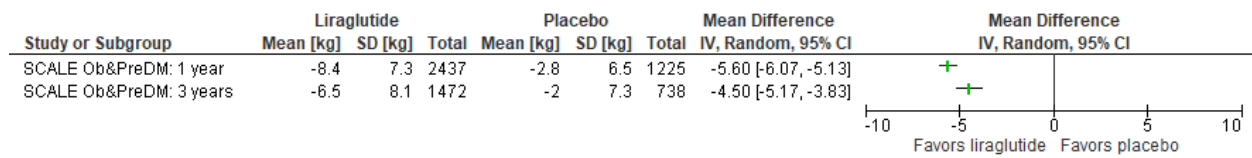
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

Figure 9. Change in BMI (kg/m^2) Over Time: Liraglutide vs. Placebo in Adults
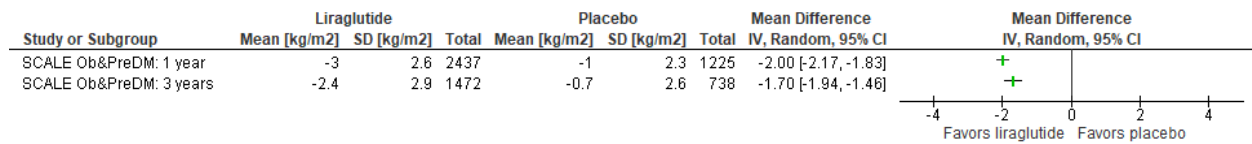
Study or Subgroup	Liraglutide Mean [kg/m2]	SD [kg/m2]	Total	Placebo Mean [kg/m2]	SD [kg/m2]	Total	Mean Difference IV, Random, 95% CI
SCALE Ob&PreDM: 1 year	-3	2.6	2437	-1	2.3	1225	-2.00 [-2.17, -1.83]
SCALE Ob&PreDM: 3 years	-2.4	2.9	1472	-0.7	2.6	738	-1.70 [-1.94, -1.46]

Mean Difference IV, Random, 95% CI: scale from -4 to 4; Favors liraglutide / Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

Comorbidity Risk Factor Outcomes

Summary of Findings (GRADE)

All pooled estimates demonstrate statistical differences in favor of liraglutide (Table 7). The CoE ranged from low to moderate, depending on the outcome, indicating some levels of uncertainty for all outcomes.

Table 7. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Liraglutide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
10 RCTs[55-57,59,62,63,65-67,69] N = 6,125[a]	●●●○ Moderate	Participants randomized to liraglutide had a small but significant reduction in SBP compared to placebo; this difference is not considered clinically meaningful MD, -2.89 mmHg (95% CI, -3.54 to -2.24); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI
Change in LDL cholesterol			
8 RCTs[55-57,62,63,65,66,69] N = 5,701[a]	●●●○ Moderate	Participants randomized to liraglutide had a small but significant reduction in LDL cholesterol compared to placebo; this difference is likely not clinically meaningful SMD, -0.12 (95% CI, -0.17 to -0.06); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in HbA1c (%)			
8 RCTs[55-57,59,62,63,67,69] N = 5,955[a]	●●○○ Low	Participants randomized to liraglutide had a significant, and clinically meaningful, reduction in percent HbA1c compared to placebo MD, -0.33% (95% CI, -0.44 to -0.21); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision • Some heterogeneity and CI crosses clinically meaningful decrease of 0.3%

Note. [a] Sample used in meta-analysis is smaller than total number randomized, although all continuous measures include full sample set according to publication.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; HbA1c: hemoglobin A1c protein; LDL: low-density lipoprotein; MA: meta-analysis; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; SBP: systolic blood pressure; SMD: standardized mean difference.

Detailed Findings

In a pooled analysis of 10 RCTs, [55-57,59,62,63,65-67,69] individuals randomized to liraglutide had a significantly greater reduction in SBP compared to individuals randomized to placebo (MD, -2.89 mmHg; 95% CI, -3.54 to -2.24; Figure 10). While there was no notable heterogeneity detected in the overall effect, some smaller studies found insignificant results; whether the differences in effect are dependent on population can only be assessed with more studies and larger sample sizes. This overall treatment effect is less than the change in SBP considered clinically meaningful (at least 5.0 mmHg decrease).

The small crossover trial (LIDO)[72] also showed that people with T1DM randomized to liraglutide achieved a lower mean SBP compared to people randomized to placebo (post-treatment values, 116 mmHg with liraglutide versus 122 mmHg with placebo; treatment effect, -6 mmHg; *P* = .007).

Figure 10. Change in Systolic Blood Pressure (mmHg): Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean [mm Hg]	SD [mm Hg]	Total	Placebo Mean [mm Hg]	SD [mm Hg]	Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 At least 1 year								
SCALE IBT	-2.8	11.6	142	-0.6	11.6	140	5.8%	-2.20 [-4.91, 0.51]
SCALE Maintenance	0.2	12	207	2.8	10.4	206	9.1%	-2.60 [-4.77, -0.43]
SCALE Ob&PreDM: 1 year	-4.2	12.2	2437	-1.5	12.4	1225	59.4%	-2.70 [-3.55, -1.85]
S-LiTE	-1.1	15	49	4.4	15	49	1.2%	-5.50 [-11.44, 0.44]
STEP 8	-2.9	13.7	127	3.2	13.4	85	3.1%	-6.10 [-9.81, -2.39]
Subtotal (95% CI)			**2962**			**1705**	**78.6%**	**-2.84 [-3.63, -2.06]**
Heterogeneity: Tau² = 0.03; Chi² = 4.10, df = 4 (P = 0.39); I² = 2%								
Test for overall effect: Z = 7.11 (P < 0.00001)								
1.10.2 With T2DM: 1 year								
SCALE Diabetes: pooled	-3	13.2	615	-0.4	13.4	211	9.8%	-2.60 [-4.69, -0.51]
SCALE Insulin	-5.6	12.4	198	-1.6	12.4	198	7.1%	-4.00 [-6.44, -1.56]
Subtotal (95% CI)			**813**			**409**	**16.9%**	**-3.19 [-4.78, -1.60]**
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 3.94 (P < 0.0001)								
1.10.3 History of GDM: 1.5 years								
Elkind-Hirsch 2020	122	12	35	123	12	37	1.4%	-1.00 [-6.55, 4.55]
Subtotal (95% CI)			**35**			**37**	**1.4%**	**-1.00 [-6.55, 4.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.72)								
1.10.4 With T1DM: 6 months								
Ghanim 2020	-5	9.2	37	-2	9.2	27	2.0%	-3.00 [-7.56, 1.56]
LIRA-1	125	17.6	50	130	14.1	50	1.1%	-5.00 [-11.25, 1.25]
Subtotal (95% CI)			**87**			**77**	**3.1%**	**-3.70 [-7.38, -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%								
Test for overall effect: Z = 1.96 (P = 0.05)								
Total (95% CI)			**3897**			**2228**	**100.0%**	**-2.89 [-3.54, -2.24]**
Heterogeneity: Tau² = 0.00; Chi² = 5.88, df = 9 (P = 0.75); I² = 0%								
Test for overall effect: Z = 8.68 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.78, df = 3 (P = 0.85), I² = 0%								

Favors liraglutide   Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

One RCT for liraglutide, the SCALE Obesity and Prediabetes study,[56,58] included an extension period that followed a subgroup of individuals with prediabetes at baseline; participants continued to receive liraglutide or placebo through 160 weeks. Systolic blood pressure rebounded slightly from 1 to 3 years in both liraglutide and placebo groups, with no change in MD over time.[56,58] SBP did not reach baseline values with liraglutide at 3 years (Figure 11).[56,58]

Figure 11. Change in Systolic Blood Pressure (mmHg) Over Time: Liraglutide in Adults
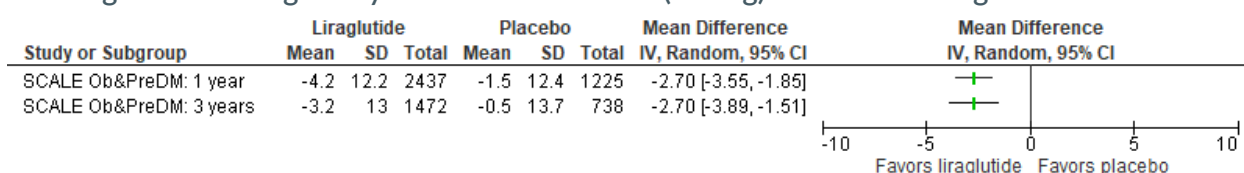
Study or Subgroup	Liraglutide Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
SCALE Ob&PreDM: 1 year	-4.2	12.2	2437	-1.5	12.4	1225	-2.70 [-3.55, -1.85]
SCALE Ob&PreDM: 3 years	-3.2	13	1472	-0.5	13.7	738	-2.70 [-3.89, -1.51]

Favors liraglutide   Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 8 RCTs,[55-57,62,63,65,66,69] individuals randomized to liraglutide experienced a small but significantly greater reduction in LDL cholesterol compared to individuals randomized to placebo (standardized mean difference [SMD], -0.12; 95% CI, -0.17 to -0.06; Figure 12).

Figure 12. Change in LDL Cholesterol: Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.12.1 At least 1 year								
SCALE IBT	-0.04	0.6	142	0.04	0.6	140	5.6%	-0.13 [-0.37, 0.10]
SCALE Maintenance	0.2	0.6	207	0.3	0.6	206	8.1%	-0.17 [-0.36, 0.03]
SCALE Ob&PreDM: 1 year	-3	21.2	2473	-1	21.2	1225	64.7%	-0.09 [-0.16, -0.03]
S-LiTE	0.2	0.7	49	0.3	0.5	49	1.9%	-0.16 [-0.56, 0.23]
STEP 8	0.9	30.2	127	-1.1	47.8	85	4.0%	0.05 [-0.22, 0.33]
Subtotal (95% CI)			**2998**			**1705**	**84.3%**	**-0.10 [-0.16, -0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 3.21 (P = 0.001)

1.12.2 With T2DM: 1 year								
SCALE Diabetes: pooled	-0.6	36.4	615	5	27.3	211	12.4%	-0.16 [-0.32, -0.01]
Subtotal (95% CI)			**615**			**211**	**12.4%**	**-0.16 [-0.32, -0.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)

1.12.3 History of GDM: 1.5 years								
Elkind-Hirsch 2020	-0.18	0.21	35	-0.08	0.21	37	1.4%	-0.47 [-0.94, -0.00]
Subtotal (95% CI)			**35**			**37**	**1.4%**	**-0.47 [-0.94, -0.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)

1.12.4 With T1DM: 6 months								
LIRA-1	2.4	1.0556	50	2.7	1.0556	50	2.0%	-0.28 [-0.68, 0.11]
Subtotal (95% CI)			**50**			**50**	**2.0%**	**-0.28 [-0.68, 0.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)

Total (95% CI)			**3698**			**2003**	**100.0%**	**-0.12 [-0.17, -0.06]**

Heterogeneity: Tau² = 0.00; Chi² = 5.39, df = 7 (P = 0.61); I² = 0%
Test for overall effect: Z = 4.10 (P < 0.0001)
Test for subgroup differences: Chi² = 3.56, df = 3 (P = 0.31), I² = 15.8%

Favors liraglutide   Favors placebo (-1, -0.5, 0, 0.5, 1)

Abbreviations. CI: confidence interval; GDM: gestational diabetes; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

To get a sense for whether the MD in change in LDL cholesterol with liraglutide compared to placebo was clinically meaningful, we pooled results from 5 RCTs[62,63,65,66,69] that reported results in units that could be compared to clinically meaningful changes reported in the literature. The overall effect in these 5 RCTs (MD, -0.10 mmol/L; 95% CI, -0.16 to -0.04; Figure 13) was *less than* the 1 mmol/L reduction that has been reported as associated with a meaningful reduction of major cardiovascular events.[62,63,65,66,69]

Figure 13. Change in LDL Cholesterol (mmol/L): Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Elkind-Hirsch 2020	-0.18	0.21	35	-0.08	0.21	37	42.5%	-0.10 [-0.20, -0.00]
LIRA-1	2.4	1.0556	50	2.7	1.0556	50	2.3%	-0.30 [-0.71, 0.11]
SCALE IBT	-0.04	0.578	142	0.04	0.578	140	22.0%	-0.08 [-0.21, 0.05]
SCALE Maintenance	0.2	0.6	207	0.3	0.6	206	29.9%	-0.10 [-0.22, 0.02]
S-LiTE	0.2	1.0444	49	0.3	0.6963	49	3.2%	-0.10 [-0.45, 0.25]
Total (95% CI)			**483**			**482**	**100.0%**	**-0.10 [-0.16, -0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 4 (P = 0.91); I² = 0%
Test for overall effect: Z = 3.11 (P = 0.002)

Favors liraglutide   Favors placebo (-1, -0.5, 0, 0.5, 1)

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

Findings from RCTs not included in the meta-analysis showed a similar lack of meaningful change with liraglutide on LDL cholesterol, when compared with placebo.

- The small crossover trial (LIDO)[72] showed no difference in change in LDL cholesterol in people with T1DM randomized to either liraglutide or placebo (post-treatment values 2.08 mmol/L with liraglutide versus 2.16 mmol/L with placebo; treatment effect, -0.09 mmol/L; *P* ≥ 05).
- The SCALE Insulin[59] trial in participants with T2DM found no difference in LDL cholesterol treatment ratios (liraglutide/placebo) between liraglutide and placebo groups (0.97 with liraglutide versus 1.01 with placebo; OR, 0.96; 95% CI, 0.91 to 1.01; *P* = .10).

In a pooled analysis of 8 RCTs,[55-57,59,62,63,67,69] individuals randomized to liraglutide experienced a significantly greater reduction in percent HbA1c compared to those randomized to placebo (MD, -0.33%; 95% CI, -0.44 to -0.21; Figure 14). The overall treatment effect is greater than what is considered clinically meaningful (a decrease of at least 0.3%). The magnitude of the effect was driven primarily by 2 RCTs in people with T2DM with higher baseline HbA1c levels, most of whom were not being treated with insulin,[57,59] which likely contributed to the majority of the heterogeneity across effects. (When the studies of T2DM are removed from the analysis, the I^2 value [the percentage of variation across studies that is due to heterogeneity and not chance] drops from 93% to 42%). Mean HbA1c levels still improved with liraglutide compared to placebo in studies of people without diabetes[55,56,62,63] (subgroup MD, -0.2%; 95% CI, -0.25 to -0.15), despite baseline HbA1c levels being within normal limits (< 5.7%) across the 4 studies (see Appendix B, Table B2, for participant baseline characteristics).

Figure 14. Change in HbA1c (%): Liraglutide vs. Placebo in Adults

Study or Subgroup	Liraglutide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI
1.14.1 At least 1 year								
SCALE IBT	-0.2	0.3	142	-0.06	0.3	140	15.4%	-0.14 [-0.21, -0.07]
SCALE Maintenance	-0.1	0.3	207	0.1	0.3	206	15.7%	-0.20 [-0.26, -0.14]
SCALE Ob&PreDM: 1 year	-0.3	0.3	2437	-0.06	0.3	1225	16.3%	-0.24 [-0.26, -0.22]
STEP 8	-0.1	0.6	127	0.1	0.5	85	12.9%	-0.20 [-0.35, -0.05]
Subtotal (95% CI)			2913			1656	60.4%	-0.20 [-0.25, -0.15]
Heterogeneity: Tau² = 0.00; Chi² = 8.40, df = 3 (P = 0.04); I² = 64%								
Test for overall effect: Z = 7.96 (P < 0.00001)								
1.14.2 With T2DM: 1 year								
SCALE Diabetes: pooled	-1.2	0.9	615	-0.3	0.9	211	13.2%	-0.90 [-1.04, -0.76]
SCALE Insulin	-1.1	1.3	198	-0.6	1.3	198	9.2%	-0.50 [-0.76, -0.24]
Subtotal (95% CI)			813			409	22.4%	-0.71 [-1.11, -0.32]
Heterogeneity: Tau² = 0.07; Chi² = 7.20, df = 1 (P = 0.007); I² = 86%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
1.14.3 With T1DM: 6 months								
Ghanim 2020	-0.4	0.2	37	-0.1	0.7	27	8.7%	-0.30 [-0.57, -0.03]
LIRA-1	-0.5	0.7	50	-0.3	0.7	50	8.6%	-0.20 [-0.47, 0.07]
Subtotal (95% CI)			87			77	17.3%	-0.25 [-0.44, -0.06]
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%								
Test for overall effect: Z = 2.54 (P = 0.01)								
Total (95% CI)			3813			2142	100.0%	-0.33 [-0.44, -0.21]
Heterogeneity: Tau² = 0.02; Chi² = 98.64, df = 7 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 5.47 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.66, df = 2 (P = 0.04), I² = 70.0%								

Favors liraglutide   Favors placebo

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Findings from RCTs not included in the meta-analysis showed more mixed results for HbA1c with liraglutide, when compared with placebo.

- The S-LiTE study by Lundgren and colleagues also demonstrated a greater improvement in HbA1c with liraglutide, as measured in units of mmol/mol (decrease of 1.4 mmol/mol with liraglutide versus increase of 0.8 mmol/mol with placebo; treatment effect, -2.2 mmol/mol [approximately -2.4% change in HbA1c]; 95% CI, -3.2 to -1.2).[65]
- The small crossover trial (LIDO) showed no difference in change in percent HbA1c in people with T1DM randomized to either liraglutide or placebo (post-treatment values 7.1% [SD, 0.1] with liraglutide versus 7.2% [SD, 0.2]; 2.16 mmol/L with placebo; treatment effect, -0.09%; P > .05).[72]

The SCALE Obesity and Prediabetes study also measured HbA1c during the extension period that followed a subgroup of individuals, with prediabetes at baseline, who received liraglutide or placebo through 160 weeks.[56,58] Percent HbA1c rebounded slightly from 1 to 3 years in both liraglutide and placebo groups, without notable change in MD over time (Figure 15).[56,58] Percent HbA1c did not reach baseline values with liraglutide at 3 years.

Figure 15. Change in HbA1c (%) Over Time: Liraglutide in Adults
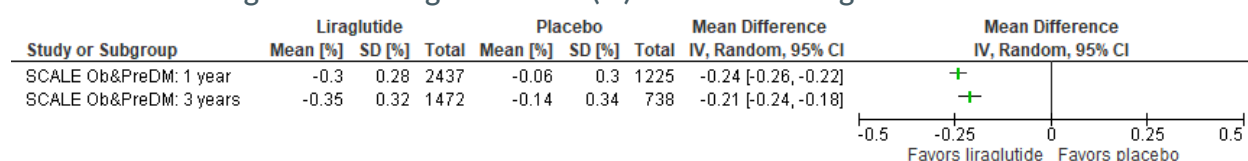
Study or Subgroup	Liraglutide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI
SCALE Ob&PreDM: 1 year	-0.3	0.28	2437	-0.06	0.3	1225	-0.24 [-0.26, -0.22]
SCALE Ob&PreDM: 3 years	-0.35	0.32	1472	-0.14	0.34	738	-0.21 [-0.24, -0.18]

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation.

Quality of Life Outcomes

Quality of life was measured in studies of people without diabetes, and in studies of people with T2DM (Table 8); QoL was not measured in people with T1DM nor in postpartum individuals with a history of gestational diabetes.

Summary of Findings

Table 8. Certainty of Evidence (GRADE) for Quality of Life: Liraglutide vs. Placebo in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Quality of life			
6 RCTs[56,57,59,61,63-65,68] N = 5,509	●●○○ Low	In general, liraglutide may slightly improve physical function QoL in persons compared to placebo; whether change is clinically meaningful may depend on population	Downgraded: 1 level for RoB • Author and funding CoI 1 level for precision[a]

Note. [a] Precision not assessable.
Abbreviations. CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In the 6 RCTs reporting some measure of QoL,[56,57,59,61,63-65,68] liraglutide did not appear to be associated with a significant and consistent improvement in QoL when compared with placebo.

- In people without diabetes, the large SCALE Obesity and Prediabetes showed significant and clinically meaningful improvements in health-related QoL using the IWQoL-Lite total score with liraglutide compared to placebo at 56 weeks (OR of achieving meaningful improvement, 1.59; 95% CI, 1.35 to 1.88) and physical components summary scores of the SF-36 survey (OR, 1.60; 95% CI, 1.35 to 1.90)[56,61]; the mental component score of the SF-36 form improved, but not at meaningful levels. At 3 years, the subgroup of individuals with prediabetes on liraglutide continued to show improvements compared to those with prediabetes on placebo across all questionnaires except for the mental health summary component of the SF-36.[56,68]
- In 2 other studies in people without diabetes (SCALE IBT and S-LiTE), there were no differences between liraglutide and placebo groups in physical function QoL.[63,65]
- In people with knee osteoarthritis, the use of liraglutide did not result in improved measures of pain, other symptoms, or impact on daily life, when compared with placebo.[64]
- In people with T2DM, the SCALE Diabetes study showed a small but significant improvement with 3.0 mg liraglutide compared to placebo using the IWQoL-Lite total score questionnaire (difference from placebo not considered clinically meaningful),[57] and the SCALE Insulin study showed no difference in physical function QoL.[59]

Safety Outcomes

Studies for liraglutide included overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE (Table 9).

Summary of Findings (GRADE)

Table 9. Certainty of Evidence (GRADE) for Safety Outcomes: Liraglutide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
11 RCTs[55-57,59,62-67,69] N = 6,480	●●●○ Moderate	Participants randomized to liraglutide were significantly more likely to withdraw due to an AE compared to individuals randomized to placebo RR, 2.20 (95% CI, 1.75 to 2.76); P < .001	Downgraded: 1 level for RoB • Author and funding CoI

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of 11 RCTs,[55-57,59,62-67,69] individuals randomized to liraglutide were more likely to experience an AE that led to study withdrawal compared to individuals randomized to placebo (RR, 2.20; 95% CI, 1.75 to 2.76; Figure 16). The moderate heterogeneity of effects within the subgroup of people without T2DM should be noted but was not enough to downgrade CoE. In the small crossover trial (LIDO), no participants withdrew because of AEs.

The proportion of withdrawals due to AEs was 9.4% with liraglutide and 4.1% with placebo across all studies in the meta-analysis.[55-57,59,62-67,69]

Figure 16. Proportion of Withdrawals Due to Adverse Events: Liraglutide in Adults

Study or Subgroup	Liraglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 At least 1 year						
LOSEIT	10	80	4	76	4.1%	2.38 [0.78, 7.25]
SCALE IBT	12	142	6	140	5.6%	1.97 [0.76, 5.11]
SCALE Maintenance	18	212	18	210	13.0%	0.99 [0.53, 1.85]
SCALE Ob&PreDM: 1 year	246	2487	47	1244	52.9%	2.62 [1.93, 3.55]
S-LiTE	1	49	0	49	0.5%	3.00 [0.13, 71.89]
STEP 8	16	127	3	85	3.5%	3.57 [1.07, 11.88]
Subtotal (95% CI)		3097		1804	79.7%	2.04 [1.32, 3.15]
Total events	303		78			
Heterogeneity: Tau² = 0.10; Chi² = 8.31, df = 5 (P = 0.14); I² = 40%						
Test for overall effect: Z = 3.21 (P = 0.001)						
1.18.2 With T2DM: 1 year						
SCALE Diabetes: pooled	57	632	7	212	8.6%	2.73 [1.27, 5.90]
SCALE Insulin	15	198	6	198	5.9%	2.50 [0.99, 6.31]
Subtotal (95% CI)		830		410	14.5%	2.63 [1.46, 4.76]
Total events	72		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 3.21 (P = 0.001)						
1.18.3 History of GDM: 1.5 years						
Elkind-Hirsch 2020	4	78	3	75	2.4%	1.28 [0.30, 5.54]
Subtotal (95% CI)		78		75	2.4%	1.28 [0.30, 5.54]
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.18.4 With T1DM: 1.8 mg at 6 months						
Ghanim 2020	3	37	2	27	1.7%	1.09 [0.20, 6.11]
LIRA-1	3	50	2	50	1.7%	1.50 [0.26, 8.60]
Subtotal (95% CI)		87		77	3.4%	1.28 [0.38, 4.35]
Total events	6		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.69)						
Total (95% CI)		4092		2366	100.0%	2.20 [1.75, 2.76]
Total events	385		98			
Heterogeneity: Tau² = 0.00; Chi² = 10.05, df = 10 (P = 0.44); I² = 1%						
Test for overall effect: Z = 6.82 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.65, df = 3 (P = 0.65), I² = 0%						

Risk Ratio M-H, Random, 95% CI — scale 0.01, 0.1, 1, 10, 100; Favors liraglutide Favors placebo

Abbreviations. CI: confidence interval; GDM: gestational diabetes; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

There were no differences in withdrawals due to AEs between the weekly 1.8 mg dose and weekly 3.0 mg dose in the SCALE Diabetes study in people with T2DM (Figure 17).[56]

Figure 17. Proportion of Withdrawals Due to Adverse Events by Dose: Liraglutide in Adults

Study or Subgroup	Liraglutide Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
SCALE Diabetes: 1.8 mg	18	211	7	212	2.58 [1.10, 6.06]
SCALE Diabetes: 3.0 mg	39	423	7	212	2.79 [1.27, 6.14]

Risk Ratio M-H, Random, 95% CI — scale 0.05, 0.2, 1, 5, 20; Favors liraglutide Favors placebo
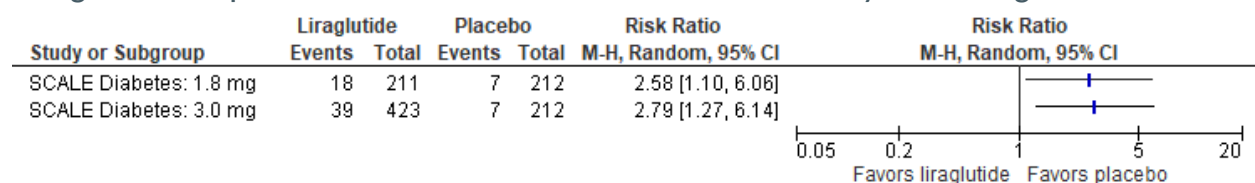
Abbreviations. CI: confidence interval.

In general, more people randomized to liraglutide experienced an AE or SAE compared to those randomized to placebo (Table 10).[55-57,59,62-67,69,72] The most frequent AEs included nausea, constipation, diarrhea, and vomiting. These common gastrointestinal AEs were also more frequently experienced by individuals who received liraglutide (see Appendix C, Tables C9 and C10, for details of AE outcomes for liraglutide). Many studies did not describe the conditions that designated an adverse event as serious, but in those that did, conditions of the gallbladder (e.g., cholecystitis, cholelithiasis) were more often reported.

Table 10. Summary of Adverse Events and Serious Adverse Events: Liraglutide in Adults

Study Name Author, Year		Adverse Events, % n of N			Serious Adverse Events, % n of N		
		Liraglutide	Placebo	P Value	Liraglutide	Placebo	P Value
Elkind-Hirsch, 2020[66]		38.5% 13 of 35[a]	19.0% 7 of 37[a]	NR	0	0	NR
Ghanim, 2020[67]		NR	NR	NR	0	0	NR
LIDO, Dubé, 2017[72]		NR	NR	NR	NR	NR	NR
LIRA-1 Dejgaard, 2016		90.0% 45 of 50	46.0% 23 of 50	NR	6.0% 3 of 50	4.0% 2 of 50	NR
LOSEIT[64] Gudbergsen, 2021		96.3% 77 of 80	93.4% 71 of 76	P ≥ .05	8.7% 7 of 80	13.1% 10 of 76	P ≥ .05
SCALE Diabetes[57] Davies, 2015	3.0 mg	92.9% 392 of 422	85.8% 182 of 212	NR	8.8% 37 of 422	6.1% 13 of 212	NR
	1.8 mg	90.5% 190 of 210		NR	8.6% 18 of 210		NR
SCALE IBT[63] Wadden, 2020		95.8% 136 of 142	88.6% 124 of 140	NR	4.2% 6 of 142	1.4% 2 of 140	NR
SCALE Insulin[59] Garvey, 2020		92.3% 180 of 195	88.8% 175 of 197	NR	8.2% 16 of 195	9.6% 19 of 197	NR
SCALE Maintenance[62] Wadden, 2013		91.5% 194 of 212	88.6% 186 of 210	NR	NR	NR	NR
SCALE Obesity and Prediabetes[56] Pi-Sunyer, 2015	58 weeks	80.3%[a] 1,992 of 2,481	63.3%[a] 786 of 1,242	NR	6.2% 154 of 2,481	5.0% 62 of 1,242	NR
	160 weeks	94.7%[a,b] 1,421 of 1,501	89.4%[a,b] 668 of 747	NR	15% 227 of 1,501	13% 96 of 747	NR
S-LiTE[65] Lundgren, 2021		95.9% 94 of 98	85.7% 42 of 49	NR	10.2% 10 of 98	4.1% 2 of 49	NR
STEP 8[55] Rubino, 2022		96.1% 122 of 127	95.3% 81 of 85	NR	11.0% 14 of 127	7.1% 6 of 85	NR

Notes. [a] Reported as total AEs where at least 5% of study cohort experienced a specific AE (e.g., injection site hematoma); [b] in subgroup of people with prediabetes at baseline.
Abbreviations. AE: adverse event; NR: not reported.

In people without diabetes, only 1 study reported deaths occurring during the randomization period[56]; the large SCALE Obesity and Prediabetes trial reported 1 death in the liraglutide group (cardiomegaly and hypertensive heart disease) and 2 deaths in the placebo group (1 death each from pulmonary fibrosis and cardiorespiratory arrest).[56] The SCALE Diabetes trial reported 1 death that occurred during the off-drug treatment phase (44 days off drug)[57]; the death was attributed to pulmonary embolism and thromboembolic stroke. There was no mention of deaths occurring during the 3 trials in people with T1DM.

Change in Medication Outcomes

Six studies of liraglutide measured changes in medication use for comorbid conditions
(Table 11).[56,57,59,67,69,72]

- The SCALE Obesity and Prediabetes study measured changes in medications for conditions of high blood pressure and dyslipidemia[56]
  - In people without diabetes, participants randomized to weekly 3.0 mg liraglutide were significantly more likely to decrease or stop use, and less likely to increase use, of medications for blood pressure and dyslipidemia after 56 weeks of treatment, compared to placebo[56]
  - The pattern of change in medication use was similar with liraglutide in the subgroup of people with prediabetes at baseline, after 108 weeks of treatment (no statistical tests for differences between treatment groups were reported)[56]
- The SCALE Diabetes study in people with T2DM[57] measured changes in oral glucose-lowering medications and found net improvements in medication use with liraglutide (more participants with liraglutide decreased or stopped use, and fewer increased use) compared with placebo
- Three studies of people with T1DM[67,69,72] and 1 RCT in people with T2DM[59] measured change in insulin use
  - In people with T2DM, the increase in total insulin use was significantly lower with weekly 3.0 mg liraglutide than with placebo[59]
  - In people with T1DM, people randomized to weekly 1.8 mg liraglutide achieved a significant reduction in net use of insulin compared with placebo in 1 RCT,[67] and lower post-treatment volume of total insulin in another RCT (this latter study, however, showed difference was not statistically significant after adjustments for weight)[69]

Table 11. Summary of Changes in Concomitant Medication Use: Liraglutide in Adults

Study Name Author, Year	Population	Decreased or Stopped Use		Increased Use		BG Difference
		Liraglutide	Placebo	Liraglutide	Placebo	
Change in blood pressure medication						
SCALE Obesity and Prediabetes[56] Pi-Sunyer, 2015	3.0 mg at 56 weeks; no diabetes	6.0% 146 of 2,437	3.8% 47 of 1,225	3.7% 90 of 2,437	5.7% 70 of 1,225	OR, 1.7 (95% CI, 1.3 to 2.1); P < .001
	3.0 mg at 108 weeks; with prediabetes	6.9% 101 of 1,472	3.8% 28 of 738	5.1% 75 of 1,472	8.7% 64 of 738	NR
Change in lipid-lowering medication						
SCALE Obesity and Prediabetes[56] Pi-Sunyer, 2015	3.0 mg at 56 weeks; no diabetes	1.5% 37 of 2,437	1.3% 16 of 1,225	2.1% 51 of 2,437	3.7% 45 of 1,225	OR, 1.5 (95% CI, 1.1 to 2.2); P = .02
	3.0 mg at 108 weeks; with prediabetes	2.4% 35 of 1,472	1.9% 14 of 738	5.2% 77 of 1,472	6.4% 47 of 738	NR

Study Name Author, Year	Population	Decreased or Stopped Use		Increased Use		BG Difference
		Liraglutide	Placebo	Liraglutide	Placebo	
Change in glucose-lowering medication						
SCALE Diabetes[57] Davies, 2015	3.0 mg at 56 weeks; with T2DM	13.1% 54 of 411	5.7% 12 of 211	5.1% 21 of 411	27% 57 of 211	OR, 5.63 (95% CI, 3.62 to 8.76); *P* < .001
	1.8 mg at 56 weeks; with T2DM	8.3% 17 of 204		9.3% 19 of 204		OR, 3.36 (95% CI, 2.07 to 5.47); *P* < .001
Change in insulin use						
SCALE Insulin[59] Garvey, 2020	3.0 mg at 56 weeks; with T2DM	NR	NR	2.8 units/day	17.8 units/day	MD. -15.0 units (95% CI, -22.0 to -8.0); *P* < .001
Ghanim, 2020[67]	1.8 mg at 26 weeks; with T1DM	Net mean, -0.03 units/kg	N/A	N/A	Net mean, +0.02 units/kg	*P* = .02
		Mean post-treatment value: liraglutide		Mean post-treatment value: placebo		BG difference
LIRA-1[69] Dejgaard, 2016	1.8 mg at 24 weeks; with T1DM	62.8 units/day (95% CI, 55.7 to 69.9)		74.0 units/day (95% CI, 66.9 to 81.1)		MD, -11.2 (95% CI, -21.2 to -1.2); *P* = .03
	Weight-adjusted values	0.7 units/kg/day (95% CI, 0.7 to 0.8)		0.8 units/kg/day (95% CI, 0.7 to 0.9)		MD, -0.1 (95% CI, -0.2 to 0.02); *P* =.12
LIDO[72] Dubé, 2017	1.8 mg at 24 weeks; with T1DM	66.7 units/day (SD, 11.9)		73.3 units/day (SD, 15.5)		MD, −6.72 (95% CI, NR); *P* > .05

Abbreviations. BG: between-group; CI: confidence interval; MD: mean difference; N/A: not applicable; NR: not reported; OR: odds ratio; SD: standard deviation; SEM: standard error of the mean; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Youth

Weight Outcomes

Summary of Findings (GRADE)

All estimates demonstrate statistical differences in favor of liraglutide in youth (Table 12). The CoE ranged from low to moderate, depending on the outcome, indicating some levels of uncertainty for all outcomes.

Table 12. Certainty of Evidence (GRADE) for Weight Outcomes: Liraglutide in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in BMI z/SD score			
2 RCTs[60,71] N = 386[a]	●●○○ Low	Youth randomized to liraglutide significantly reduced BMI z/SD scores compared to placebo; this difference is clinically meaningful according to some estimates, but not all MD, -0.21 SDs (95% CI, -0.31 to -0.11); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision • CI crossed over clinically meaningful change of 0.15 to 0.25 SDs
Change in BMI (%)			
1 RCT[60] N = 251	●●○○ Low	Adolescents randomized to liraglutide had significantly reduced percent BMI compared to placebo at a level just under what is considered clinically meaningful MD, -4.64% (95% CI, -7.12 to -2.16); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision • CI crossed over clinically meaningful change of ≥ 5%
Change in body weight (%)			
1 RCT[60] N = 251	●●●○ Moderate	Adolescents randomized to liraglutide lost a significantly greater percentage of body weight compared to placebo; measure not valid to assess for meaningful change in youth because change in weight depends on growth in height and development MD, -5.02% (95% CI, -7.63 to -2.41); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI
Change in BMI (kg/m^2)			
1 RCT[60] N = 251	●●●○ Moderate	Adolescents randomized to liraglutide had significantly reduced BMI levels compared to placebo; correlated with percent change in BMI, and likely not at meaningful levels MD, -1.58 kg/m^2 (95% CI, -2.47 to -0.69); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI
Proportion with ≥ 5% weight loss			
Not reported			
Proportion with ≥ 10% weight loss			
Not reported			

Note. [a] *Sample used in meta-analysis is smaller than total number randomized, although all continuous measures include full sample set according to publication.*

Abbreviations. BMI: body mass index; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio; SD: standard deviation.

Detailed Findings

In a pooled analysis of 2 RCTs,[60,71] youth randomized to liraglutide achieved a statistically significant reduction in BMI z/SD score compared to those randomized to placebo (MD, -0.21 SDs; 95% CI, -0.3 to -0.1; Figure 18). The overall treatment effect is borderline for a clinically meaningful difference, with some publications reporting a BMI z/SD score reduction of 0.15 SDs as clinically meaningful, while others suggest reductions of 0.25 SDs better reflect improved overall health outcomes in children and adolescents.

Figure 18. Change in BMI z/SD Score: Liraglutide vs. Placebo in Youth
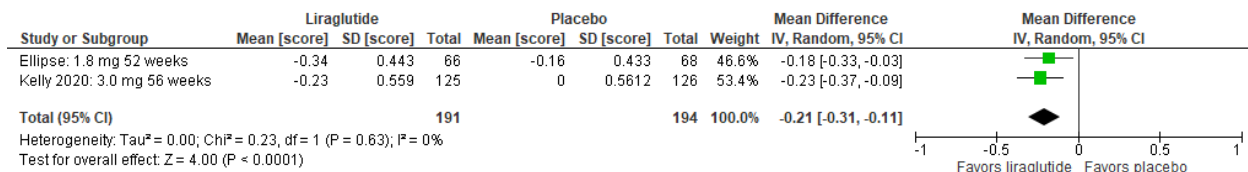
Study or Subgroup	Liraglutide Mean [score]	SD [score]	Total	Placebo Mean [score]	SD [score]	Total	Weight	Mean Difference IV, Random, 95% CI
Ellipse: 1.8 mg 52 weeks	-0.34	0.443	66	-0.16	0.433	68	46.6%	-0.18 [-0.33, -0.03]
Kelly 2020: 3.0 mg 56 weeks	-0.23	0.559	125	0	0.5612	126	53.4%	-0.23 [-0.37, -0.09]
Total (95% CI)			191			194	100.0%	-0.21 [-0.31, -0.11]

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 4.00 (P < 0.0001)

Favors liraglutide Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

In the RCT by Kelly and colleagues,[60] compared to placebo, adolescents with liraglutide had:

- Significantly greater reductions in percent BMI (MD, -4.64%; 95% CI, -7.14 to -2.14); this improvement is under the level considered clinically meaningful, although the CI suggests some adolescents may experience meaningful weight loss
- Significantly greater percent body weight loss (MD, -5.02%; 95% CI, -7.63 to -2.41)
- Significantly greater reductions in BMI (MD, -1.58 kg/m^2; 95% CI, -2.47 to -0.69)
- A significantly higher proportion who achieved at least 5% reduction in BMI (45.1% with liraglutide, 19.0% with placebo; *P* < .001)
- A significantly higher proportion who achieved at least 10% reduction in BMI (29.2% with liraglutide, 8.6% with placebo; *P* < .001)

Comorbidity Risk Factor Outcomes
Summary of Findings (GRADE)

Table 13. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Liraglutide in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
2 RCTs[60,71] N = 386	●●●○ Moderate	Youth randomized to liraglutide had a small but significant reduction in SBP compared to placebo; this difference is not considered clinically meaningful MD, -2.06 mmHg (95% CI, -4.06 to -0.05); *P* = .04	Downgraded: 1 level for RoB • Author and funding CoI
Change in LDL cholesterol (ratio of mmol/L from baseline)			
2 RCTs[60,71] N = 386	●●●○ Moderate	No difference in LDL cholesterol comparing liraglutide with placebo in youth MD, 0.0 (95% CI, -0.05 to 0.05); *P* = .75	Downgraded: 1 level for RoB • Author and funding CoI

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in HbA1c (%)			
2 RCTs[60,71] N = 386	●○○○ Very low	No difference in change in percent HbA1c comparing liraglutide with placebo in youth; effects may vary depending on baseline levels and diabetes status MD, -0.65% (95% CI, -1.85 to 0.55); P = .29	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Considerable heterogeneity 1 level for imprecision • Wide CIs

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; HgA1c: hemoglobin A1c protein; LDL: low-density lipoprotein; MD: mean difference; RoB: risk of bias; SBP: systolic blood pressure.

Detailed Findings

In a pooled analysis of 2 RCTs,[60,71] youth randomized to liraglutide achieved a small but statistically significant decrease in SBP at 52 weeks, compared to placebo (MD, -2.06 mmHg; 95% CI, -4.07 to -0.04; P = .05; Figure 19); the Ellipse study[71] showed no difference at 26 weeks. This overall treatment effect is less than the change in SBP considered clinically meaningful (at least 5.0 mmHg decrease).

Figure 19. Change in Systolic Blood Pressure: Liraglutide vs. Placebo in Youth
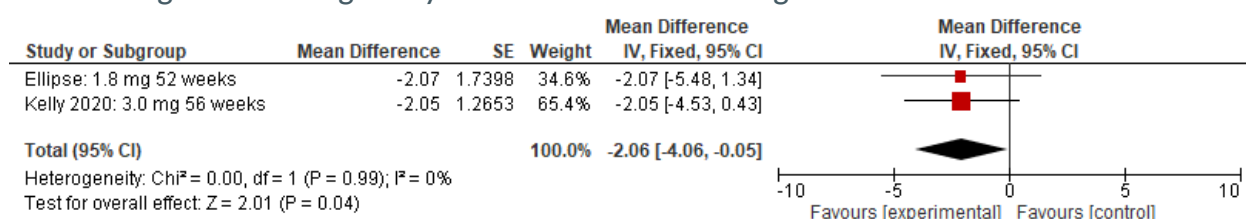
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 2 RCTs,[60,71] there was no difference in geometric mean ratios of LDL cholesterol between youth randomized to liraglutide and placebo groups (Figure 20).

Figure 20. Change in LDL Cholesterol (Treatment Ratio): Liraglutide vs. Placebo in Youth
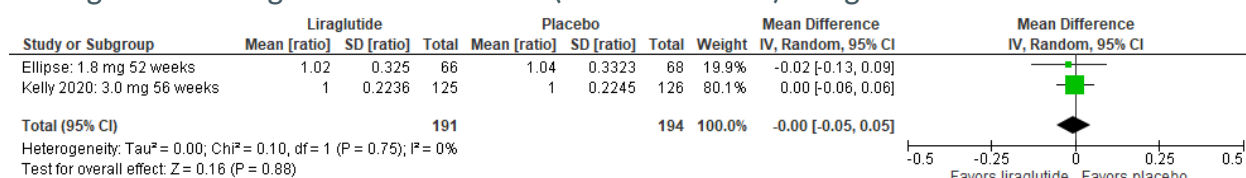
Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation.

In a pooled analysis of 2 RCTs,[60,71] youth who received liraglutide had similar changes in HbA1c by percentage when compared with placebo (MD, -0.65; 95% CI, -1.85 to 0.55; Figure 21). While it is likely that the considerable heterogeneity between effects is due to the differences in

populations studied (including differences in T2DM status and baseline HbA1c levels of over 7% in the Ellipse study,[71] and within normal range [5.3%]) in the study by Kelly and colleagues[60]), this can only be confirmed with more studies and larger sample sizes.

Figure 21. Change in HbA1c (%): Liraglutide vs. Placebo in Youth
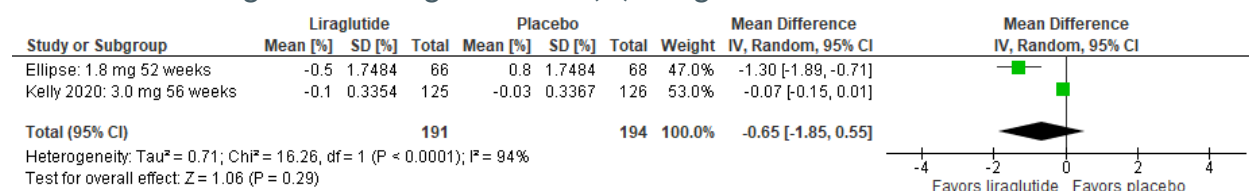
	Liraglutide			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ellipse: 1.8 mg 52 weeks	-0.5	1.7484	66	0.8	1.7484	68	47.0%	-1.30 [-1.89, -0.71]	
Kelly 2020: 3.0 mg 56 weeks	-0.1	0.3354	125	-0.03	0.3367	126	53.0%	-0.07 [-0.15, 0.01]	
Total (95% CI)			191			194	100.0%	-0.65 [-1.85, 0.55]	

Heterogeneity: Tau² = 0.71; Chi² = 16.26, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 1.06 (P = 0.29)

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation.

Quality of Life Outcomes
Summary Findings (GRADE)

Table 14. Certainty of Evidence (GRADE) for Quality of Life: Liraglutide vs. Placebo in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in IWQoL-Kids total score			
1 RCT[60] N = 251	●●●○ Moderate	No difference in QoL scores with liraglutide compared to placebo in adolescents at 52 weeks	Downgraded: 1 level for RoB • Author and funding CoI

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; IWQoL: impact of weight on quality of life; MD: mean difference; RoB: risk of bias.

Detailed Findings
Only 1 study reported on QoL; participants in both liraglutide and placebo groups reported higher scores on the IWQoL-Kids than at baseline, and there was no significant difference between groups at 56 weeks (*P* = .38).[60] We did not downgrade CoE for precision despite the somewhat small sample size from 1 study.

Safety Outcomes
Studies reported overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE (Table 15).

Summary of Findings (GRADE)

Table 15. Certainty of Evidence (GRADE) for Safety Outcomes: Liraglutide vs. Placebo in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
2 RCTs[60,71] N = 386	●○○○ Very low	No statistical difference in withdrawals due to AEs with liraglutide compared to placebo in youth at 52 weeks RR, 5.23 (95% CI, 0.17 to 165.66); P = .08	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Substantial heterogeneity 1 level for imprecision • Low number of events

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of 2 RCTs[60,71] using a random effects model, there was no difference in the likelihood of withdrawal due to an AE in youth randomized to liraglutide or placebo (RR, 5.23; 95% CI, 0.17 to 165.66; Figure 22). However, if a fixed effects model is used, liraglutide is associated with an increased risk of withdrawal due to AEs (RR, 9.82; 95% CI, 1.83 to 52.67; Figure 23). The heterogeneity suggests that the variation in effects is likely more than due to change alone, and whether any can be explained by population differences would require more studies and larger sample sizes. The proportion of withdrawals due to AEs was 7.3% with liraglutide and 0.5% with placebo across the 2 studies.[60,71]

Figure 22. Withdrawal Due to Adverse Events: Liraglutide vs. Placebo (Random Effects)
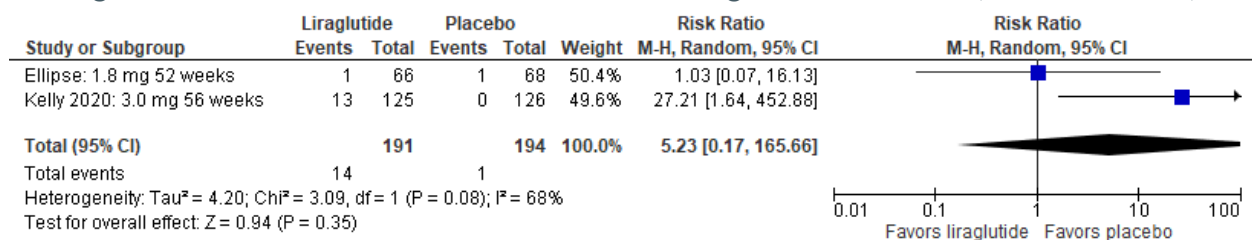
Abbreviations. AE: adverse event; CI: confidence interval.

Figure 23. Withdrawal Due to Adverse Events: Liraglutide vs. Placebo (Fixed Effects)

Study or Subgroup	Liraglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ellipse: 1.8 mg 52 weeks	1	66	1	68	66.4%	1.03 [0.07, 16.13]
Kelly 2020: 3.0 mg 56 weeks	13	125	0	126	33.6%	27.21 [1.64, 452.88]
Total (95% CI)		**191**		**194**	**100.0%**	**9.82 [1.83, 52.67]**
Total events	14		1			

Heterogeneity: Chi² = 3.09, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 2.67 (P = 0.008)

Favors liraglutide   Favors placebo
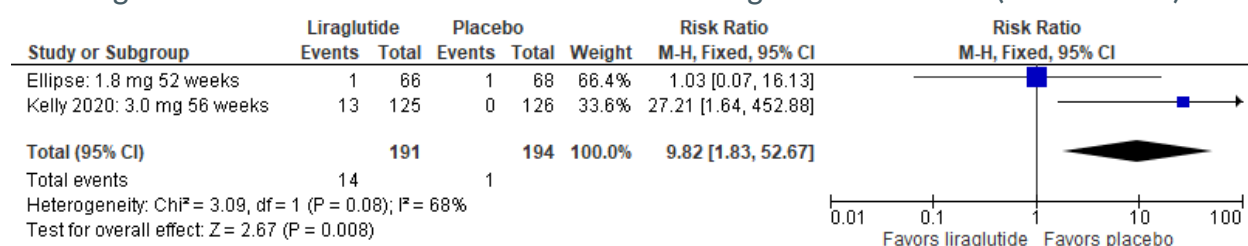
Abbreviations. AE: adverse event; CI: confidence interval; IV: inverse variance RR: risk ratio.

In general, more children and adolescent who received liraglutide experienced an AE or SAE than those who received placebo at 52 weeks (Table 16).[60,71] The most frequent AEs included nausea and vomiting; both were experienced more frequently in the liraglutide groups (see Appendix C, Tables C9 and C10, for details of AE outcomes for liraglutide).

Table 16. Summary of Adverse Events and Serious Adverse Events: Liraglutide in Youth

Author, Year Study Name	Adverse Events, % n of N			Serious Adverse Events, % n of N		
	Liraglutide	Placebo	P Value	Liraglutide	Placebo	P Value
Youth						
Kelly, 2020[60]	88.8% 111 of 125	84.9% 107 of 126	P = .07	2.4% 3 of 125	4.0% 5 of 126	P = .72
Ellipse[71] Tamborlane, 2019	84.8% 56 of 66	80.9% 55 of 68	P = .54[a]	13.6% 9 of 66	5.9% 4 of 68	P = .13[a]

Note. [a] P value calculated by Center from published risk ratio statistic.
Abbreviation. NR: not reported.

In the Ellipse trial of children and adolescents with T2DM, the percentage of participants who experienced hypoglycemic episodes and the incidence of hypoglycemia were higher with liraglutide than with placebo.[71] Of note, both groups received metformin as background therapy.

No deaths were reported in either of the included studies for liraglutide in youth.[60,71]

Change in Medication Outcomes
The included studies for liraglutide in youth did not report change in medication outcomes for obesity-related comorbidities.

Semaglutide

Summary of Included Studies
We identified 8 RCTs in 9 publications[55,73-80] that compared semaglutide with placebo (Table 17). The STEP 8 trial was a head-to-head trial of semaglutide and liraglutide in adults, and also compared semaglutide with placebo[55]; the trial comparison of semaglutide with liraglutide is reported in a separate section. Seven RCTs in 8 publications were in adults,[55,73-77,79,80] and 1 RCT was in adolescents.[78]

Across the 7 RCTs for semaglutide in adults,[55,73-77,79,80] there were differences in population (e.g., with or without diabetes), doses evaluated, background treatments, and requirements for weight loss prior to randomization.

- Five RCTs excluded persons with diabetes,[55,73,74,79,80] the STEP 5 trial included only persons with T2DM,[75] and participants with T2DM from Japan were eligible in the STEP 6 trial,[76] but the condition was not a required inclusion criteria (approximately 25% were with T2DM at randomization).
- All 7 RCTs utilized a weekly 2.4 mg dose of semaglutide delivered subcutaneously; 2 studies also included lower doses (1.0 mg[75] and 1.7 mg[76]) as comparators, in addition to placebo. Doses other than weekly 2.4 mg were not included in the meta-analyses and GRADE assessments.
- Six RCTs included diet and exercise therapy as background treatment[55,74-76,79,80]; the STEP 3 RCT[73] included intensive diet and exercise behavioral therapy as background treatment.
- All trials followed randomized participants for 68 weeks except for the STEP 5 trial[79] which followed participants for 104 weeks.
- The STEP 4 RCT in adults without diabetes was a medication withdrawal study[74]; all participants received semaglutide over 20 weeks during the run-in period and were then randomized to semaglutide or placebo for an additional 48 weeks.

In the STEP TEENS RCT for semaglutide in adolescents,[78] participants with or without T2DM were eligible, and those taking any glucose-lowering drug other than metformin were excluded; approximately 4% were with T2DM at study enrollment. Adolescents were randomized to weekly 2.4 mg semaglutide or placebo, provided background treatment of diet and exercise, and then followed 68 weeks.[78]

Table 17. Overview of Study Characteristics: Semaglutide

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Conditions
Adults								
STEP 1[77,80] Wilding, 2021 RCT Moderate RoB	Yes	68 + 52	Diet and exercise	1,961	• SC semaglutide 2.4 mg weekly • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m^2 with ≥ 1 comorbidity	None
STEP 2[75] Davies, 2021 RCT Moderate RoB	Yes	68	Diet and exercise	1,210	• SC semaglutide 2.4 mg weekly • SC semaglutide 1.0 mg weekly • Placebo	With T2DM	BMI ≥ 27 kg/m^2	None
STEP 3[73] Wadden, 2021 Moderate RoB	Yes	68 + 7	IBT	611	• SC semaglutide 2.4 mg weekly • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m^2 with ≥ 1 comorbidity	None
STEP 4[74] Rubino, 2021 RCT Moderate RoB	Yes	20^b + 48 + 7	Diet and exercise	803	• SC semaglutide 2.4 mg weekly • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m^2 with ≥ 1 comorbidity	None

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Conditions
STEP 5[79] Garvey, 2022 Moderate RoB	Yes	104 + 7	Diet and exercise	304	• SC 2.4 mg weekly • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m^2 with ≥ 1 comorbidity	None
STEP 6[76] Kadowaki, 2022 RCT Moderate RoB	No	68 + 7	Diet and exercise	401	• SC semaglutide 2.4 mg weekly • SC semaglutide 1.7 mg weekly • Placebo	With or without T2DM [c]; 25% T2DM	BMI ≥ 27 kg/m^2 and ≥ 2 comorbidities, or ≥ 35 kg/m^2 and ≥ 1 comorbidity	None
STEP 8[55] Rubino, 2022[a] RCT Moderate RoB	Yes	68 + 7	Diet and exercise	338	• SC semaglutide 2.4 mg weekly • SC liraglutide 3.0 mg daily • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m^2 with ≥ 1 comorbidity	None
Youth								
STEP TEENS[78] Weghuber, 2022 RCT Moderate RoB	Yes	68 + 7	Diet and exercise	201	• SC semaglutide 2.4 mg weekly • Placebo	With or without T2DM; 4% T2DM	BMI ≥ 95th percentile or ≥ 85th with ≥ 1 comorbidity	None

Note. [a] Head-to-head trial included under liraglutide and semaglutide drug categories; [b] All participants were on semaglutide for 20 weeks followed by a 48-week randomized period; [c] In Japanese population only; diabetes excluded in participants from other countries.

Abbreviations. BMI: body mass index; IBT: intensive behavioral therapy; F/U: follow-up; RCT: randomized controlled trial; RoB: risk of bias; SC: subcutaneous; T2DM: type 2 diabetes.

All studies for semaglutide were rated as having moderate RoB primarily because of author and study funding conflicts of interest.

Adults

Weight Outcomes

Summary of Findings (GRADE)

All pooled estimates demonstrate statistical differences in favor of semaglutide (Table 18). The CoE ranged from low to moderate, depending on the outcome, indicating some levels of uncertainty for all outcomes.

Table 18. Certainty of Evidence (GRADE) for Weight Outcomes: Semaglutide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
7 RCTs[55,73-76,79,80] N = 4,997	●●○○ Low	Participants randomized to semaglutide lost a significantly greater percentage of body weight compared to placebo; the overall effect was above what is considered clinically meaningful MD, -11.59% (95% CI, -14.09 to -9.09); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Considerable heterogeneity
Change in body weight (kg)			
6 RCTs[55,73,74,76,79,80] N = 4,190	●●●○ Moderate	Participants randomized to semaglutide lost significantly more body weight, in kg, compared to placebo MD, -12.00 kg (95% CI, -13.32 to -10.68); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI
Change in BMI (kg/m^2)			
5 RCTs[73,74,76,79,80] N = 3,979	●●●○ Moderate	Participants randomized to semaglutide had significantly reduced BMI levels compared to placebo MD, -4.25 kg/m^2 (95% CI, -4.75 to -3.76); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI
Proportion with ≥ 5% weight loss			
6 RCTs[73-76,79,80] N = 4,786[a]	●●○○ Low	Participants randomized to semaglutide were more likely to lose at least 5% body weight compared to placebo RR, 2.34 (95% CI, 1.93 to 2.83); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Considerable heterogeneity
Proportion with ≥ 10% weight loss			
7 RCTs[55,73-76,79,80] N = 4,727[a]	●●○○ Low	Participants randomized to semaglutide were more likely to lose at least 10% body weight compared to placebo RR, 4.70 (95% CI, 3.53 to 6.26); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Considerable heterogeneity

Note. [a] Sample used in meta-analysis is smaller than total number randomized.
Abbreviations. BMI: body mass index; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of all 7 RCTs,[55,73-76,79,80] individuals randomized to semaglutide lost significantly more percent body weight compared with individuals randomized to placebo (MD, -11.59%; 95% CI, -14.09 to -9.09; Figure 24). The treatment effect is above the decrease in percent body weight considered clinically meaningful of at least 5% weight loss. Despite the

large overall effect, we still downgraded the CoE for inconsistency because of the heterogeneity within the subgroup of 6 trials of individuals mostly without T2DM.

The STEP 2[75] RCT in people with T2DM had a lower treatment effect compared to the pooled effect of the 5 studies in people without diabetes (6.2% weight loss in STEP 2 versus 12.5% in people mostly without diabetes). Whether this difference in effect is due to population differences (i.e., STEP 2 had a lower proportion of participants identifying as female, and about 90% of participants were also on metformin, which can also cause weight loss) or due to chance is unclear with only 1 study in this population.

Figure 24. Change in Body Weight (%): Semaglutide vs. Placebo in Adults

Study or Subgroup	Semaglutide Mean [%]	SD [%]	Total	Control Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 At least 1 year								
STEP 1	-14.9	10.1	1306	-2.4	10.12	655	15.0%	-12.50 [-13.45, -11.55]
STEP 3	-16	10.11	407	-5.7	10.1	204	14.3%	-10.30 [-12.00, -8.60]
STEP 4	-7.9	8.2	535	6.9	8.3	268	14.8%	-14.80 [-16.01, -13.59]
STEP 5: 1 year	-15.6	8.6	152	-3	8.6	152	14.0%	-12.60 [-14.53, -10.67]
STEP 6: 2.4 mg	-13.2	7.1	199	-2.1	8	101	14.1%	-11.10 [-12.95, -9.25]
STEP 8	-15.8	10.2	126	-1.9	9.7	85	13.0%	-13.90 [-16.62, -11.18]
Subtotal (95% CI)			2725			1465	85.1%	-12.53 [-13.91, -11.15]
Heterogeneity: Tau² = 2.20; Chi² = 23.00, df = 5 (P = 0.0003); I² = 78%								
Test for overall effect: Z = 17.80 (P < 0.00001)								
2.1.2 With T2DM: 68 weeks								
STEP 2: 2.4 mg	-9.64	8.0399	404	-3.42	8.0299	403	14.9%	-6.22 [-7.33, -5.11]
Subtotal (95% CI)			404			403	14.9%	-6.22 [-7.33, -5.11]
Heterogeneity: Not applicable								
Test for overall effect: Z = 11.00 (P < 0.00001)								
Total (95% CI)			3129			1868	100.0%	-11.59 [-14.09, -9.09]
Heterogeneity: Tau² = 10.65; Chi² = 125.39, df = 6 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 9.08 (P < 0.00001)								
Test for subgroup differences: Chi² = 48.83, df = 1 (P < 0.00001), I² = 98.0%								

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

In the STEP 6 RCT, the higher dose of weekly 2.4 mg semaglutide resulted in a greater loss of percent body weight compared to placebo, than the lower dose of weekly 1.7 mg semaglutide[76] (Figure 25); no statistical tests for differences were reported.

Figure 25. Change in Weight (%) by Dose: Semaglutide vs. Placebo in Adults

Study or Subgroup	Semaglutide Mean [%]	SD [%]	Total	Control Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI
STEP 6: 1.7 mg	-9.6	8.0399	101	-2.1	8.04	51	-7.50 [-10.21, -4.79]
STEP 6: 2.4 mg	-13.2	7.05	199	-2.1	8.04	51	-11.10 [-13.51, -8.69]
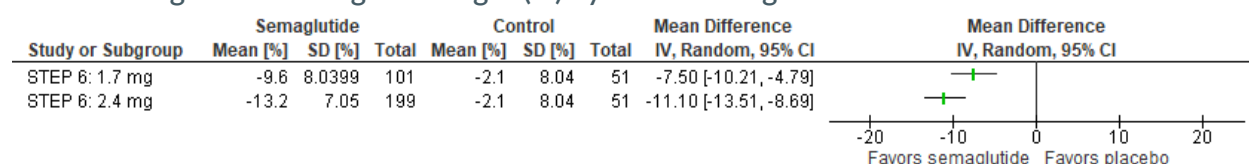
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

The STEP 5[79] RCT measured change in percent body weight at 1- and 2-year time points (Figure 26). Percent change in body weight increased slightly from 52 to 104 weeks in both semaglutide and placebo groups, resulting in nearly identical MDs between groups at both time points.[79]

Figure 26. Change in Weight (%) Over Time: Semaglutide vs. Placebo in Adults
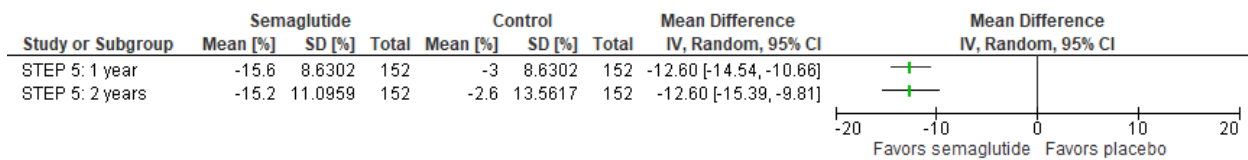
Study or Subgroup	Semaglutide Mean [%]	SD [%]	Total	Control Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
STEP 5: 1 year	-15.6	8.6302	152	-3	8.6302	152	-12.60 [-14.54, -10.66]	
STEP 5: 2 years	-15.2	11.0959	152	-2.6	13.5617	152	-12.60 [-15.39, -9.81]	

-20 -10 0 10 20
Favors semaglutide Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 6 RCTs,[55,73,74,76,79,80] individuals randomized to semaglutide lost significantly more body weight, as measured in kg, compared to individuals randomized to placebo (MD, -12.0 kg; 95% CI, -13.32 to -10.68; Figure 27); however, the impact of losing around 6 kg more than with placebo alone will vary depending on the baseline weight and overall height. Correlated with percent change in body weight, this effect is also likely clinically meaningful. The STEP 2 trial in people with T2DM analyzed this measure as exploratory only[75]; we did not include this data in the report.

Figure 27. Change in Weight (kg): Semaglutide vs. Placebo in Adults

Study or Subgroup	Semaglutide Mean [kg]	SD [kg]	Total	Control Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
STEP 1	-15.3	10.7	1306	-2.6	10.7	655	21.9%	-12.70 [-13.70, -11.70]	
STEP 3	-16.8	11	407	-6.2	11	204	16.8%	-10.60 [-12.45, -8.75]	
STEP 4	-7.1	7.1	535	6.1	8.3	268	21.0%	-13.20 [-14.36, -12.04]	
STEP 5: 2 years	-16.1	12.3	152	-3.2	14.8	152	10.7%	-12.90 [-15.96, -9.84]	
STEP 6: 2.4 mg	-11.3	6.4	199	-1.7	6.4	101	18.7%	-9.60 [-11.13, -8.07]	
STEP 8	-15.3	11.3	126	-1.6	10.7	85	10.9%	-13.70 [-16.71, -10.69]	
Total (95% CI)			**2725**			**1465**	**100.0%**	**-12.00 [-13.32, -10.68]**	

Heterogeneity: Tau² = 1.82; Chi² = 18.87, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 17.78 (P < 0.00001)

-20 -10 0 10 20
Favors semaglutide Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 5 RCTs,[73,74,76,79,80] BMI was significantly reduced in individuals randomized to semaglutide compared to individuals randomized to placebo (MD, -4.25 kg/m^2; 95% CI, -4.75 to -3.76; Figure 28); however, the impact of reducing BMI further by 4 to 4.5 units will vary depending on the baseline BMI, and whether the change leads to a drop in the obesity class of clinical severity. We did not downgrade for imprecision because of the relatively narrow overall CI. Note that only 2-year data for BMI was reported for the STEP 5 trial[79]; change in BMI at 2 years was relatively consistent compared to measures at 1 year in other trials. The STEP 2[75] trial in people with T2DM analyzed this measure as exploratory only; we did not include this data in the report.

Figure 28. Change in BMI (kg/m^2): Semaglutide vs. Placebo in Adults

Study or Subgroup	Semaglutide Mean [kg/m2]	SD [kg/m2]	Total	Control Mean [kg/m2]	SD [kg/m2]	Total	Weight	Mean Difference IV, Random, 95% CI
STEP 1	-5.5	3.7	1306	-0.9	3.7	655	26.1%	-4.60 [-4.95, -4.25]
STEP 3	-6	3.9	407	-2.2	3.9	204	19.6%	-3.80 [-4.46, -3.14]
STEP 4	-2.6	2.4	535	2.2	3.3	268	24.1%	-4.80 [-5.24, -4.36]
STEP 5: 2 years	-5.9	4.9	152	-1.6	7.4	152	8.7%	-4.30 [-5.71, -2.89]
STEP 6: 2.4 mg	-4.2	2.4	199	-0.6	2.4	101	21.4%	-3.60 [-4.17, -3.03]
Total (95% CI)			2599			1380	100.0%	-4.25 [-4.75, -3.76]

Heterogeneity: Tau² = 0.21; Chi² = 15.06, df = 4 (P = 0.005); I² = 73%
Test for overall effect: Z = 16.83 (P < 0.00001)

Mean Difference IV, Random, 95% CI — scale from -10 to 10. Favors semaglutide   Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 6 RCTs,[73-76,79,80] individuals randomized to semaglutide were significantly more likely to lose at least 5% of their initial weight compared to individuals randomized to placebo (RR, 2.34; 95% CI, 1.93 to 2.83; Figure 29). It is unclear if the heterogeneous effects across studies are impacted by different study populations (people from different countries, different proportion with T2DM) or designs (duration, background treatment); more studies with similar characteristics could provide more insight.

The proportion of individuals who lost 5% or more body weight from baseline (which is considered a clinically meaningful level of weight loss) was 83.8% with semaglutide and 35.0% with placebo across all studies included in the meta-analysis.[73-76,79,80]

The STEP 8[55] study by Rubino and colleagues analyzed this measure as exploratory only; we did not include this data in the report.

Figure 29. Proportion With at Least 5% Weight Loss: Semaglutide vs. Placebo in Adults

Study or Subgroup	Semaglutide Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 At least 68 weeks						
STEP 1	1047	1212	182	577	19.0%	2.74 [2.42, 3.09]
STEP 3	352	407	97	204	18.3%	1.82 [1.57, 2.11]
STEP 4	475	535	128	268	18.8%	1.86 [1.63, 2.11]
STEP 5: 2 years	111	144	44	128	15.1%	2.24 [1.74, 2.89]
STEP 6: 2.4 mg	160	193	21	100	11.3%	3.95 [2.68, 5.80]
Subtotal (95% CI)		2491		1277	82.4%	2.33 [1.85, 2.95]
Total events	2145		472			

Heterogeneity: Tau² = 0.06; Chi² = 36.11, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 7.09 (P < 0.00001)

2.6.2 With T2DM: 68 weeks						
STEP 2: 2.4 mg	267	388	107	376	17.6%	2.42 [2.03, 2.88]
Subtotal (95% CI)		388		376	17.6%	2.42 [2.03, 2.88]
Total events	267		107			

Heterogeneity: Not applicable
Test for overall effect: Z = 9.96 (P < 0.00001)

Total (95% CI)		2879		1653	100.0%	2.34 [1.93, 2.83]
Total events	2412		579			

Heterogeneity: Tau² = 0.05; Chi² = 36.78, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 8.65 (P < 0.00001)
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%

Risk Ratio M-H, Random, 95% CI — scale from 0.05 to 20. Favors placebo   Favors semaglutide

Abbreviations. CI: confidence interval; T2DM: type 2 diabetes.

In a pooled analysis of all 7 RCTs,[55,73-76,79,80] individuals randomized to semaglutide were significantly more likely to lose at least 10% of their initial weight compared to those who received placebo (RR, 4.69; 95% CI, 3.52 to 6.25; Figure 30). More studies with similar study characteristic may provide insight as to whether the heterogeneous effects between studies are impacted by different study designs or populations. The proportion of individuals who lost 10% or more body weight from baseline (clinically meaningful amount of weight loss) was 67.8% with semaglutide and 14.0% with placebo across all studies included in the meta-analysis.[55,73-76,79,80]

Figure 30. Proportion With at Least 10% Weight Loss: Semaglutide vs. Placebo in Adults
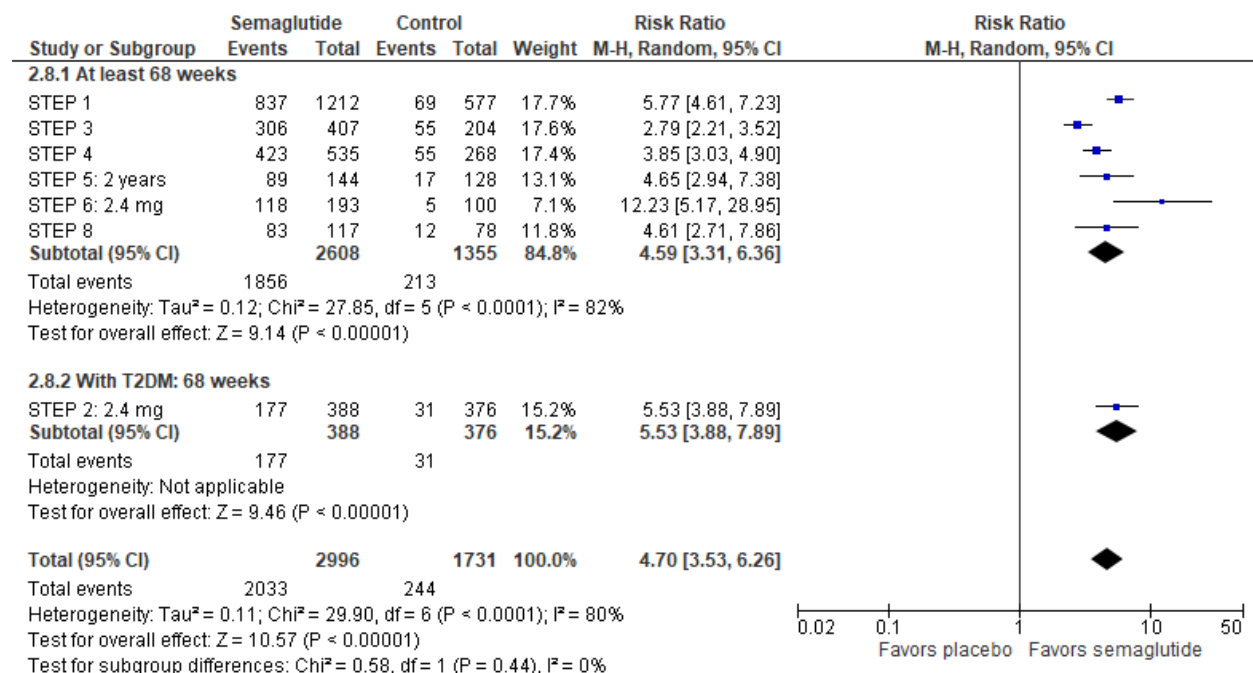
Abbreviations. CI: confidence interval; T2DM: type 2 diabetes.

Comorbidity Risk Factor Outcomes

Summary of Findings (GRADE)

All pooled estimates demonstrate statistical differences in favor of semaglutide (Table 19). The CoE was low for all outcomes, indicating some level of uncertainty for all outcomes.

Table 19. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Semaglutide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
7 RCTs[55,73-76,79,80] N = 4,997	●●○○ Low	Participants randomized to semaglutide had a small but significant reduction in SBP compared to placebo; this overall difference is less than what is considered clinically meaningful MD, -4.65 mmHg (95% CI, -5.65 to -3.66); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision • CI crosses over clinically meaningful change of 5 mmHg

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in LDL cholesterol			
5 RCTs[55,73,74,76,79] N = 2,221[a]	●●○○ Low	Participants randomized to semaglutide had a small but significant reduction in LDL cholesterol compared to placebo; this difference is likely not clinically meaningful SMD, -0.21 (95% CI, -0.33 to -0.09); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision • Wide CI
Change in HbA1c (%)			
7 RCTs[55,73-76,79,80] N = 4,997	●●○○ Low	Participants randomized to semaglutide had a significant, and clinically meaningful, reduction in percent HbA1c compared to placebo MD, -0.43% (95% CI, -0.55 to -0.30); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Considerable heterogeneity

Note. [a] Sample used in meta-analysis is smaller than total number randomized, although all continuous measures include full sample set according to publication.
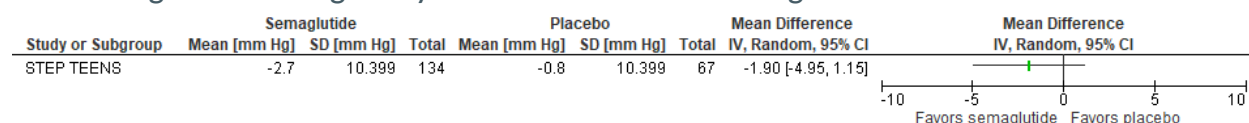
Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; HgA1c: hemoglobin A1c protein; LDL: low-density lipoprotein; MD: mean difference; RoB: risk of bias; SBP: systolic blood pressure; SMD: standardized mean difference.

Detailed Findings

In a pooled analysis of all 7 RCTs,[55,73-76,79,80] individuals randomized to semaglutide had a significantly greater reduction in SBP, as measured in mmHg, compared to individuals randomized to placebo (MD, -4.65 mmHg; 95% CI, -5.65 to -3.66; Figure 31). This overall treatment effect is less than what is considered a clinically meaningful decrease of at least 5.0 mmHg, although the CI suggests some may experience meaningful decreases in blood pressure.
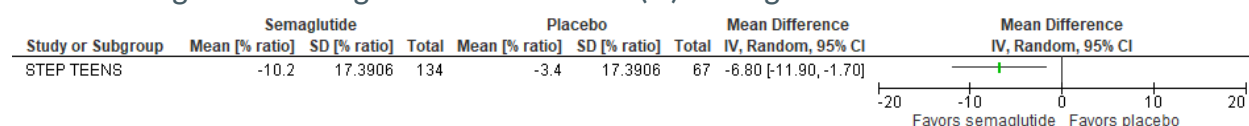
Figure 31. Change in Systolic Blood Pressure (mmHg): Semaglutide vs. Placebo in Adults
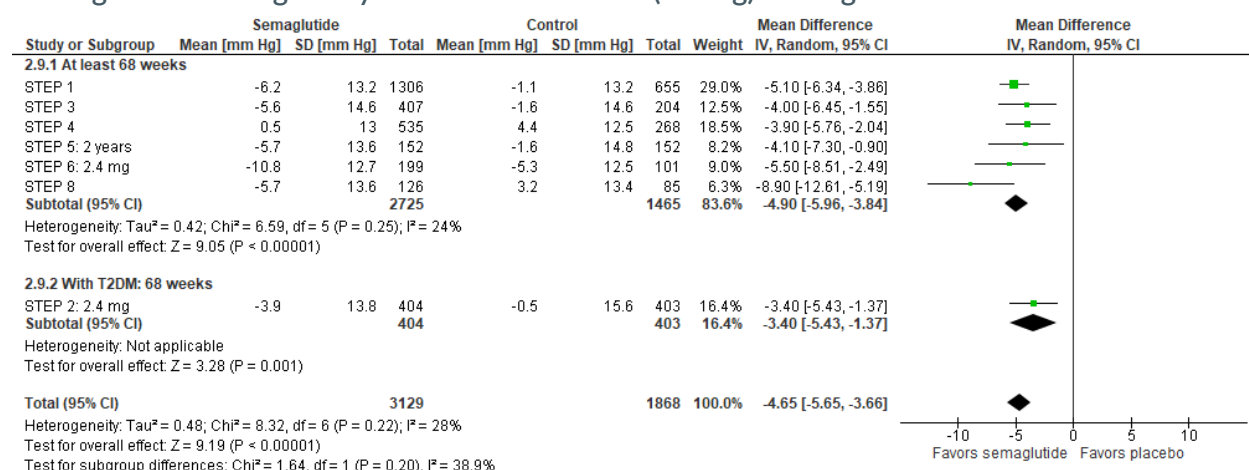
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

In a pooled analysis of 5 RCTs,[55,73,74,76,79] individuals randomized to semaglutide experienced a significantly greater reduction in LDL cholesterol compared to individuals randomized to placebo (SMD, -0.21; 95% CI, -0.33 to -0.9; Figure 32). However, this change is likely not clinically meaningful (MD in percent change values reported range from 3.5% to 7.3% compared to placebo in 3 studies using these units,[55,74,79] and the expectations with statins is more than a 50% reduction in LDL cholesterol). The STEP 2[75] trial in people with T2DM analyzed this measure as exploratory only; we did not include this data in the report.

The STEP 1[80] RCT in people without diabetes also found improvements in LDL cholesterol with semaglutide compared to placebo. They used ratios of lipid levels of week 68 to baseline (difference in ratio of semaglutide and placebo, 0.96 [95% CI, 0.94 to 0.98]; no *P* value reported).[80]

Figure 32. Change in LDL Cholesterol: Semaglutide vs. Placebo in Adults
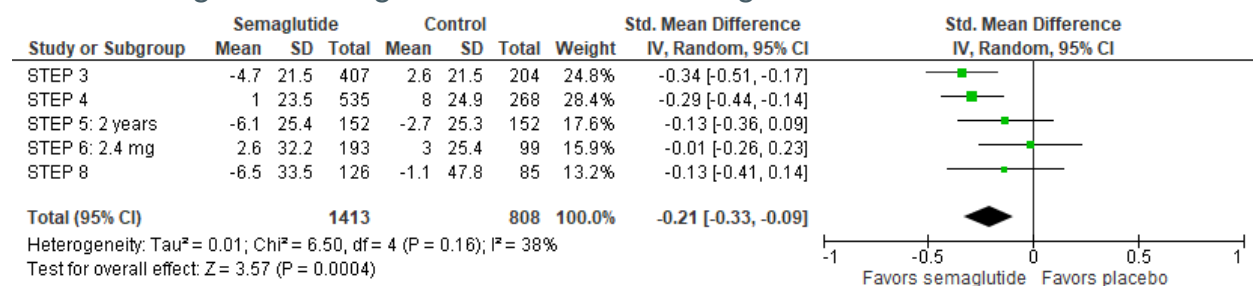
Study or Subgroup	Semaglutide Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
STEP 3	-4.7	21.5	407	2.6	21.5	204	24.8%	-0.34 [-0.51, -0.17]
STEP 4	1	23.5	535	8	24.9	268	28.4%	-0.29 [-0.44, -0.14]
STEP 5: 2 years	-6.1	25.4	152	-2.7	25.3	152	17.6%	-0.13 [-0.36, 0.09]
STEP 6: 2.4 mg	2.6	32.2	193	3	25.4	99	15.9%	-0.01 [-0.26, 0.23]
STEP 8	-6.5	33.5	126	-1.1	47.8	85	13.2%	-0.13 [-0.41, 0.14]
Total (95% CI)			**1413**			**808**	**100.0%**	**-0.21 [-0.33, -0.09]**

Heterogeneity: Tau² = 0.01; Chi² = 6.50, df = 4 (P = 0.16); I² = 38%
Test for overall effect: Z = 3.57 (P = 0.0004)

Favors semaglutide   Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation.

In a pooled analysis of all 7 RCTs,[55,73-76,79,80] individuals randomized to semaglutide experienced a significantly greater reduction in percent HbA1c compared to those randomized to placebo (MD, 0.43%; 95% CI, -0.55 to -0.30; Figure 33). The overall treatment effect is greater than what is considered clinically meaningful (a decrease of least a 0.3%).

The magnitude of the effect was driven primarily by 2 RCTs; the STEP 2 trial[75] where all participants had T2DM, and the STEP 6 trial[76] with approximately 25% of individuals having T2DM. The mean baseline levels of percent HbA1c were above normal values (8% in STEP 2, 6.4% in STEP 6),[75,76] while all other studies[55,73,74,79,80] had baseline levels below 6%, and most within normal limits (< 5.7%). These differences likely explain the outlier effects of these 2 studies; however, the I² statistic still remained high at 71% even after removing the results of these 2 studies[75,76] from the meta-analysis, indicating considerable heterogeneity among the remaining studies.

Figure 33. Change in HbA1c (%): Semaglutide vs. Placebo in Adults

Study or Subgroup	Semaglutide Mean [%]	SD [%]	Total	Control Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI
2.11.1 At least 68 weeks								
STEP 1	-0.5	0.3	1306	-0.2	0.3	655	16.8%	-0.30 [-0.33, -0.27]
STEP 3	-0.5	0.3	407	-0.3	0.3	204	16.5%	-0.20 [-0.25, -0.15]
STEP 4	-0.1	1.2	535	0.1	0.008	268	15.2%	-0.20 [-0.30, -0.10]
STEP 5: 2 years	-0.4	0.4	152	-0.1	0.4	152	15.6%	-0.30 [-0.39, -0.21]
STEP 6: 2.4 mg	-0.9	0.7	199	-0.03	0.7	101	13.0%	-0.87 [-1.04, -0.70]
STEP 8	-0.2	0.6	126	0.1	0.5	85	13.6%	-0.30 [-0.45, -0.15]
Subtotal (95% CI)			2725			1465	90.7%	-0.34 [-0.44, -0.24]
Heterogeneity: Tau² = 0.01; Chi² = 61.62, df = 5 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 6.40 (P < 0.00001)								
2.11.2 With T2DM: 68 weeks								
STEP 2: 2.4 mg	-1.6	2	404	-0.4	2	403	9.3%	-1.20 [-1.48, -0.92]
Subtotal (95% CI)			404			403	9.3%	-1.20 [-1.48, -0.92]
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.52 (P < 0.00001)								
Total (95% CI)			3129			1868	100.0%	-0.43 [-0.55, -0.30]
Heterogeneity: Tau² = 0.02; Chi² = 103.54, df = 6 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 6.70 (P < 0.00001)								
Test for subgroup differences: Chi² = 32.76, df = 1 (P < 0.00001), I² = 96.9%								

Favors semaglutide   Favors placebo

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

Quality of Life Outcomes

Five studies measured QoL in people with and without T2DM.

Summary of Findings

Table 20. Certainty of Evidence (GRADE) for Quality of Life: Semaglutide vs. Placebo in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Quality of life			
5 RCTs[73-77] N = 4,481	●●○○ Low	Participants randomized to semaglutide experienced small but significant improvements in physical function QoL compared to placebo; improvements likely not clinically meaningful	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision[a]

Note. [a] Precision not assessable.

Abbreviations. CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In the 5 RCTs reporting some measure of QoL,[73-77] individuals randomized to semaglutide did appear to have some improvements in physical functioning QoL compared with individuals randomized to placebo, but none likely at clinically meaningful levels.

- In the 4 RCTs of mostly people without diabetes, all utilized the SF-36 physical function survey.[73,74,76,77] Scores improved more with weekly 2.4 mg semaglutide across all studies, with 3 of 4 studies demonstrating statistically significant improvements, but all differences were small (less than 2.5 point change), and likely not clinically meaningful. The SF-36

physical function survey was also used in the STEP 2 trial of people with T2DM[75]; the 1.5-point improvement with semaglutide was statistically significant compared to placebo, but not near meaningful levels of change.

- Three RCTs also measured QoL using the IWQoL physical function component survey.[75-77] Results aligned with those from the SF-36 questionnaires across all 3 studies. Again, the differences compared to placebo were small and likely not important changes.

Safety Outcomes

Studies for semaglutide included overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE (Table 21).

Summary of Findings (GRADE)

Table 21. Certainty of Evidence (GRADE) for Safety Outcomes: Semaglutide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
7 RCTs[55,73-76,79,80] N = 4,995	●●●○ Moderate	More participants assigned to semaglutide experienced withdrawals due to AEs compared to placebo RR, 1.81 (95% CI, 1.34 to 2.44); $P < .001$	Downgraded: 1 level for RoB • Author and funding CoI

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of all 7 studies,[55,73-76,79,80] individuals randomized to semaglutide were more likely to experience an AE that led to study withdrawal compared to individuals randomized to placebo (RR, 1.81; 95% CI, 1.34 to 2.44; Figure 34). While there was no notable heterogeneity detected in the overall effect, several individual studies found no effect. The proportion of withdrawals due to AEs was 5.5% with liraglutide and 3.1% with placebo across all studies.[55,73-76,79,80]

Figure 34. Proportion of Withdrawals Due to Adverse Events: Semaglutide vs. Placebo in Adults

Study or Subgroup	Semaglutide Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 At least 68 weeks						
STEP 1	92	1306	20	655	40.3%	2.31 [1.44, 3.71]
STEP 3	24	407	6	204	11.7%	2.00 [0.83, 4.83]
STEP 4	13	535	6	268	9.9%	1.09 [0.42, 2.82]
STEP 5: 2 years	9	152	7	152	9.8%	1.29 [0.49, 3.36]
STEP 6: 2.4 mg	5	199	1	101	2.0%	2.54 [0.30, 21.43]
STEP 8	4	126	3	85	4.2%	0.90 [0.21, 3.92]
Subtotal (95% CI)		2725		1465	77.9%	1.82 [1.29, 2.56]
Total events	147		43			

Heterogeneity: Tau² = 0.00; Chi² = 3.63, df = 5 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)

Study or Subgroup	Semaglutide Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.2 With T2DM: 68 weeks						
STEP 2: 2.4 mg	25	403	14	402	22.1%	1.78 [0.94, 3.38]
Subtotal (95% CI)		403		402	22.1%	1.78 [0.94, 3.38]
Total events	25		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)

Study or Subgroup	Semaglutide Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		3128		1867	100.0%	1.81 [1.34, 2.44]
Total events	172		57			

Heterogeneity: Tau² = 0.00; Chi² = 3.63, df = 6 (P = 0.73); I² = 0%
Test for overall effect: Z = 3.86 (P = 0.0001)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

Abbreviations. AE: adverse event; CI: confidence interval; T2DM: type 2 diabetes.

There were no meaningful differences in withdrawals due to AEs between the weekly 1.7 mg dose and weekly 2.4 mg dose in the STEP 6[76] (Figure 35).

Figure 35. Proportion of Withdrawals Due to AEs by Dose: Semaglutide vs. Placebo in Adults
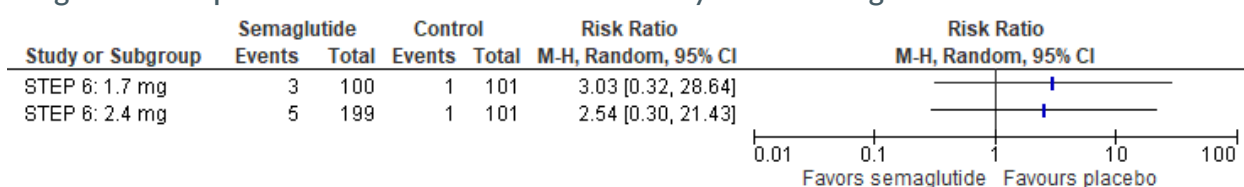
Study or Subgroup	Semaglutide Events	Total	Control Events	Total	Risk Ratio M-H, Random, 95% CI
STEP 6: 1.7 mg	3	100	1	101	3.03 [0.32, 28.64]
STEP 6: 2.4 mg	5	199	1	101	2.54 [0.30, 21.43]

Abbreviations. AE: adverse event; CI: confidence interval.

In general, more people randomized to semaglutide experienced an AE or SAE compared to those randomized to placebo (Table 22).[55,73-76,79,80] The most frequent AEs included nausea, constipation, diarrhea, and vomiting. These common gastrointestinal AEs were also more frequently experienced by individuals who received semaglutide (see Appendix D, Tables D9 and D10, for details of AE outcomes for semaglutide).

Only the STEP 1 RCT provided some detail about the SAEs experienced[80]; serious gastrointestinal disorders and serious hepatobiliary disorders were experienced more frequently with semaglutide compared to placebo.

Table 22. Summary of Adverse Events and Serious Adverse Events: Semaglutide in Adults

Author, Year Study Name		Adverse Events, % n of N			Serious Adverse Events, % n of N		
		Semaglutide	Placebo	P Value	Semaglutide	Placebo	P Value
Adults							
STEP 1[80] Wilding, 2020		89.7% 1171 of 1,306	86.4% 566 of 655	NR	9.8% 128 of 1,306	6.4% 42 of 655	NR
STEP 2[a,75] Davies, 2011		87.6% 353 of 403	76.9% 309 of 402	NR	9.9% 40 of 403	9.2% 37 of 402	NR
STEP 3[73] Wadden, 2020		95.8% 390 of 407	96.1% 196 of 204	NR	9.1% 37 of 407	2.9% 6 of 204	NR
STEP 4[74] Rubino, 2021		81.3% 435 of 535	75.0% 201 of 268	NR	7.7% 41 of 535	5.6% 15 of 268	NR
STEP 5[79] Garvey, 2022		96.1% 146 of 152	89.5% 136 of 152	NR	7.9% 12 of 152	11.8% 18 of 152	NR
STEP 6[76] Kadowaki, 2022	2.4 mg	86% 171 of 199	79.0% 80 of 101	NR	5.0% 10 of 199	7.0% 7 of 101	NR
	1.7 mg	82% 82 of 100	79.0% 80 of 101	NR	7.0% 7 of 100	7.0% 7 of 101	NR
STEP 8[55] Rubino, 2022		95.2% 120 of 126	95.3% 81 of 85	NR	7.9% 10 of 126	7.1% 6 of 85	NR

Note. ª For 2.4 mg dose only.
Abbreviation. NR: not reported

Nine deaths were reported in 4 studies[74,75,79,80]; none were considered related to treatment. All deaths were evenly distributed across intervention and placebo groups, excepted the 2-year STEP 5 trial[79] with 1 death in the semaglutide group and none in the placebo group. This death was considered unrelated to trial product.

Change in Medication Outcomes

Five studies of semaglutide measured changes in medication use for comorbidities (Table 23).[74-76,79,80] ***All analyses in all studies were considered exploratory only, and should be interpreted with caution***. Importantly, most of the measures include a relatively small subgroup of the study populations.

- Three studies in people mostly without diabetes measured changes in blood pressure and lipid-lowering medications[74,76,79]; more people randomized to semaglutide decreased or stopped use of medications used to treat high blood pressure and high blood cholesterol compared to placebo, and fewer increased use.
- Change in oral glucose-lowering medications was measured in the STEP 2[75] study of people with T2DM, and in the subgroup of people with T2DM in the STEP 6 trial[76]; more people randomized to semaglutide decreased or stopped use of glucose-lowering medications compared to placebo over 68 weeks, and fewer increased use.

Table 23. Summary of Changes in Concomitant Medication Use: Semaglutide [a]

Study Name Author, Year	Population	Decreased or Stopped Use		Increased Use		Between-Group Difference
		Semaglutide	Placebo	Semaglutide	Placebo	
Change in blood pressure medication						
STEP 1[80] Wilding, 2021	2.4 mg at 68 weeks; no diabetes	34% NR [b]	16% NR [b]	12% NR [b]	22% NR [b]	NR
STEP 4[74] Rubino, 2021	2.4 mg at 68 weeks (including 20-week drug run-in); no diabetes	25.5% 38 of 149	11.9% 8 of 67	9.4% 14 of 149	16.4% 11 of 67	NR
STEP 5[79] Garvey, 2022	2.4 mg at 104 weeks; no diabetes	32% 16 of 50	16.4% 10 of 61	6% 3 of 50	23% 14 of 61	NR
Change in lipid-lowering medication						
STEP 1[80] Wilding, 2021	2.4 mg at 68 weeks; no diabetes	21% NR [b]	17% NR [b]	10% NR [b]	20% NR [b]	NR
STEP 4[74] Rubino, 2021	2.4 mg at 68 weeks (including 20-week drug run-in); no diabetes	11.4% 8 of 70	1.6% 4 of 36	4.3% 3 of 70	13.9% 5 of 36	NR
STEP 5[79] Garvey, 2022	2.4 mg at 104 weeks; no diabetes	11.0% 6 of 58	9.6% 5 of 52	7.7% 2 of 26	17.2% 5 of 29	NR
Change in glucose-lowering medication						
STEP 2[75] Davies, 2021	2.4 mg at 68 weeks; with T2DM	28.6% 106 of 371	7.1% 26 of 364	4.9% 18 of 371	24.2% 88 of 364	NR
STEP 6[76] Kadowaki, 2022	2.4 mg at 68 weeks; with T2DM	18.4% 9 of 49	0% 0 of 25	6.1% 3 of 49	28% 7 of 25	NR
	1.7 mg at 68 weeks; with T2DM	8.0% 2 of 25		0% 0 of 25		NR

Note. [a] Analyses were reported as exploratory only across all studies; [b] The treatment policy estimand assesses treatment effect regardless of treatment discontinuation or rescue intervention.
Abbreviations. NR: not reported; T2DM: type 2 diabetes.

Youth

Weight Outcomes

Summary of Findings (GRADE)

The STEP TEENS RCT demonstrated significant differences in favor of semaglutide in adolescents across all weight outcomes (Table 24). The CoE was moderate for all weight

outcomes, indicating some level of uncertainty. However, outcomes were not downgraded further for lower overall sample size from 1 study because of the relatively large effects.

Table 24. Certainty of Evidence (GRADE) for Weight Outcomes: Semaglutide vs. Placebo in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in BMI z/SD score			
1 RCT[78] N = 201	●●●○ Moderate	Adolescents randomized to semaglutide significantly reduced BMI z/SD scores compared to placebo; the effect is considered clinically meaningful MD, -1.00 SDs (95% CI, -1.30 to -0.70); *P* <.001	Downgraded:[b] 1 level for RoB • Author and funding CoI
Change in BMI (%)			
1 RCT[78] N = 201	●●●○ Moderate	Adolescents randomized to semaglutide had a statistically significant, and clinically meaningful, reduction in percent BMI compared to placebo MD, -16.70% (95% CI, -20.25 to -13.15); *P* < .001	Downgraded:[b] 1 level for RoB • Author and funding CoI
Change in body weight (%)			
1 RCT[78] N = 201	●●●○ Moderate	Adolescents randomized to semaglutide lost a significantly greater percentage of body weight compared to placebo; this measure not valid to assess for meaningful change in youth because change in weight depends on growth in height and development MD, -17.40% (95% CI, -21.10 to -13.70); *P* < .001	Downgraded:[b] 1 level for RoB • Author and funding CoI
Proportion with ≥ 5% weight loss			
1 RCT[78] N = 201[a]	●●●○ Moderate	Adolescents randomized to semaglutide were more likely to lose at least 5% body weight compared to placebo RR, 4.09 (95% CI, 2.37 to 7.06); *P* < .001	Downgraded:[b] 1 level for RoB • Author and funding CoI
Proportion with ≥ 10% weight loss			
1 RCT[78] N = 201[a]	●●●○ Moderate	Adolescents randomized to semaglutide were more likely to lose at least 10% body weight compared to placebo RR, 7.67 (95% CI, 3.27 to 17.96): *P* < .001	Downgraded:[b] 1 level for RoB • Author and funding CoI

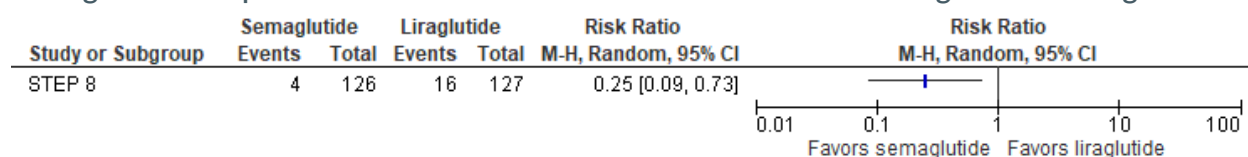*Notes. [a] Sample used in meta-analysis is smaller than total number randomized; [b] Consistency not assessable with 1 study.*

Abbreviations. BMI: body mass index; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio; SD: standard deviation.

Detailed Findings

In 1 RCT,[78] adolescents randomized to semaglutide achieved a statistically greater reduction in BMI z/SD score compared to those randomized to placebo at 68 weeks (MD, -1.0 SDs; 95% CI, -1.3 to -0.7; Figure 36). The treatment effect in this single study is above what is

considered a clinically meaningful difference in change in BMI z/SD score of at least 0.15 or 0.25 SDs.

Figure 36. Change in BMI z/SD Score: Semaglutide vs. Placebo in Youth
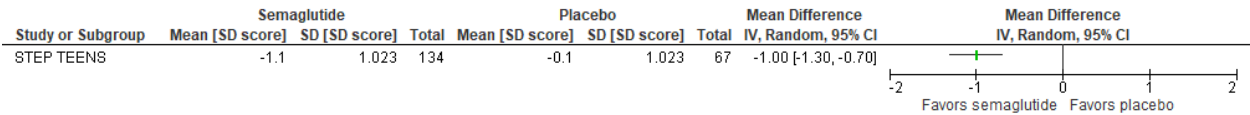
Study or Subgroup	Semaglutide Mean [SD score]	SD [SD score]	Total	Placebo Mean [SD score]	SD [SD score]	Total	Mean Difference IV, Random, 95% CI
STEP TEENS	-1.1	1.023	134	-0.1	1.023	67	-1.00 [-1.30, -0.70]

Mean Difference IV, Random, 95% CI — scale from -2 to 2. Favors semaglutide Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

In 1 RCT,[78] adolescents randomized to semaglutide achieved a statistically significant reduction in percent BMI compared to those randomized to placebo (MD, -16.7%; 95% CI, -20.3 to -13.2; Figure 37). The treatment effect in this single study is above what is considered clinically meaningful of at least 5% difference.

Figure 37. Change in BMI (%): Semaglutide vs. Placebo in Youth
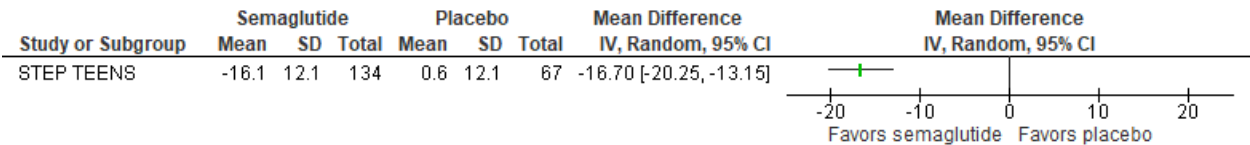
Study or Subgroup	Semaglutide Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
STEP TEENS	-16.1	12.1	134	0.6	12.1	67	-16.70 [-20.25, -13.15]

Mean Difference IV, Random, 95% CI — scale from -20 to 20. Favors semaglutide Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

In 1 RCT,[78] adolescents randomized to semaglutide achieved a statistically greater percent body weight loss compared to those randomized to placebo at 68 weeks (MD, -17.4%; 95% CI, -21.1 to -13.7; Figure 38). Changes in body weight alone have limited usefulness in assessing whether weight loss is clinically meaningful in children and adolescents because weight must account for healthy development and growth in height.

Figure 38. Change in Body Weight (%): Semaglutide vs. Placebo in Youth
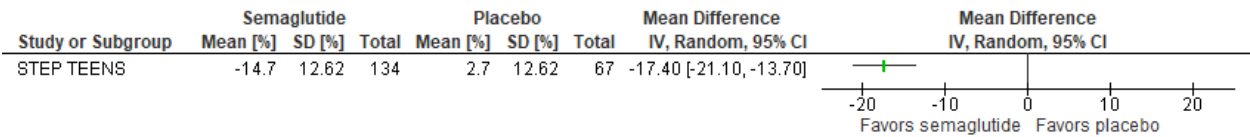
Study or Subgroup	Semaglutide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI
STEP TEENS	-14.7	12.62	134	2.7	12.62	67	-17.40 [-21.10, -13.70]

Mean Difference IV, Random, 95% CI — scale from -20 to 20. Favors semaglutide Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In 1 RCT,[78] adolescents randomized to semaglutide were significantly more likely to lose least 5% (RR, 4.09; 95% CI, 2.4 to 7.1; *P* < .001) and at least 10% (RR, 7.67; 95% CI, 3.3 to 18.0; *P* < .001) of body weight from baseline, compared to placebo at 68 weeks (Figure 39). Again, because body weight gain in youth must account for the needed gains for healthy growth and development, this measure has limited value to assess whether change is clinically meaningful. However, the large risk ratio of over 4 indicates that semaglutide can impact a large proportion of youth.

The proportion of individuals who lost 5% or more body weight from baseline was 72.5% with semaglutide and 17.7% with placebo.[78] The proportion of individuals who lost 10% or more body weight from baseline values was 61.8% with semaglutide and 8.1% with placebo.[78]

Figure 39. Proportion With at Least 5% and 10% Weight Loss: Semaglutide vs. Placebo
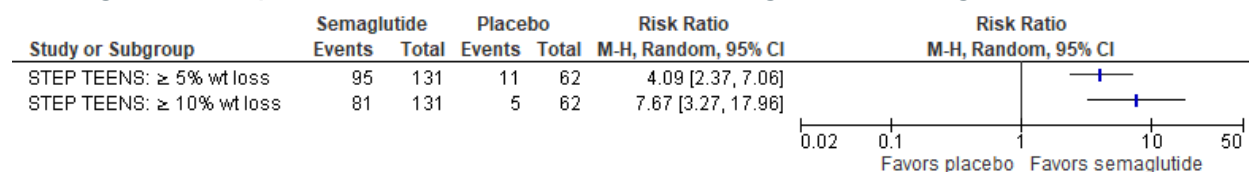
Study or Subgroup	Semaglutide Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
STEP TEENS: ≥ 5% wt loss	95	131	11	62	4.09 [2.37, 7.06]	
STEP TEENS: ≥ 10% wt loss	81	131	5	62	7.67 [3.27, 17.96]	

0.02   0.1   1   10   50
Favors placebo   Favors semaglutide

Abbreviation. CI: confidence interval.

Comorbidity Risk Factor Outcomes

Summary of Findings (GRADE)

Table 25. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Semaglutide in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
1 RCT[78] N = 201	●●●○ Moderate	Improvements in SBP with semaglutide were not significantly different compared to placebo in adolescents MD, -1.90 mmHg (95% CI, -4.95 to 1.15); P = .22	Downgraded:[a] 1 level for RoB • Author and funding CoI
Change in LDL cholesterol (relative percentage difference)			
1 RCT[78] N = 201	●●●○ Moderate	Adolescents randomized to semaglutide had significant reductions in percent LDL cholesterol compared to placebo; this change is likely not clinically meaningful MD, -6.80% (95% CI, -11.90 to -1.70); P = .009	Downgraded:[a] 1 level for RoB • Author and funding CoI
Change in HbA1c (%)			
1 RCT[78] N = 201	●●○○ Low	Adolescents randomized to semaglutide had significant reductions in percent HbA1c compared to placebo, and the effect is just at clinically meaningful levels MD, -0.30 (95% CI, -0.35 to -0.25); P < .001	Downgraded:[a] 1 level for RoB • Author and funding CoI 1 level for imprecision • CI crosses clinically meaningful change of 0.3%

Note. [a] Consistency not assessable with 1 study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; HgA1c: hemoglobin A1c protein;

LDL: low-density lipoprotein; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; SBP: systolic blood pressure.

Detailed Findings

In 1 RCT,[78] the small overall improvement in SBP, as measured in mmHg, with semaglutide was not statistically different at 68 weeks compared with placebo in adolescents (MD, -1.9 mmHg; 95% CI, -5.0 to 1.2; Figure 40). Approximately 13% of participants had hypertension at baseline in the STEP TEENS study[78] (see Appendix B, Table B2, for study participant characteristics).

Figure 40. Change in Systolic Blood Pressure: Semaglutide vs. Placebo in Youth

Study or Subgroup	Semaglutide Mean [mm Hg]	SD [mm Hg]	Total	Placebo Mean [mm Hg]	SD [mm Hg]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
STEP TEENS	-2.7	10.399	134	-0.8	10.399	67	-1.90 [-4.95, 1.15]	Favors semaglutide Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In 1 RCT,[78] adolescents randomized to semaglutide had significantly greater reductions in LDL cholesterol relative percentage difference from baseline compared to placebo (MD, -6.8%; 95% CI, -11.9 to -1.7; Figure 41). With the baseline geometric mean LDL cholesterol as 90.4 mg/dL across both groups pre-treatment,[78] a decrease of 6.8% is around 6 to 6.5 mg/dL, which is well below the recognized meaningful decrease of at least 38.7 mg/dL (1 mmol/L), a level which has been shown to notably reduce risks of cardiovascular events in adults. Approximately 15% of participants were with dyslipidemia at baseline in the STEP TEENS study[78] (see Appendix B, Table B2, for study participant characteristics).

Figure 41. Change in LDL Cholesterol (%): Semaglutide vs. Placebo in Youth

Study or Subgroup	Semaglutide Mean [% ratio]	SD [% ratio]	Total	Placebo Mean [% ratio]	SD [% ratio]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
STEP TEENS	-10.2	17.3906	134	-3.4	17.3906	67	-6.80 [-11.90, -1.70]	Favors semaglutide Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation.

In 1 RCT,[78] adolescents randomized to semaglutide achieved statistically greater reductions in percent HbA1c compared with adolescents randomized to placebo at 68 weeks (MD, -0.3%; 95% CI, -0.4 to -0.25; Figure 42). The treatment effect is just at the level of improvement considered clinically meaningful of at least 0.3%, but based on the CI, some participants may not reach this meaningful change. Approximately 4% of adolescents were identified as having T2DM at baseline[78]; the proportion on concomitant glucose-lowering medication (i.e., metformin) was not reported.

Figure 42. Change in HbA1c (%): Semaglutide vs. Placebo in Youth
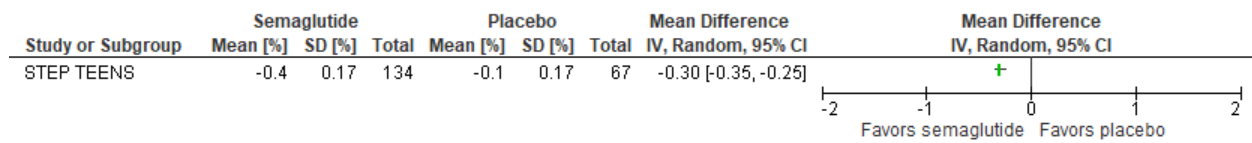
Study or Subgroup	Semaglutide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
STEP TEENS	-0.4	0.17	134	-0.1	0.17	67	-0.30 [-0.35, -0.25]	

Favors semaglutide   Favors placebo

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation.

Quality of Life Outcomes

QoL was not measured in the STEP TEENS study that compared semaglutide with placebo in youth.

Safety Outcomes

The STEP TEENS study reported overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE.

Summary of Findings (GRADE)

Table 26. Certainty of Evidence (GRADE) for Safety Outcomes: Semaglutide in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
1 RCT[78] N = 200	●●○○ Low	No difference in withdrawals due to AEs between semaglutide and placebo groups RR, 1.01 (95% CI, 0.26 to 3.9); *P* = .99	Downgraded:[a] 1 level for RoB • Author and funding CoI 1 level for imprecision • Very low number of events

Note. [a] Consistency not assessable with 1 study.
Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In 1 RCT,[78] there was no difference in the likelihood of withdrawal due to an AE in youth randomized to semaglutide or placebo at 68 weeks (RR, 1.01; 95% CI, 0.9 to 2.5; Figure 43). The proportion of withdrawals due to AEs was 4.5% for both semaglutide and placebo groups.[78]

Figure 43. Withdrawal Due to Adverse Events: Semaglutide vs. Placebo in Youth

Study or Subgroup	Semaglutide Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
STEP TEENS	6	133	3	67	1.01 [0.26, 3.90]	

Favors semaglutide   Favors placebo
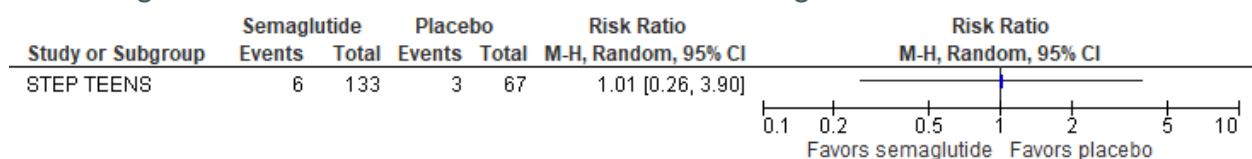
Abbreviations. AE: adverse event; CI: confidence interval.

In the STEP TEENS RCT,[78] more AEs overall were experienced by adolescents who received placebo compared to those who received semaglutide (Table 27), but more gastrointestinal events, including nausea, diarrhea, vomiting and abdominal pain, were experienced by those who received semaglutide (see Appendix D, Tables D9 and D10, for details of AE outcomes for semaglutide). Also, more participants with semaglutide experienced SAEs compared to placebo.[78] No further descriptions of the SAEs were reported. Five participants in the semaglutide group and no participants in the placebo group experienced cholelithiasis.[78]

Table 27. Summary of Adverse Events and Serious Adverse Events: Semaglutide in Youth

Author, Year Study Name	Adverse Events, % n of N			Serious Adverse Events, % n of N		
	Semaglutide	Placebo	P Value	Semaglutide	Placebo	P Value
Youth						
STEP TEENS[78] Weghuber, 2022	79.0% 105 of 133	82.0% 55 of 67	NR	11.0% 15 of 133	9.0% 6 of 67	NR

Abbreviation. NR: not reported.

There were no deaths reported in the STEP TEENS study for semaglutide in adolescents.[78]

Change in Medication Outcomes

The STEP TEENS study for semaglutide in adolescents did not report change in medication outcomes for obesity-related comorbidities.

Semaglutide Compared to Liraglutide

Summary of Included Studies

We identified 1 head-to-head trial (STEP 8) that compared semaglutide with liraglutide.[55] We included the placebo comparisons of the STEP 8 trial in the respective semaglutide and liraglutide sections of this report (above). This section only includes findings for the comparison of semaglutide with liraglutide. The overview of study characteristics for STEP 8 can be found in Tables 5 and 17; details of study and participant characteristics can be found in Appendix B, Tables B1 and B2.

The STEP 8 RCT compared weekly 2.4 mg semaglutide with daily 3.0 mg liraglutide in adults without diabetes.[55] Randomized participants received a background treatment of general diet and exercise

We assessed the STEP 8 RCT as having moderate RoB overall, primarily because of serious author and study funding conflicts of interest. Importantly, randomization to semaglutide or liraglutide was not masked (active treatments against placebo were double-blinded, however). This open-label design between active treatments increased the RoB, which is reflected in our assessments for CoE by further downgrading for the comparisons of liraglutide and semaglutide.

Adults

Weight Outcomes

Summary of Findings (GRADE)

The STEP 8 RCT demonstrated significant differences in favor of semaglutide compared to liraglutide in adults across all weight outcomes (Table 28). The CoE was low for all reported weight outcomes, indicating some level of uncertainty. However, outcomes were not downgraded further for lower overall sample size from 1 study because of the relatively large effects.

Table 28. Certainty of Evidence (GRADE) for Weight Outcomes: Semaglutide vs. Liraglutide

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
1 RCT[55] N = 253	●●○○ Low	Participants randomized to semaglutide lost a significantly greater percentage of body weight compared to liraglutide; the effect is considered clinically meaningful MD, -9.40% (95% CI, -11.82 to -6.98); *P* < .001	Downgraded:[a] 2 levels for RoB • Author and funding CoI • Open-label/unblinded design
Change in body weight (kg)			
1 RCT[55] N = 253	●●○○ Low	Participants randomized to semaglutide lost significantly more kg body weight (as kg) compared to liraglutide; correlated with change in percent body weight, and so also likely at meaningful levels MD, -8.50 kg (95% CI, -11.19 to -5.81); *P* < .001	Downgraded:[a] 2 levels for RoB • Author and funding CoI • Open-label/unblinded design
Change in BMI (kg/m²)			
Not reported			
Proportion with ≥ 5% weight loss			
Not reported			
Proportion with ≥ 10% weight loss			
1 RCT[55] N = 253[a]	●●○○ Low	Participants randomized to semaglutide were more likely to lose at least 10% body weight compared to liraglutide RR, 2.77 (95% CI, 1.99 to 3.85); *P* < .001	Downgraded:[a] 2 levels for RoB • Author and funding CoI • Open-label/unblinded design

Note. [a] Consistency not assessable with 1 study; [b] Sample used in meta-analysis is smaller than total number randomized.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In 1 RCT,[55] adults without diabetes randomized to semaglutide lost significantly more percent body weight compared with individuals randomized to liraglutide (MD, -9.40%; 95% CI, -11.82 to -6.98; Figure 44). This treatment effect is above the level considered clinically meaningful, of at least 5% weight loss.

Figure 44. Change in Body Weight (%): Semaglutide vs. Liraglutide
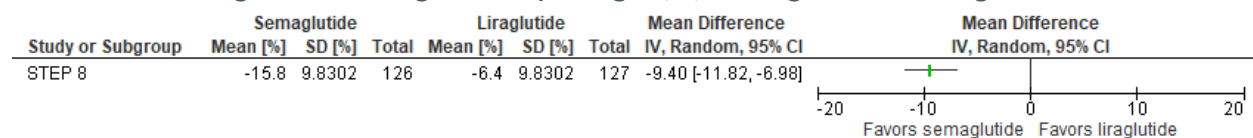
Study or Subgroup	Semaglutide Mean [%]	SD [%]	Total	Liraglutide Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
STEP 8	-15.8	9.8302	126	-6.4	9.8302	127	-9.40 [-11.82, -6.98]	

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In 1 RCT,[55] adults randomized to semaglutide lost significantly more body weight, as measured in kg, compared to individuals randomized to liraglutide (MD, -8.5 kg; 95% CI, -11.19 to -5.81; Figure 45); however, the impact of losing an additional 8.5 kg more will vary depending on the baseline weight and overall height. Correlated with percent change in body weight, this effect is also likely at clinically meaningful levels.

Figure 45. Change in Weight (kg): Semaglutide vs. Liraglutide
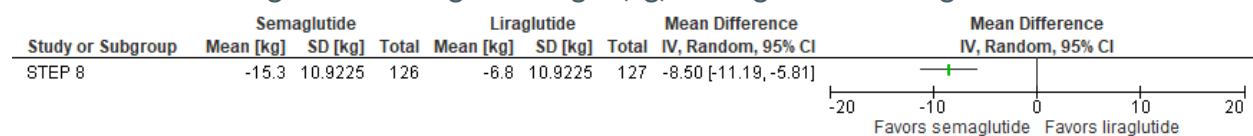
Study or Subgroup	Semaglutide Mean [kg]	SD [kg]	Total	Liraglutide Mean [kg]	SD [kg]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
STEP 8	-15.3	10.9225	126	-6.8	10.9225	127	-8.50 [-11.19, -5.81]	

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In 1 RCT,[55] individuals randomized to semaglutide were significantly more likely to lose at least 10% of their initial weight compared to those who received liraglutide (RR, 2.77; 95% CI, 1.99 to 3.85; Figure 46). The proportion of individuals who lost 10% or more body weight from baseline (above clinically meaningful amount of weight loss) was 70.9% with semaglutide and 25.6% with liraglutide.[55]

Figure 46. Proportion With at Least 10% Weight Loss: Semaglutide vs. Liraglutide
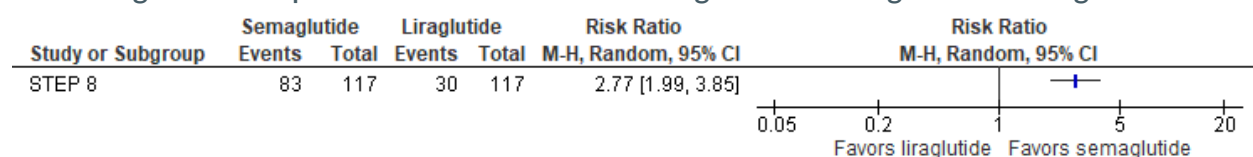
Study or Subgroup	Semaglutide Events	Total	Liraglutide Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
STEP 8	83	117	30	117	2.77 [1.99, 3.85]	

Abbreviation. CI: confidence interval.

Comorbidity Risk Factor Outcomes

Summary of Findings (GRADE)

Table 29. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Semaglutide vs. Liraglutide

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
1 RCT[55] N = 253	●○○○ Very low	Improvements in SBP with semaglutide are not statistically significant compared to liraglutide MD, -2.80 mmHg (95% CI, -5.97 to 0.37); *P* = .08	Downgraded:[a] 2 levels for RoB • Author and funding CoI • Open-label/unblinded design 1 level for imprecision • CI crosses over clinically meaningful change of 5 mmHg
Change in LDL cholesterol (%)			
1 RCT[55] N = 253	●●○○ Low	Improvements in percent LDL cholesterol with semaglutide are not statistically significant compared to liraglutide MD, -7.40% (95% CI, -14.9 to 1.0); *P* value not reported	Downgraded:[a] 2 levels for RoB • Author and funding CoI • Open-label/unblinded design
Change in HbA1c (%)			
1 RCT[55] N = 253	●●○○ Low	Participants randomized to semaglutide had statistically lower percent HbA1c levels compared to liraglutide, but not by a clinically meaningful reduction MD, -0.2% (95% CI, -0.2 to -0.1); *P* value not reported	Downgraded:[a] 2 levels for RoB • Author and funding CoI • Open-label/unblinded design

Note. [a] Consistency not assessable with 1 study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; HbA1c: hemoglobin A1c; LDL: low-density lipoprotein; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; SBP: systolic blood pressure.

Detailed Findings

In STEP 8,[55] the small improvement in mean SBP with semaglutide compared with liraglutide was not statistically different in adults at 68 weeks (MD, -2.80 mmHg; 95% CI, -6.2 to 0.6; Figure 47); 38% in the semaglutide group and 43% in the liraglutide group were reported as having hypertension at baseline.

Figure 47. Change in Systolic Blood Pressure (mmHg): Semaglutide vs. Liraglutide
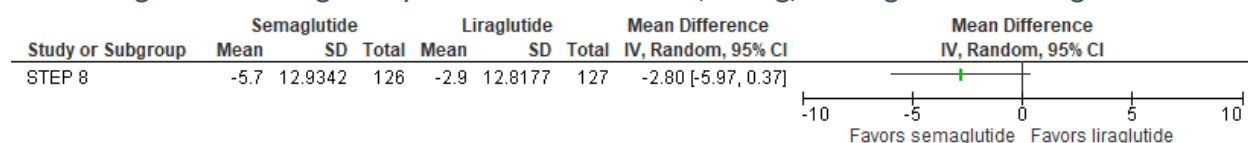
Study or Subgroup	Semaglutide Mean	SD	Total	Liraglutide Mean	SD	Total	Mean Difference IV, Random, 95% CI
STEP 8	-5.7	12.9342	126	-2.9	12.8177	127	-2.80 [-5.97, 0.37]

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In STEP 8,[55] the small improvement in mean percent change in LDL cholesterol with semaglutide compared with liraglutide was reported as not statistically different in adults at 68 weeks (reported 95% CI, -14.9 to 1.0), however our unadjusted calculation demonstrates borderline levels (MD, -7.4%; 95% CI, -14.71 to -0.09; Figure 48); 48% in the semaglutide group and 51% in the liraglutide group were reported as having dyslipidemia at baseline.

Figure 48. Change in LDL Cholesterol (%): Semaglutide vs. Liraglutide
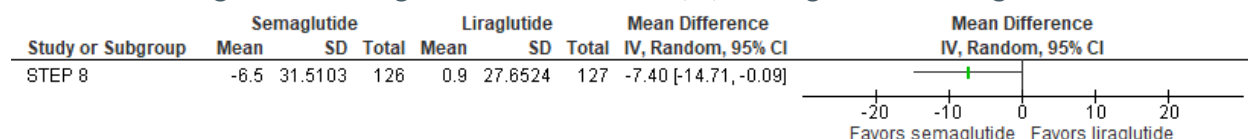
Study or Subgroup	Semaglutide Mean	SD	Total	Liraglutide Mean	SD	Total	Mean Difference IV, Random, 95% CI
STEP 8	-6.5	31.5103	126	0.9	27.6524	127	-7.40 [-14.71, -0.09]

Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation.

In STEP 8,[55] the reported improvements in percent HbA1c with semaglutide were very small, but statistically greater, compared with liraglutide (MD, -0.2%; 95% CI, −0.2 to −0.1; *P* value not reported) and not at clinically meaningful levels. We are reporting published results for this outcome; we were unable to reproduce the findings in RevMan because of adjustments to the statistical model made by study authors. The proportion of individuals with prediabetes at baseline in STEP 8 were 34% in the semaglutide group and 35% in the liraglutide group.[55]

Quality of Life Outcomes
QoL was not measured in the STEP 8 study that compared semaglutide with liraglutide.

Safety Outcomes
The STEP 8 study reported overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE (Table 30).

Summary of Findings (GRADE)

Table 30. Certainty of Evidence (GRADE) for Safety: Semaglutide vs. Liraglutide

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
1 RCT[55] N = 253	●○○○ Very low	Participants randomized to semaglutide were significantly less likely to withdraw due to an AE compared to individuals randomized to liraglutide • RR (risk of withdrawal for semaglutide compared to liraglutide), 0.25 (95% CI, 0.09 to 0.73); P = .01 • RR (risk for liraglutide compared to semaglutide), 3.97 (95% CI, 1.4 to 11.5)	Downgraded:[a] 2 levels for RoB • Author and funding CoI • Open-label/unblinded design 1 level for imprecision • Low events in single study with low overall sample size

Note. [a] Consistency not assessable with 1 study.

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In 1 RCT,[55] adults randomized to semaglutide were less likely to experience an AE that led to study withdrawal compared to individuals randomized to liraglutide (RR, 0.25; 95% CI, 0.09 to 0.73; Figure 49) The proportion of withdrawals due to AEs was 3.2% with semaglutide and 12.6% with liraglutide.[55]

Figure 49. Proportion of Withdrawals Due to Adverse Events: Semaglutide vs. Liraglutide

Study or Subgroup	Semaglutide Events	Total	Liraglutide Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
STEP 8	4	126	16	127	0.25 [0.09, 0.73]	

0.01 0.1 1 10 100
Favors semaglutide   Favors liraglutide

Abbreviations. AE: adverse event; CI: confidence interval.

In the STEP 8 trial, individuals in both semaglutide and liraglutide groups experienced similar numbers of adverse events overall, and slightly more individuals who received liraglutide experienced an SAE compared to those who received semaglutide (Table 31).[55] There were no further descriptions of the SAEs, or whether they were considered related to the study drugs. Gastrointestinal disorders, including nausea, constipation, diarrhea, and vomiting, were the most frequent AEs experienced across both groups, and were slightly more likely to be experienced by individuals in the semaglutide group (see Appendix E, Tables E7 and E8, for details of AE outcomes for the STEP 8 study).[55]

Table 31. Summary of Adverse Events and Serious Adverse Events: Semaglutide vs. Liraglutide

Author, Year Study Name	Adverse Events, % n of N			Serious Adverse Events, % n of N		
	Semaglutide	Liraglutide	P Value	Semaglutide	Liraglutide	P Value
Adults						
STEP 8[55] Rubino, 2022	95.2% 120 of 126	96.1% 122 of 127	NR	7.9% 10 of 126	11.0% 14 of 127	NR

Abbreviation. NR: not reported.

There were no deaths reported in the STEP 8 study in adults.[55]

Change in Medication Outcomes

The STEP 8 study did not report change in medication outcomes for obesity-related comorbidities.

Tirzepatide

Summary of Included Study

We identified 1 RCT for tirzepatide that aligned with our PICOS and was eligible for this review (Table 32). The SURMOUNT-1 RCT followed participants randomized to 1 of 3 doses of tirzepatide or placebo in adults without diabetes over 72 weeks.[81]

Study authors report that the subgroup of individuals with prediabetes at baseline will continue to receive treatment after 72 weeks, through 2 years[81]; these results have not yet been published.

Table 32. Overview of Study Characteristics: Tirzepatide

Study Name Author, Year Study Design RoB	Includes US?	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Condition
Adults								
SURMOUNT-1[81] Jastreboff, 2022 RCT Moderate RoB	Yes	72 + 4	Diet and exercise	2,539	• SC tirzepatide 15.0 mg weekly • SC 10.0 mg weekly • SC 5.0 mg weekly • Placebo	None	BMI ≥ 30 or ≥ 27 kg/m² with ≥ 1 comorbidity	None

Abbreviations. BMI: body mass index; F/U: follow-up; RCT: randomized controlled trial; RoB: risk of bias; SC: subcutaneous.

We assessed the SURMOUNT-1 trial as having moderate RoB in light of serious conflicts of interest of study authors and funding.

Weight Outcomes

Summary of Findings (GRADE)

The SURMOUNT-1 study measured percent change in weight, and proportion with at least 5% and 10% weight loss for this outcome, with a primary end point of 72 weeks. The randomized interventional period for this study was longer than most studies included for liraglutide and semaglutide, except for those few with extension periods.

Table 33. Certainty of Evidence (GRADE) for Weight Outcomes: Tirzepatide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
1 RCT[81] N = 2,539	●●●○ Moderate	Participants randomized to tirzepatide lost a significantly greater percentage of body weight compared to placebo; the effect was above what is considered clinically meaningful MD, -15.37% (95% CI, -16.68 to -14.06); *P* < .001	Downgraded:[a] 1 level for RoB • Author and funding CoI
Change in body weight (kg)			
Not reported			
Change in BMI (kg/m^2)			
Not reported			
Proportion with ≥ 5% weight loss			
1 RCT[81] N = 2,539	●●●○ Moderate	Participants randomized to tirzepatide were more likely to lose at least 5% body weight compared to placebo RR, 2.56 (95% CI, 2.30 to 2.85); *P* < .001	Downgraded:[a] 1 level for RoB • Author and funding CoI
Proportion with ≥ 10% weight loss			
1 RCT[81] N = 2,539	●●●○ Moderate	Participants randomized to tirzepatide were more likely to lose at least 10% body weight compared to placebo RR, 4.08 (95% CI, 3.47 to 4.80); *P* < .001	Downgraded:[a] 1 level for RoB • Author and funding CoI

Note. [a] Consistency not assessable with 1 study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.
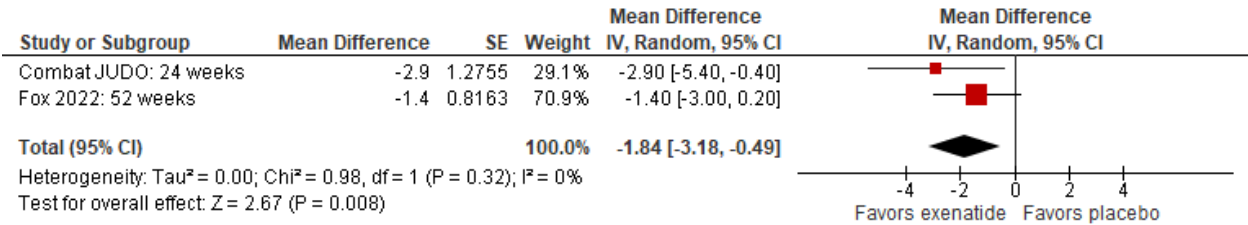
Detailed Findings

In a pooled analysis of 3 doses of tirzepatide in the single SURMOUNT-1 study,[81] individuals randomized to tirzepatide lost significantly more percent body weight compared to individuals randomized to placebo (MD, -15.37%; 95% CI, -16.68 to -114.06; Figure 50). The overall treatment effect is well above change in percent body weight considered clinically meaningful (of at least 5% weight loss).

There also appeared to be the trend towards a dose effect over the 72-week trial, with percent of body weight lost from baseline as -15.0%, 19.5%, and 20.9%, in people who received weekly 5 mg, 10 mg, and 15 mg doses of tirzepatide, respectively (Figure 51).[81] All doses achieved

clinically meaningful decreases in percent body weight, with even the lowest ends of all confidence intervals reaching meaningful improvements.[81]

Figure 50. Change in Weight (%): Tirzepatide vs. Placebo in Adults
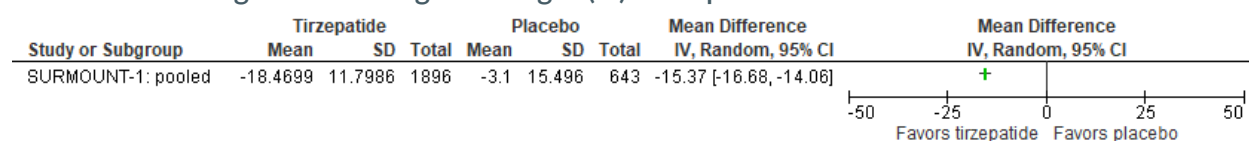
Study or Subgroup	Tirzepatide Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
SURMOUNT-1: pooled	-18.4699	11.7986	1896	-3.1	15.496	643	-15.37 [-16.68, -14.06]	

-50 -25 0 25 50
Favors tirzepatide Favors placebo

Abbreviations. CI: confidence interval; GDM: IV: inverse variance; SD: standard deviation.

Figure 51. Change in Weight (%) by Dose: Tirzepatide vs. Placebo in Adults
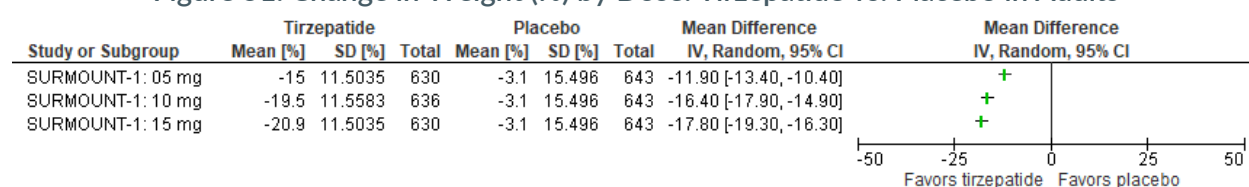
Study or Subgroup	Tirzepatide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
SURMOUNT-1: 05 mg	-15	11.5035	630	-3.1	15.496	643	-11.90 [-13.40, -10.40]	
SURMOUNT-1: 10 mg	-19.5	11.5583	636	-3.1	15.496	643	-16.40 [-17.90, -14.90]	
SURMOUNT-1: 15 mg	-20.9	11.5035	630	-3.1	15.496	643	-17.80 [-19.30, -16.30]	

-50 -25 0 25 50
Favors tirzepatide Favors placebo

Abbreviations. CI: confidence interval; GDM: IV: inverse variance; SD: standard deviation.

In a pooled analysis of 3 doses of tirzepatide in the single SURMOUNT-1 study,[81] individuals randomized to tirzepatide were significantly more likely to lose at least 5% of their baseline weight compared to individuals randomized to placebo (RR, 2.56; 95% CI, 2.30 to 2.85; Figure 52). The proportion of individuals who lost 5% or more body weight from baseline (which is considered a clinically meaningful level of weight loss) was 88.3% with tirzepatide and 34.5% with placebo.[81]

Figure 52. Proportion With at Least 5% Weight Loss: Tirzepatide vs. Placebo in Adults
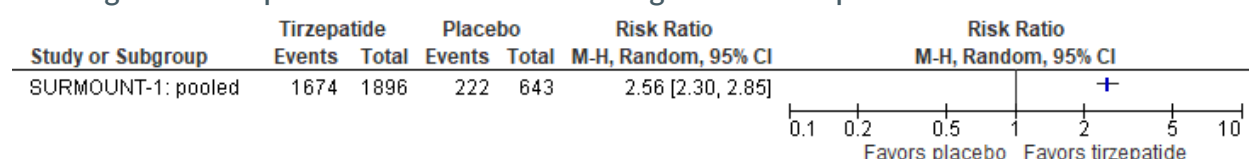
Study or Subgroup	Tirzepatide Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
SURMOUNT-1: pooled	1674	1896	222	643	2.56 [2.30, 2.85]	

0.1 0.2 0.5 1 2 5 10
Favors placebo Favors tirzepatide

Abbreviation. CI: confidence interval.

In a pooled analysis of 3 doses of tirzepatide in the single SURMOUNT-1 study,[81] individuals randomized to tirzepatide were significantly more likely to lose at least 10% of their baseline weight compared to individuals randomized to placebo (RR, 4.08; 95% CI, 3.47 to 4.80; Figure 53). The proportion of individuals who lost 10% or more body weight from baseline (above clinically meaningful levels of weight loss) was 76.7% with tirzepatide and 18.8% with placebo.[81]

Figure 53. Proportion With at Least 10% Weight Loss: Tirzepatide vs. Placebo in Adults
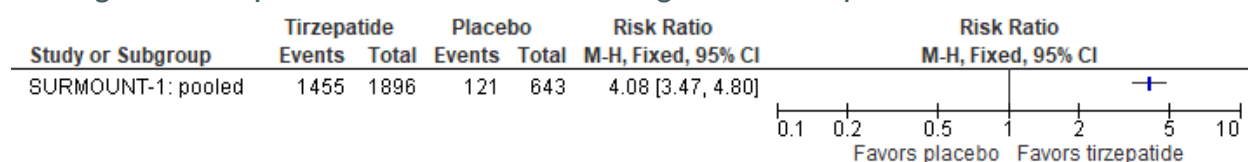
Study or Subgroup	Tirzepatide Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
SURMOUNT-1: pooled	1455	1896	121	643	4.08 [3.47, 4.80]

Abbreviation. CI: confidence interval.

Comorbidity Risk Factor Outcomes
Summary of Findings (GRADE)

Table 34. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Tirzepatide in Adults

| Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
1 RCT[81] N = 2,539	●●○○ Low	Participants randomized to tirzepatide had a significant, and clinically meaningful, reduction in SBP compared to placebo MD, -6.20 mmHg (95% CI, -7.61 to -4.79); $P < .001$	Downgraded:[a] 1 level for RoB • Author and funding CoI 1 level for imprecision • CI crosses over clinically meaningful change of 5 mmHg
Change in LDL cholesterol (% change of mg/dL)			
1 RCT[81] N = 2,539	●●●○ Moderate	Participants randomized to tirzepatide had a significantly greater reduction in LDL cholesterol compared to placebo; this difference is likely not clinically meaningful MD, -4.10% (95% CI, -7.20 to -1.00); $P = .009$	Downgraded:[a] 1 level for RoB • Author and funding CoI
Change in HbA1c (%)			
1 RCT[81] N = 2,539	●●●○ Moderate	Participants randomized to tirzepatide had a significant, and clinically meaningful, reduction in percent HbA1c compared to placebo MD, -0.40% (95% CI, -0.42 to -0.37); $P < .001$	Downgraded:[a] 1 level for RoB • Author and funding CoI

Note. [a] Consistency not assessable with 1 study.
Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In a pooled analysis of 3 doses of tirzepatide in the single SURMOUNT-1 study,[81] individuals randomized to tirzepatide had a significantly greater reduction in SBP compared to individuals randomized to placebo (MD, -6.20 mmHg; 95% CI, -7.61 to -4.79; Figure 54). This treatment effect is considered a clinically meaningful reduction in SBP of at least 5.0 mmHg, although the

CI suggests some may not experience meaningful improvements. No dose affect was apparent across the 5 mg, 10 mg, or 15 mg dose groups.

Figure 54. Change in Systolic Blood Pressure (mmHg): Tirzepatide vs. Placebo in Adults
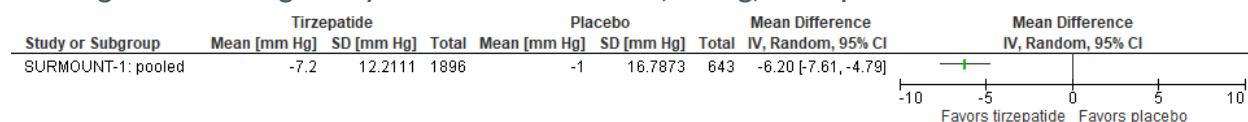
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 3 doses of tirzepatide in the single SURMOUNT-1 study,[81] individuals randomized to tirzepatide had a significantly greater reduction in percentage of LDL cholesterol compared to individuals who received placebo (MD, -4.1%; 95% CI, -7.2 to -1.0; Figure 55). With the baseline geometric mean LDL cholesterol at 109.5 mg/dL for all participants,[81] a decrease by 4.1% is about 4.5 mg/dL, which is well below the level considered a meaningful change of a decrease of at least 38.7 mg/dL (about 1 mmol/L). Approximately 29% of participants were with dyslipidemia at baseline in this SURMOUNT-1 study[81] (see Appendix B, Table B2, for study participant characteristics).

Figure 55. Change in LDL Cholesterol (%): Tirzepatide vs. Placebo in Adults
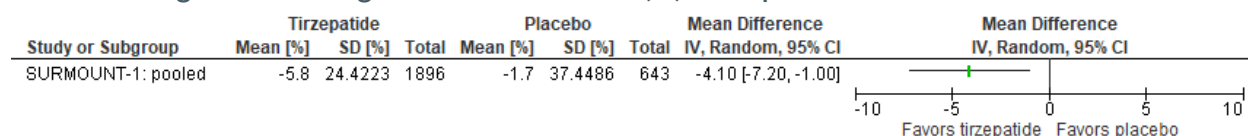
Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation.

In a pooled analysis of 3 doses of tirzepatide in the SURMOUNT-1 study,[81] individuals randomized to tirzepatide had a significantly greater reduction in percentage of HbA1c compared to individuals who received placebo (MD, -0.40%; 95% CI, -0.42 to -0.37; Figure 56). This treatment effect is considered a clinically meaningful improvement of at least 0.3%. A small dose effect was also evident; mean changes from baseline were -0.40%, -0.49%, and -0.51% in the 5 mg, 10 mg, and 15 mg dose groups, respectively.[81]

Figure 56. Change in HbA1c (%): Tirzepatide vs. Placebo in Adults
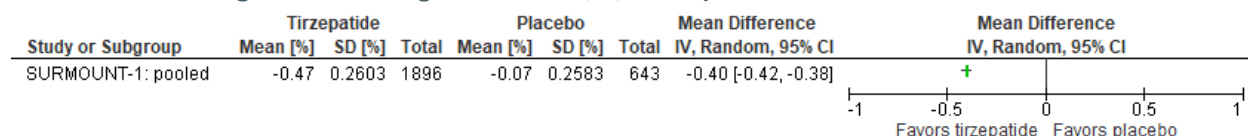
Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c Protein; IV: inverse variance; SD: standard deviation.

Quality of Life Outcomes

Summary Findings (GRADE)

Table 35. Certainty of Evidence (GRADE) for Quality of Life: Tirzepatide vs. Placebo in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in SF-36 physical function score			
1 RCT[81] N = 1,909[a]	●●●○ Moderate	Participants randomized to 10 mg and 15 mg doses of tirzepatide experienced a small but statistically significant improvement in physical function QoL compared to placebo; likely not considered clinically meaningful MD, 1.9 points (95% CI, 0.9 to 2.9); *P* = .002	Downgraded:[b] 1 level for RoB • Author and funding CoI, smaller cohort used for this analysis

Note. [a] This measure was not reported in participants who received the 5 mg dose; [b] Consistency not assessable with 1 study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MA: meta-analysis; MD: mean difference; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias; SF-36: Short-Form Health Survey, 36 questions.

Detailed Findings

Participants randomized to the 2 higher doses of tirzepatide (pooled result of 10 mg and 15 mg doses) experienced a small but statistically significant improvement in self-reported physical function QoL compared to placebo[81] (MD, 1.9 points; 95% CI, 0.9 to 2.9; *P* value not reported). The authors considered this difference as not clinically meaningful.

Safety Outcomes

The SURMOUNT-1 study reported overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE (Table 36).

Summary of Findings (GRADE)

Table 36. Certainty of Evidence (GRADE) for Safety Outcomes: Tirzepatide vs. Placebo in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
1 RCT[81] N = 2,539	●●●○ Moderate	Participants randomized to liraglutide were significantly more likely to withdraw due AEs compared to individuals randomized to placebo RR, 2.21 (95% CI, 1.34 to 3.66); *P* = .002	Downgraded:[a] 1 level for RoB • Author and funding CoI

Note. [a] Consistency not assessable with 1 study.

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of 3 doses of tirzepatide in the single SURMOUNT-1 study,[81] individuals randomized to tirzepatide were more likely to experience an AE that led to study withdrawal compared to individuals randomized to placebo (RR, 2.21; 95% CI, 1.3 to 3.7; Figure 57). The proportion of withdrawals due to AEs was 5.9% with across all tirzepatide doses and 2.6% with placebo in this study.[81] A dose effect was evident with withdrawals due to AEs as 4.3%, 7.1%, and 6.2% with weekly 5 mg, 10 mg, and 15 mg of tirzepatide,[81] respectively.

Figure 57. Proportion of Withdrawals Due to Adverse Events: Tirzepatide in Adults
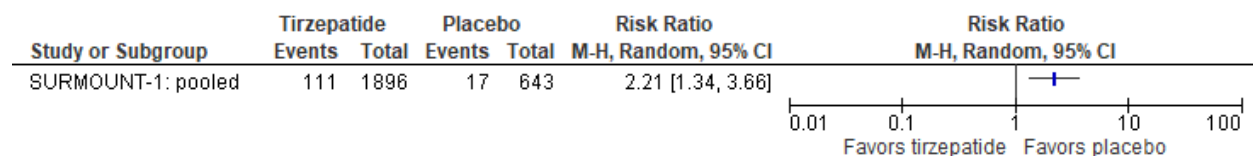
Study or Subgroup	Tirzepatide Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
SURMOUNT-1: pooled	111	1896	17	643	2.21 [1.34, 3.66]	

0.01   0.1   1   10   100
Favors tirzepatide   Favors placebo

Abbreviations. AE: adverse event; CI: confidence interval; IV: inverse variance; SD: standard deviation.

Individuals randomized to tirzepatide (all dose groups) experienced slightly more AEs overall compared to placebo (Table 37).[81] However, SAEs were distributed evenly across groups; over 20% were considered related to COVID-19.[81] Nausea, diarrhea, constipation, and vomiting were the most frequently experienced AEs and all were more common in tirzepatide groups (see Appendix F, Tables F7 and F8, for details of AE outcomes for tirzepatide). Individuals in the higher 15 mg and 10 mg dose groups experienced more vomiting compared to the low-dose group, however all other gastrointestinal events were distributed relatively even across dose groups.[81]

Table 37. Summary of Adverse Events and Serious Adverse Events: Tirzepatide in Adults

Dose	Adverse Events, % n of N			Serious Adverse Events, % n of N		
	Tirzepatide	Placebo	P Value	Tirzepatide	Placebo	P Value
SURMOUNT-1 (Jastreboff, 2022)[81]						
Pooled doses	81.6% 1,527 of 1,895	72.0% 463 of 643	NR	6.1% 116 of 1,895	6.8% 44 of 643	NR
15 mg weekly	78.9% 497 of 630	72.0% 463 of 643	NR	5.1% 32 of 630	6.8% 44 of 643	NR
10 mg weekly	81.8% 520 of 636	72.0% 463 of 643	NR	6.9% 44 of 636	6.8% 44 of 643	NR
5 mg weekly	81.0% 510 of 630	72.0% 463 of 643	NR	6.3% 40 of 630	6.8% 44 of 643	NR

Abbreviation. NR: not reported.

Over the 72-week study duration, 7 participants died in the tirzepatide groups and 4 died in the placebo group.[81] Three deaths in the tirzepatide groups were attributed to COVID-19. Cardiovascular events were reported as the cause of death in 2 individuals in the placebo group, and 1 individual who received tirzepatide.[81]

Change in Medication Outcomes

The SURMOUNT-1 study for tirzepatide did not report change in medication outcomes for obesity-related comorbidities.

Youth

No studies for tirzepatide in youth were identified for this report.

Exenatide

Summary of Included Studies

We identified 3 RCTs for exenatide; 1 RCT compared exenatide with glibenclamide in adults,[84] and 2 RCTs compared exenatide with placebo in youth[82,83] (Table 38).

In the RCT by Derosa and colleagues for exenatide in adults,[84] they compared daily 20 µg exenatide administered subcutaneously, with daily 15 mg glibenclamide administered orally (pill form) in overweight adults with T2DM and poor glycemic control (HbA1c > 8%) and on background metformin therapy (in addition to diet and exercise). Glibenclamide, also known as glyburide, is a common second-generation sulfonylurea used to treat T2DM by promoting the release of insulin from the pancreas.

In the 2 RCTs for exenatide in youth,[82,83] there were differences in eligibility criteria, requirements for weight loss prior to randomization, and study duration.
- The RCT by Fox and colleagues[82] assessed maintenance of weight loss over 52 weeks in adolescents with severe obesity, but without diabetes; participants who achieved 5% or more weight loss during a 4-week calorie-restricted (meal replacement program) run-in period were randomized to weekly 2.0 mg exenatide or placebo.
- The Combat-JUDO study[83] followed children and adolescents without diabetes who were randomized to weekly 2.0 mg exenatide or placebo, over 24 weeks.

Table 38. Overview of Study Characteristics: Exenatide

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Conditions
Adults								
Derosa, 2010[84] RCT High RoB	No	52	Metformin, diet and exercise	128	• SC exenatide 20 µg daily • Oral glibenclamide 15 mg daily	With T2DM	BMI ≥ 25 and < 30 kg/m²	None
Youth								
Combat-JUDO[83] Weghuber, 2020 RCT Moderate RoB	No	24 + 2	Diet and exercise	44	• SC exenatide 2.0 mg weekly • Placebo	None	Age-adapted BMI ≥ 30 kg/m²	None

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Diabetes Status	Weight Criteria	Other Conditions
							Eligibility	
Fox, 2022[82] RCT Moderate RoB	Yes	52	MRT run-in followed by diet and exercise	66	• SC exenatide 2.0 mg weekly • Placebo	None	BMI ≥ 1.2x 95th percentile or ≥ 35 kg/m²	≥ 5% weight loss during run-in

Abbreviations. BMI: body mass index; F/U: follow-up; MRT: meal replacement therapy; RCT: randomized controlled trial; RoB: risk of bias; SC: subcutaneous; T2DM: type 2 diabetes.

We assessed the RCT in adults as high RoB because of limited blinding (single-blind only) and poor reporting of methods and results. We assessed the 2 RCTs in youth as moderate RoB primarily because of author conflicts of interest, and also shorter duration in 1 study[83] and moderate discrepant attrition in the other.[82]

Adults

Weight Outcomes

This single study reported baseline and 12-month post-treatment values of absolute body weight and change in BMI for weight measures only; mean change values from baseline were not reported.

Summary of Findings (GRADE)

Table 39. Certainty of Evidence (GRADE) for Weight: Exenatide vs. Glibenclamide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
Not reported			
Change in body weight (kg)			
1 RCT[84] N = 128	●●●○ Moderate	Participants with T2DM randomized to exenatide lost significantly more kg body weight compared to glibenclamide; this difference may be considered clinically meaningful MD[a], -12.70 kg (95% CI, -15.60 to -9.80); *P* < .001	Downgraded:[b] 1 level for RoB • Single-blind; poor reporting of results
Change in BMI (kg/m²)			
1 RCT[84] N = 128	●●●○ Moderate	Participants with T2DM randomized to exenatide had significantly reductions in BMI compared to glibenclamide MD[a], -4.10 kg/m² (95% CI, -4.59 to -3.61); *P* < .001	Downgraded:[b] 1 level for RoB • Single-blind; poor reporting of results

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Proportion with ≥ 5% weight loss			
Not reported			
Proportion with ≥ 10% weight loss			
Not reported			

Note. [a] Calculated from post-treatment values; [b] Consistency not assessable with 1 study.
Abbreviations. CI: confidence interval; CoE: certainty of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In 1 RCT,[84] overweight (BMI ≥ 25 and < 30 kg/m^2) individuals who were randomized to exenatide had statistically lower post-treatment body weight measures in kg, compared to individuals randomized to glibenclamide (MD-12.7 kg; 95% CI, -15.8 to -9.6; Figure 58). From reported baseline (82.0 kg with exenatide, 82.4 kg with glibenclamide) and post-treatment body weight measures,[84] mean weight loss values can be calculated as -8 kg with exenatide and +4.3 with glibenclamide. The calculated MD between groups is 12.3 kg, which translates to an approximately 15 percentage point-difference in body weight between groups; this difference could be considered clinically meaningful.

Figure 58. Change in Weight (kg): Exenatide vs. Glibenclamide in Adults

Study or Subgroup	Exenatide Mean [kg]	SD [kg]	Total	Glibenclamide Mean [kg]	SD [kg]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Derosa 2010	74	4.1	63	86.7	11.2	65	-12.70 [-15.60, -9.80]	

Favors exenatide   Favors glibenclamide
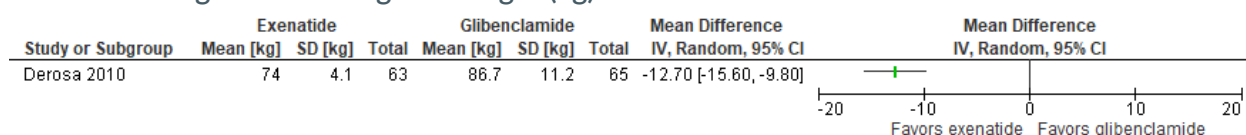
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In 1 RCT,[84] individuals randomized to exenatide had statistically lower post-treatment BMI values compared to individuals randomized to glibenclamide (MD, -4.1 kg/m^2; 95% CI, -4.6 to -3.7; Figure 59). The impact of reducing BMI further by nearly just over 4 kg/m^2 will vary depending on the baseline BMI, and whether the change leads to a drop in class of obesity clinical severity.

Figure 59. Change in BMI (kg/m^2): Exenatide vs. Glibenclamide in Adults
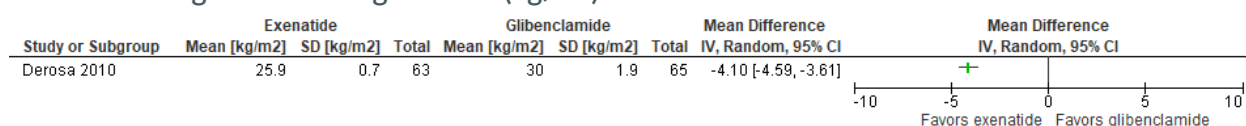
Study or Subgroup	Exenatide Mean [kg/m2]	SD [kg/m2]	Total	Glibenclamide Mean [kg/m2]	SD [kg/m2]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Derosa 2010	25.9	0.7	63	30	1.9	65	-4.10 [-4.59, -3.61]	

Favors exenatide   Favors glibenclamide

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

Comorbidity Risk Factor Outcomes

The RCT for exenatide in adults did not measure cardiovascular risk factor outcomes of interest; long-term blood glucose control was measured as HbA1c levels, however (Table 40).

Summary of Findings (GRADE)

Table 40. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Exenatide vs. Glibenclamide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure			
Not reported			
Change in LDL cholesterol			
Not reported			
Change in HbA1c (%)			
1 RCT[84] N = 128	●●○○ Low	No difference in change in percent HbA1c between exenatide and glibenclamide groups	Downgraded:[a] 2 levels for RoB • Single-blind; minimal outcomes reporting

Note. [a] Consistency not assessable with 1 study.

Abbreviations. CoE: certainty of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MC: mean change; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In 1 RCT,[84] improvements in percent HbA1c from baseline were reported in both exenatide and glibenclamide groups (at 52 weeks, 7.3% [SD, 0.3] with exenatide and 7.1% [SD, 0.2] with glibenclamide), but the difference in reduction was reported as not statistically significant between the groups (*P* value not reported).

Quality of Life Outcomes

QoL was not measured in the single RCT that compared exenatide with glibenclamide in adults.

Safety Outcomes

The single study of exenatide in adults reported limited details of safety outcomes; however, we assessed the CoE for withdrawals due to AEs using GRADE (Table 41).

Summary of Findings (GRADE)

Table 41. Certainty of Evidence (GRADE) for Safety: Exenatide vs. Glibenclamide in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
1 RCT[84] N = 128	●●○○ Low	No difference in withdrawals due to AEs between exenatide and glibenclamide groups RR, 0.59 (95% CI, 0.18 to 1.92); *P* = .26	Downgraded:[a] 1 level for RoB • Single-blind; poor reporting of results 1 level for imprecision • Low number of events

Note. [a] Consistency not assessable with 1 study.

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; GRADE: Grading of

Detailed Findings

In 1 RCT,[84] although more individuals randomized to glibenclamide withdrew because of an AE compared to individuals in the exenatide group, the difference was not statistically significant (RR, 0.59; 95% CI, 0.18 to 1.92; Figure 60). Most AEs leading to withdrawal were gastrointestinal side effects that were experienced relatively equally across groups (nausea, diarrhea and vomiting), while 3 persons in the glibenclamide group (and none with exenatide) withdrew because of hypoglycemic events.[84] The proportion of withdrawals due to AEs was 6.4% with exenatide and 10.8% with glibenclamide in this study.[84]

Figure 60. Withdrawal Due to Adverse Events: Exenatide vs. Glibenclamide in Adults

Study or Subgroup	Exenatide Events	Total	Glibenclamide Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Derosa 2010	4	63	7	65	0.59 [0.18, 1.92]	

0.01   0.1   1   10   100
Favors exenatide   Favors glibenclamide
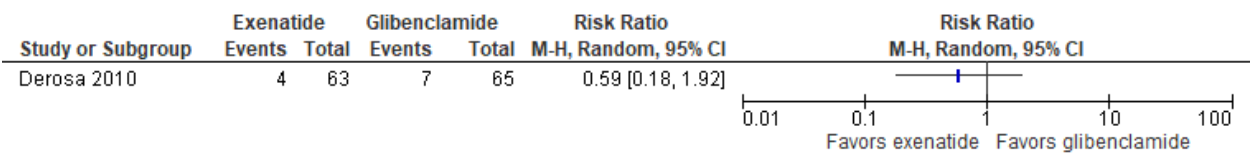
Abbreviations. AE: adverse event; CI: confidence interval.

For overall AEs, the study by Derosa and colleagues only reported that there were no differences in gastrointestinal complaints between exenatide and glibenclamide groups; SAEs were not mentioned.[84] No deaths were reported over the 52-week study period.

Change in Medication Outcomes

Change in medication outcomes for obesity-related comorbidities were not reported in the study by Derosa and colleagues.

Youth

Weight Outcomes

Summary of Findings (GRADE)

Table 42. Certainty of Evidence (GRADE) for Weight Outcomes: Exenatide in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in BMI z/SD score			
1 RCT[83] N = 44	●○○○ Very low	Youth randomized to exenatide had significant reductions in BMI z/SD scores compared to placebo at 24 weeks; this difference is not at clinically meaningful levels MD, −0.09 SDs (95% CI, −0.18 to −0.00); *P < .05* (as reported)	Downgraded:[a] 2 levels for RoB • Short study duration • Author and funding CoI 1 level for imprecision • CI crosses clinically meaningful level of at least -0.15 SDs
Change in BMI (%)			
1 RCT[82] N = 66	●○○○ Very low	The greater reduction in change in percent BMI with exenatide compared to placebo was not significantly different MD, -4.1% (95% CI, -8.6 to 0.5); *P = .08*	Downgraded:[a] 2 levels for RoB • Discrepant values between groups after run-in • Author and funding CoI 1 level for imprecision • CI crosses clinically meaningful level of at least 5%
Percent of 95th BMI percentile (%)			
2 RCTs[82,83] N = 110	●●○○ Low	Youth randomized to exenatide significantly reduced percent of 95th BMI percentile compared to placebo, but may depend on duration of treatment MD, -1.84% (95% CI, -3.18 to -0.49); *P = .008*	Downgraded: 1 level for RoB • Some funding and author CoI 1 level for imprecision • Low overall sample size
Proportion with ≥ 5% weight loss			
Not reported			
Proportion with ≥ 10% weight loss			
Not reported			

Note. ᵃ Consistency not assessable with 1 study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In the Combat-JUDO study,[83] youth randomized to exenatide had a significant reduction in BMI SD scores compared to youth randomized to placebo at 24 weeks (MD, −0.09 SDs; 95% CI, −0.18 to −0.00; *P < .05* [as reported]). This treatment effect is less than what is considered

clinically meaningful (an increase by at least 0.15 SDs). However, the confidence interval suggests that some who are treated with exenatide may experience meaningful improvements.

In the study by Fox and colleagues,[82] adolescents randomized to exenatide after weight loss using meal replacement therapy regained a smaller percent BMI compared to those who received placebo over the 52-week randomized period, but this difference was not statistically different (MD, -4.1%; 95% CI, -8.6 to 0.5); *P* = .08 [as reported]). However, based on the CI, some participants with exenatide may reach meaningful improvements in change in percent BMI.

Both studies reported the outcome for change in percent of the 95th BMI percentile,[82,83] so a pooled analysis of this measure was conducted in order to compare results across studies. The percentage of the 95th percentile of BMI chart was developed to address the limitations of the CDC growth charts to assess and track growth in children with severe obesity, and defines a child's BMI as a percentage of the 95th percentile.[115] In the pooled analysis, youth randomized to exenatide achieved a greater percent reduction in 95th BMI percentile compare to those randomized to placebo (MD, -1.84%; 95% CI, -3.18 to -0.49; Figure 61). Independently, 1 study demonstrated statistically significant reductions at 24 weeks,[83] but the other study showed the reduction was not significant at 52 weeks.[82]

Figure 61. Percent of 95th BMI Percentile: Exenatide vs. Placebo in Youth

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Combat JUDO: 24 weeks	-2.9	1.2755	29.1%	-2.90 [-5.40, -0.40]
Fox 2022: 52 weeks	-1.4	0.8163	70.9%	-1.40 [-3.00, 0.20]
Total (95% CI)			100.0%	-1.84 [-3.18, -0.49]
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 1 (P = 0.32); I² = 0%				
Test for overall effect: Z = 2.67 (P = 0.008)				

Mean Difference IV, Random, 95% CI

-4   -2   0   2   4
Favors exenatide   Favors placebo

Abbreviation. CI: confidence interval.

Both studies also measured change in BMI, as kg/m^2; this measure was not assessed for CoE using GRADE.
- Individuals randomized to exenatide had greater reductions in BMI compared to placebo in both studies, but the difference was only statistically different at 24 weeks,[83] and not in the study that followed individuals through 52 weeks.[82]

Comorbidity Risk Factor Outcomes
Summary of Findings (GRADE)

Table 43. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Exenatide in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
2 RCTs[82,83] N = 110	●●○○ Low	No difference in change SBP between exenatide and placebo groups in youth MD, -2.20 mmHg (95% CI, -5.57 to 1.18); P = .2	Downgraded: 1 level for RoB • Author and funding CoI 1 level for imprecision • Wide CIs
Change in LDL cholesterol			
2 RCTs[82,83] N = 110	●○○○ Very low	Mixed results • 1 RCT showed a small but significant reduction in LDL cholesterol with exenatide compared to placebo at 24 weeks in youth • 1 RCT showed greater rebound in LDL cholesterol with exenatide after a weight-loss run-in period in adolescents, but was not statistically different from placebo	Downgraded: 2 levels for RoB • Discrepant values between groups after run-in • Author and funding CoI 1 level for inconsistency
Change in HbA1c (%)			
1 RCT N = 66	●●○○ Low	No difference in change in percent HbA1c comparing exenatide with placebo in adolescents at 52 weeks MD, 0.10% (95% CI, -0.02 to 0.22); P = .11	Downgraded:[a] 2 levels for RoB • Discrepant values between groups after run-in • Author and funding CoI

Note. [a] Consistency not assessable with single study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; HbA1c: hemoglobin A1c; LDL: low-density lipoprotein; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings
In a pooled analysis of 2 RCTs[82,83] there was no statistical difference between exenatide and placebo groups in youth (MD, -2.2 mmHg; 95% CI, -5.6 to 1.2; Figure 62).

Figure 62. Change in Systolic Blood Pressure (mmHg): Exenatide vs. Placebo in Youth
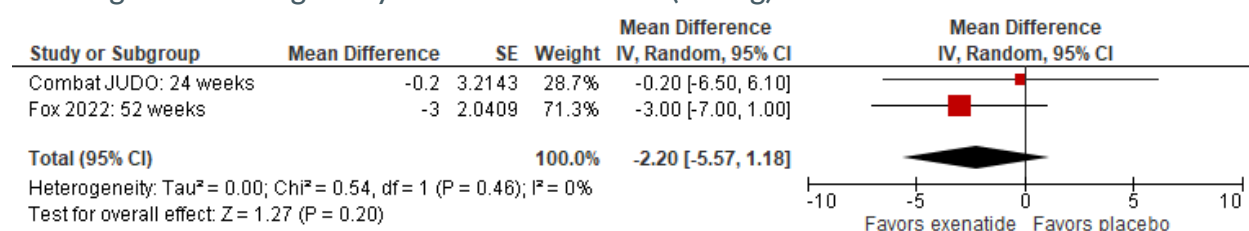
Abbreviations. CI: confidence interval; IV: inverse variance; SE: standard error.

There were mixed results for change in LDL cholesterol (Figure 63). The different study design and discrepant baseline levels in 1 study likely contributed to the difference in effects, but more studies with the same characteristics are needed to confirm this assumption.

- In the Combat-JUDO RCT,[83] children and adolescents randomized to exenatide had small but statistically greater reductions in LDL cholesterol levels compared to placebo at 24 weeks (MD, −7.3 mg/dL; 95% CI, −14.2 to −0.4; P < .05 [as reported]; this difference is well below the level considered clinically meaningful of at least 38.7 mg/dL.
- In the RCT by Fox and colleagues,[82] adolescents randomized to exenatide had greater *increases* in LDL cholesterol compared to those randomized to placebo at 52 weeks, although the difference was not statistically significant (P = .16). However it is important to note that individuals in the exenatide group experienced greater reductions in LDL cholesterol during the 4-week calorie-restricted run-in period, compared to those in the placebo group (at randomization LDL cholesterol was 78.6 mg/dL in the exenatide group and 81.3 mg/dL in the placebo group; prior to the run-in period, the average level for the entire cohort was 95 mg/dL).[82]

Figure 63. Change in LDL Cholesterol (mg/dL): Exenatide vs. Placebo in Youth

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Combat JUDO: 24 weeks	-7.3	3.5205	51.2%	-7.30 [-14.20, -0.40]
Fox 2022: 52 weeks	5.8	4.0817	48.8%	5.80 [-2.20, 13.80]
Total (95% CI)			100.0%	-0.91 [-13.75, 11.92]

Heterogeneity: Tau² = 71.28; Chi² = 5.91, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.14 (P = 0.89)
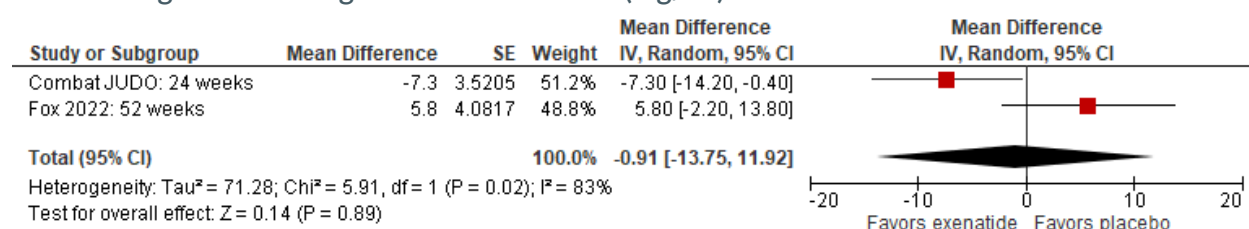
Abbreviations. CI: confidence interval; LDL: low-density lipoprotein; IV: inverse variance; SE: standard error.

One RCT measured change in HbA1c levels. In the RCT by Fox and colleagues,[82] there was no difference in change in percent HbA1c between exenatide and placebo groups at 52 weeks (P = .88; Figure 64). Mean percent HbA1c levels at enrollment and mean baseline levels at randomization after successful weight loss, were within normal limits (5.5% and 5.2%, respectively).[82]

Figure 64. Change in HbA1c (%): Exenatide vs. Placebo in Youth
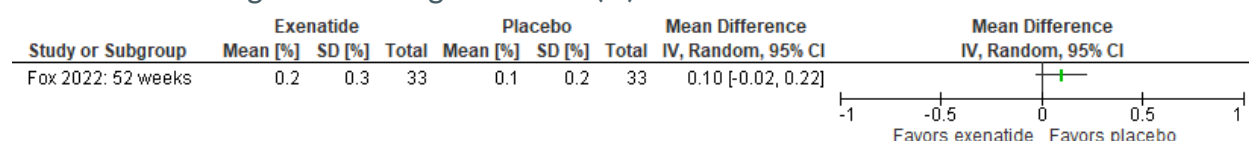
Study or Subgroup	Exenatide Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI
Fox 2022: 52 weeks	0.2	0.3	33	0.1	0.2	33	0.10 [-0.02, 0.22]

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation.

Quality of Life Outcomes

Summary Findings (GRADE)

Table 44. Certainty of Evidence (GRADE) for Quality of Life: Exenatide vs. Placebo in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in IWQoL-Kids total score			
1 RCT N = 66	●●○○ Low	No difference in mean change in IWQoL-Kids total score comparing exenatide with placebo in adolescents at 1 year	Downgraded:[a] 2 levels for RoB • Discrepant baseline values between groups after run-in • Author and funding CoI

Note. [a] Consistency not assessable with single study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; IWQoL: impact of weight on quality of life; MD: mean difference; RoB: risk of bias.

Detailed Findings

The 1 RCT that reported QoL measures found no difference between exenatide and placebo groups in change in IWQoL-Kids total score at 52 weeks (MD, -5.70 points; P = 0.12).[82] After improvements in QoL scores from enrollment to the end of the run-in phase, adolescents in the exenatide group had a slight rebound (a decrease in QoL score), while those in the placebo group had further improvements in QoL, although the overall difference between the groups was not statistically significant.[82]

Safety Outcomes

The 2 RCTs in youth reported overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE.

Summary Findings (GRADE)

Table 45. Certainty of Evidence (GRADE) for Safety Outcomes: Exenatide vs. Placebo in Youth

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
2 RCTs[82,83] N = 110	●○○○ Very low	There was only 1 withdrawal due to an AE in an individual randomized to exenatide; there were no withdrawals due to an AE in youth randomized to placebo	Downgraded: 1 level for RoB • Author and funding CoI 2 level for imprecision • Very low number of events, low overall sample size

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

For withdrawals due to AEs, the weight loss maintenance study by Fox and colleagues reported none over the 52 week study period.[82] In the Combat-JUDO study, only 1 individual in the exenatide group withdrew from the 24-week study due to an AE; no further description of the event was reported.[83]

One RCT reported AEs as number of individuals who experienced an AE,[82] and 1 RCT reported only total number of AEs experienced overall (Table 46).[83] In the 2 studies, more individuals experienced an AE and more events were experienced overall, in youth randomized to exenatide compared to placebo (Table 46).[82,83] No SAEs considered related to the study drug were reported over 24 weeks in the Combat-JUDO study,[83] and the single SAE experienced by an individual randomized to exenatide in the study by Fox and colleagues, was also reported as not related to the study drug.[82]

Gastrointestinal symptoms of nausea, diarrhea, vomiting and constipation were experienced more frequently with exenatide compared with placebo in both studies.[82,83] Headaches were more common with exenatide compared to placebo in the weight loss maintenance study,[82] and problems of the nervous system (headache, dizziness, syncope, tremor of hands, and paresthesia) were more common with exenatide in the Combat-JUDO study.[83] See Appendix G, Tables G7 and G8, for details of AE outcomes for exenatide.

Table 46. Summary of Adverse Events and Serious Adverse Events: Exenatide in Youth

Study Name Author, Year	Adverse Events, % n of N			Serious Adverse Events, % n of N		
	Exenatide	Placebo	P Value	Exenatide	Placebo	P Value
Youth						
Combat-JUDO[83] Weghuber, 2020	83 total events	108 total events	NR	NR	NR	NR
Fox, 2022[82]	97.0% 32 of 33	90.9% 30 of 33	NR	3% 1 of 33	0% 0 of 33	NR

Abbreviation. NR: not reported.

There were no deaths reported in the either study of exenatide in youth.[82,83]

Change in Medication Outcomes

The included studies for exenatide in youth did not report change in medication outcomes for obesity-related comorbidities.

Naltrexone-Bupropion

Summary of Included Studies

We identified 5 RCTs in 6 publications[85-90] for naltrexone-bupropion in adults (Table 47). No studies of naloxone-bupropion in children or adolescents were identified for this review.

Across 4 RCTs[85,86,88,89] that compared a daily oral dose of 32 mg naltrexone combined with 360 mg bupropion (32/360 mg) with placebo, there were differences in population (e.g., with or without T2DM), background treatment, and requirements for weight loss prior to randomization
- The COR-I[85] study also included a lower dose of 16/360 mg naltrexone-bupropion.

- The COR-Diabetes[88] study included only individuals with T2DM; all other RCTs that compared naltrexone-bupropion with placebo excluded people with diabetes.
- The COR-BMOD study[89] included intensive behavioral therapy as background treatment; all other RCTs that compared naltrexone-bupropion with placebo provided more general diet and exercise therapy as background treatment.
- In the COR-II study,[86] between weeks 28 and 44, participants in the naltrexone-bupropion group who did not lose at least 5% were re-randomized to the same (32/360 mg) or higher dose (48/260 mg) for the remainder of the study; for the primary analyses those re-randomized to 32/360 mg were double-weighted and those in the 48/360 mg group were excluded.[86]

The RCT by Halseth and colleagues was a 26-week, open-label study that compared a commercially available comprehensive lifestyle intervention program (CLI) plus daily 32/360 mg naltrexone-bupropion with usual care, described as "general advice that patients might receive from their physician."[87,90] At 26 weeks, those randomized to usual care transitioned to the active intervention (drug plus lifestyle intervention), and were followed for an additional uncontrolled 52-week period.[90]

Table 47. Overview of Study Characteristics: Naltrexone-Bupropion in Adults

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Condition
Adults								
COR-I[85] Greenway, 2010 RCT Moderate RoB	Yes	56	Diet and exercise	1,742	• Oral NalBup 32/360 mg daily • Oral NalBup 16/360 mg daily • Placebo	None	BMI 30 to 45 or 27 to 45 kg/m² with HTN or dyslipidemia	None
COR-II[86] Apovian, 2013 RCT Moderate RoB	Yes	56	Diet and exercise	1,496	• Oral NalBup 32/360 mg daily • Placebo	None	BMI 30 to 45 or 27 to 45 kg/m² with HTN or dyslipidemia	None
COR-BMOD[89] Wadden, 2011 RCT High RoB	Yes	56	IBT	793	• Oral NalBup 32/360 mg daily • Placebo	None	BMI 30 to 45 or 27 to 45 kg/m² with HTN or dyslipidemia	None
COR-Diabetes[88] Hollander, 2013 RCT Moderate RoB	Yes	56	Diet and exercise	505	• Oral NalBup 32/360 mg daily • Placebo	With T2DM	BMI ≥ 27 and ≤ 45 kg/m²	None
Halseth, 2017[87,90] RCT open-label High RoB	Yes	26 + 52	At week 25 all received NalBup + CLI	242	• Oral NalBup 32/360 mg daily + CLI • Usual care	None	BMI ≥ 27 kg/m² with HTN or dyslipidemia	None

Overall, we assessed 3 of the 5 RCTs as moderate RoB,[85,86,88] and 2 RCTs as high RoB.[89,90]
- The COR-I[85] and COR-II[86] RCTs were rated as having moderate RoB for serious study author and funding conflicts of interest, and notable participant attrition (870 of 1,742 participants [49.9%] completed treatment in the COR-I trial; 805 of 1,496 [53.8%] completed treatment in the COR-II trial).
- The COR-Diabetes study[88] was rated as moderate RoB for author and funding conflicts of interest, as well as concerns around participant study withdrawal (275 of 505 [54.4%] completed treatment).
- The COR-BMOD study[89] was rated as high RoB for author and funding conflicts of interest, as well as limited reporting of methods including baseline characteristics, and notable participant attrition (460 of 793 [58%] completed treatment).
- The RCT that compared naltrexone-bupropion plus CLI with usual care[90] was rated as high RoB because of the lack of blinding, a short randomized period, differential withdrawals between groups at 26 weeks (82 of 153 [53.6%] in the active treatment group versus 82 of 89 [92.1%] in the usual care group), and serious author and funding conflicts of interest.

Adults

We included the 4 RCTs that compared naltrexone-bupropion with placebo in our GRADE assessments for CoE; the trial that compared naltrexone-bupropion plus CLI with usual care is reported separately under each outcome category if measured. The results for the 2 doses in the COR-I RCT were pooled for all outcomes unless otherwise stated.

Weight Outcomes
Summary of Findings (GRADE)

Table 48. Certainty of Evidence (GRADE) for Weight Outcomes: Naltrexone-Bupropion in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
4 RCTs[85,86,88,89] N = 4,122[a]	●●○○ Low	Participants randomized to naltrexone-bupropion lost a significantly greater percentage of body weight compared to placebo; this difference is not considered clinically meaningful MD, -4.25% (95% CI, -5.07 to -3.42); *P* < .001	Downgraded: 1 level for RoB[b] • CoI, attrition 1 level for imprecision • CI crosses over clinically meaningful change of ≥ 5%

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (kg)			
2 RCTs[85,86] N = 3,023[a]	●●○○ Low	Participants randomized to naltrexone-bupropion lost significantly more body weight, in kg, compared to placebo; correlated with change in percent body weight, this difference is also likely not at meaningful levels MD, -4.49 kg (95% CI, -5.28 to -3.71); $P <$ .001	Downgraded: 1 level for RoB[b] • CoI, attrition 1 level for inconsistency • Substantial heterogeneity
Change in BMI (kg/m^2)			
Not reported			
Proportion with ≥ 5% weight loss			
4 RCTs[85,86,88,89] N = 3,710[a]	●●○○ Low	Participants randomized to naltrexone-bupropion were more likely to lose at least 5% body weight compared to placebo RR, 2.31 (95% CI, 1.66 to 3.23); $P <$ .001	Downgraded: 1 level for RoB[b] • CoI, attrition 1 level for inconsistency • Considerable heterogeneity
Proportion with ≥ 10% weight loss			
4 RCTs[85,86,88,89] N = 3,035[a]	●●○○ Low	Participants randomized to naltrexone-bupropion were more likely to lose at least 10% body weight compared to placebo RR, 3.12 (95% CI, 2.07 to 4.68); $P <$ .001	Downgraded: 1 level for RoB[b] • CoI, attrition 1 level for inconsistency • Considerable heterogeneity

Note. [a] Sample used in meta-analysis is smaller than total number randomized, although all continuous measures include full sample set according to publication; [b] While we are relatively confident that naltrexone-bupropion contributed to greater weight loss, we are less confident in the magnitude of the effect because of concerns around RoB.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of 4 RCTs,[85,86,88,89] individuals randomized to naltrexone-bupropion lost significantly more percent body weight compared to individuals randomized to placebo at 56 weeks (MD, -4.25%; 95% CI, -5.07 to -3.42; Figure 65). The overall treatment effect is just under the change in percent body weight considered clinically meaningful (at least 5% weight loss); based on the effect CI, some individuals may reach meaningful weight loss. We did not downgrade CoE for heterogeneity despite moderate to substantial levels, primarily driven by subgroup differences. More studies in these subpopulations need to be conducted to better assess if differences in effects are because of population differences.

The 26-week study by Halseth and colleagues[90] also showed that individuals randomized to naltrexone-bupropion plus CLI achieved a significantly greater reduction in percent body weight compared to individuals randomized to usual care (MD, -8.52% [95% CI, -12.4 to -4.6], $P <$ .001;

Figure 66). This effect is clinically meaningful, but it is not clear how much of the effect is due to naltrexone-bupropion, and how much is due to the CLI program.
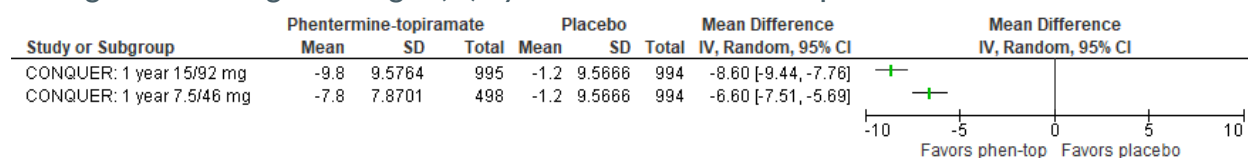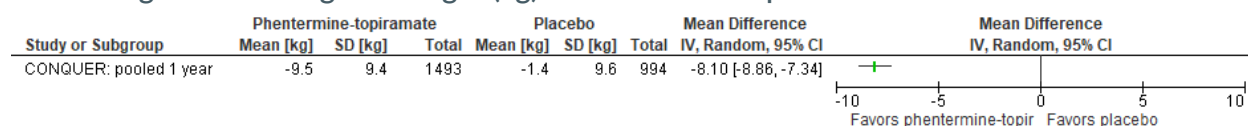
Figure 65. Change in Weight (%): Naltrexone-Bupropion vs. Placebo in Adult
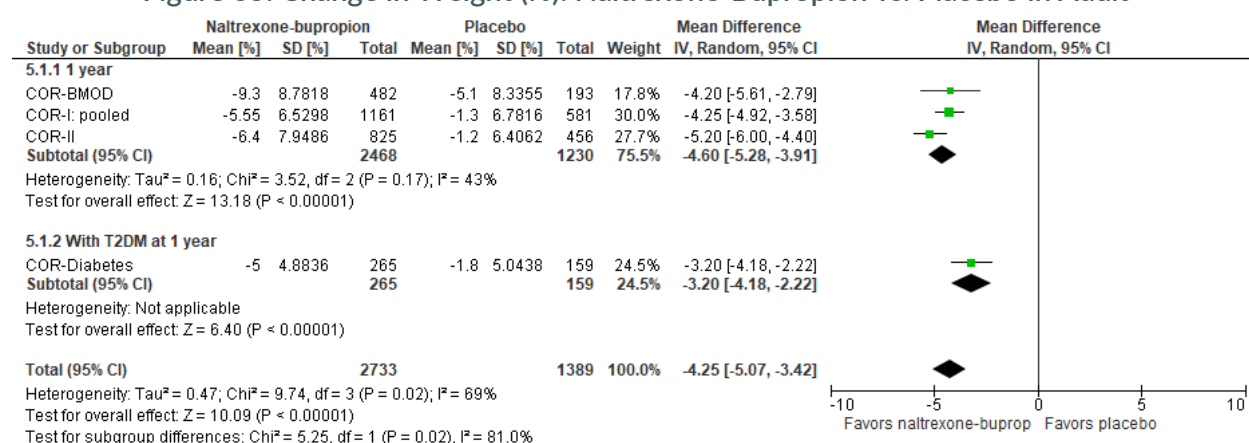
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

Figure 66. Change in Weight (%): Naltrexone-Bupropion Plus CLI vs. Usual Care in Adults
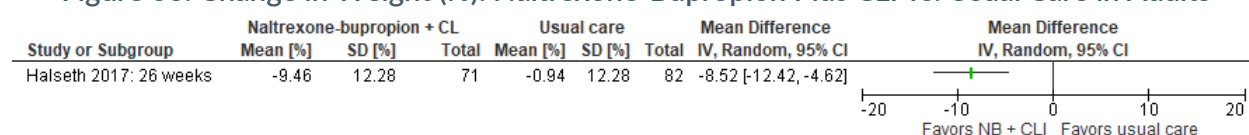
Abbreviations. CI: confidence interval; CLI: comprehensive lifestyle intervention; IV: inverse variance; SD: standard deviation.

In the COR-I RCT,[85] the higher dose of daily 36/360 mg naltrexone-bupropion resulted in a greater percent loss of body weight compared to placebo (-4.8%), than the lower dose of 16/360 mg (-3.7%; Figure 67); no statistical tests for differences were reported.
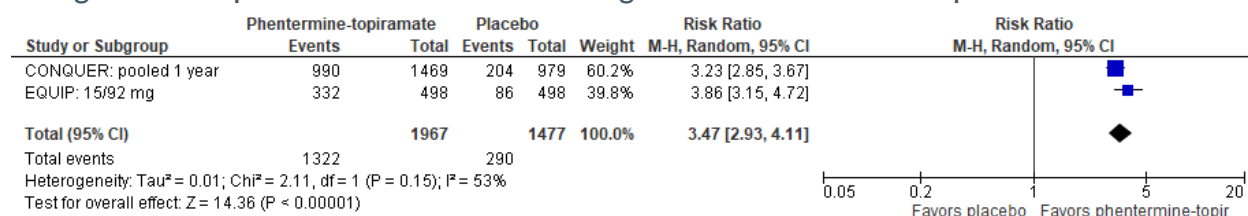
Figure 67. Change in Weight (%) by Dose: Naltrexone-Bupropion vs. Placebo in Adults
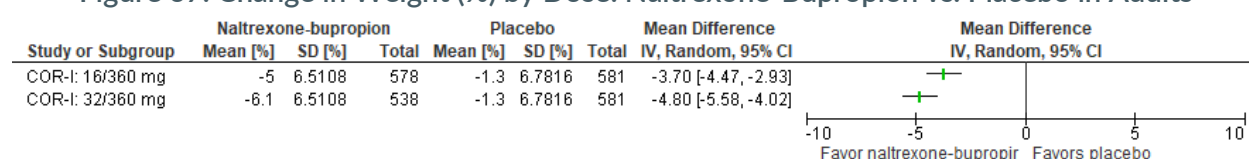
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 2 RCTs,[85,86] individuals randomized to naltrexone-bupropion lost significantly more body weight, as measured in kg, compared to individuals randomized to placebo (MD, -4.49 kg; 95% CI, -5.28 to -3.71; Figure 68); however, the impact of losing around 4.5 kg more than with placebo alone will vary depending on baseline weight and overall height. Because this measure is correlated with percent change in body weight, this difference is also likely not at a clinically meaningful level. No other studies reported this outcome.

Figure 68. Change in Weight (kg): Naltrexone-Bupropion vs. Placebo in Adults
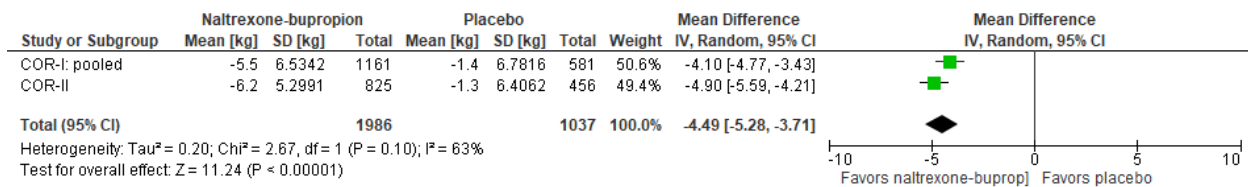
Study or Subgroup	Naltrexone-bupropion Mean [kg]	SD [kg]	Total	Placebo Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
COR-I: pooled	-5.5	6.5342	1161	-1.4	6.7816	581	50.6%	-4.10 [-4.77, -3.43]	
COR-II	-6.2	5.2991	825	-1.3	6.4062	456	49.4%	-4.90 [-5.59, -4.21]	
Total (95% CI)			**1986**			**1037**	**100.0%**	**-4.49 [-5.28, -3.71]**	

Heterogeneity: Tau² = 0.20; Chi² = 2.67, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 11.24 (P < 0.00001)

Favors naltrexone-buprop] Favors placebo (scale -10 to 10)

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 4 RCTs,[85,86,88,89] individuals randomized to naltrexone-bupropion were significantly more likely to lose at least 5% of their initial weight compared to individuals randomized to placebo (RR, 2.31; 95% CI, 1.66 to 3.23; Figure 69). The proportion of individuals who lost 5% or more body weight from baseline (which is considered a clinically meaningful level of weight loss) was 50.4% with naltrexone-bupropion and 20.8% with placebo across all 4 studies included in the meta-analysis.[85,86,88,89]

The 26-week study by Halseth and colleagues[90] also showed that individuals randomized to naltrexone-bupropion plus CLI were more likely to achieve at least 5% weight loss compared to usual care (60 of 71 [84.5%] in the naltrexone-bupropion plus CLI group versus 10 of 82 [12.3%] in the usual care group; RR, 6.93; 95% CI, 3.8 to 12.5; *P* < .001). Again, it is not clear how much of the weight loss effect is due to naltrexone-bupropion, and how much is due to the CLI program.

Figure 69. Proportion With at Least 5% Weight Loss: Naltrexone-Bupropion vs. Placebo

Study or Subgroup	Naltrexone-bupropion Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.1 1 year							
COR-BMOD	320	482	82	193	26.6%	1.56 [1.31, 1.86]	
COR-I: pooled	412	942	84	511	25.8%	2.66 [2.16, 3.28]	
COR-II	355	702	78	456	25.7%	2.96 [2.38, 3.67]	
Subtotal (95% CI)		**2126**		**1160**	**78.1%**	**2.30 [1.51, 3.49]**	
Total events	1087		244				

Heterogeneity: Tau² = 0.13; Chi² = 26.34, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.91 (P < 0.0001)

5.3.2 With T2DM at 1 year							
COR-Diabetes	118	265	30	159	21.9%	2.36 [1.66, 3.35]	
Subtotal (95% CI)		**265**		**159**	**21.9%**	**2.36 [1.66, 3.35]**	
Total events	118		30				

Heterogeneity: Not applicable
Test for overall effect: Z = 4.82 (P < 0.00001)

Total (95% CI)		**2391**		**1319**	**100.0%**	**2.31 [1.66, 3.23]**	
Total events	1205		274				

Heterogeneity: Tau² = 0.10; Chi² = 26.36, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.92 (P < 0.00001)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

Favors placebo   Favors naltrexone-buprop (scale 0.02 to 50)

Abbreviations. CI: confidence interval; T2DM: type 2 diabetes.

In a pooled analysis of 4 RCTs,[85,86,88,89] individuals randomized to naltrexone-bupropion were significantly more likely to lose at least 10% of their initial weight compared to individuals randomized to placebo (RR, 3.12; 95% CI, 2.07 to 4.68; Figure 70). The proportion of individuals who lost 10% or more body weight from baseline (more than what is considered clinically

meaningful weight loss) was 27.6% with naltrexone-bupropion and 8.5% with placebo across all 4 studies included in the meta-analysis.[85,86,88,89]

The 26-week study by Halseth and colleagues[90] also showed that individuals randomized to naltrexone-bupropion plus CLI were more likely to achieve at least 10% weight loss compared to usual care (30 of 71 [42.3%] participants in the naltrexone-bupropion plus CLI group versus 3 of 82 [3.7%] in the usual care group; RR, 11.55; 95% CI, 3.7 to 36.2; *P* < .001).

Figure 70. Proportion With at Least 10% Weight Loss: Naltrexone-Bupropion vs. Placebo
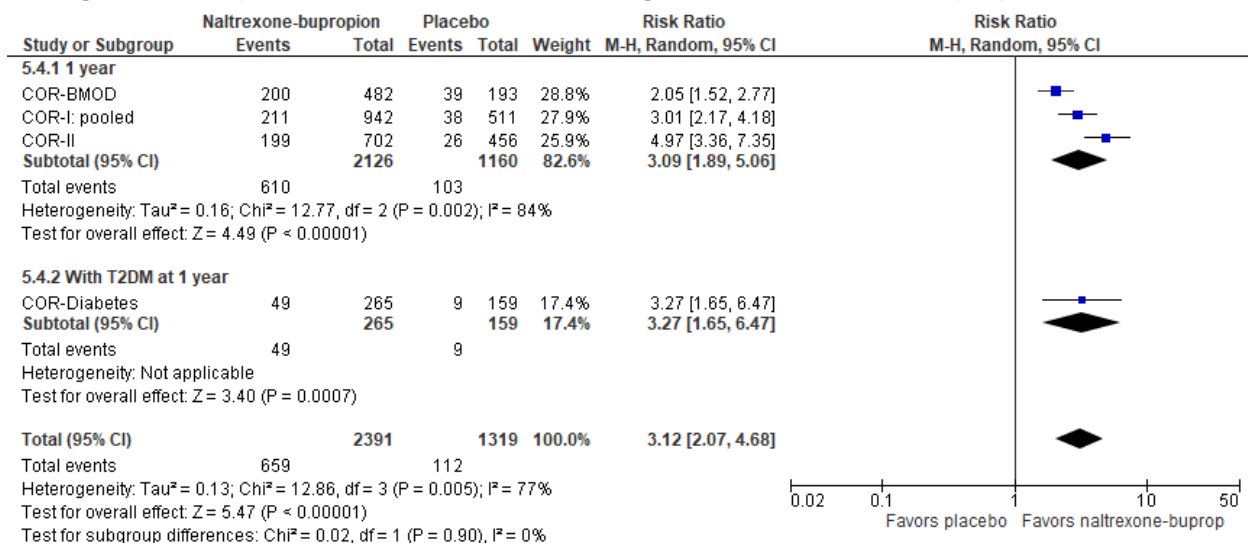
Abbreviations. CI: confidence interval; T2DM: type 2 diabetes.

Comorbidity Risk Factor Outcomes

Summary of Findings (GRADE)

Table 49. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Naltrexone-Bupropion

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
3 RCTs[85,86,88] N = 3,447[a]	●●○○ Low	Participants randomized to naltrexone-bupropion had a significantly greater *increase* in SBP compared to placebo, but the difference was small and not clinically meaningful MD, 1.54 mmHg (95% CI, 0.91 to 2.17); *P* < .001	Downgraded: 2 levels for RoB • CoI, notable attrition, no sensitivity analysis for this outcome after re-randomization in 1 RCT

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in LDL cholesterol			
4 RCTs[85,86,88,89] N = 4,122[a]	●●○○ Low	Participants randomized to naltrexone-bupropion had a small but significant decrease in LDL cholesterol compared to placebo; this difference is likely not considered clinically meaningful SMD, -0.09 (95% CI, -0.15 to -0.02); P = .01	Downgraded: 2 levels for RoB • CoI, notable attrition, no sensitivity analysis for this outcome after re-randomization in 1 RCT
Change in HbA1c (%)			
1 RCT[88] N = 424[a]	●○○○ Very low	Participants with T2DM randomized to naltrexone-bupropion had a significant reduction in percent HbA1c compared to placebo, and the effect is considered clinically meaningful MD, -0.50% (95% CI, -0.78 to -0.22); P < .001	Downgraded:[b] 2 levels for RoB • CoI, notable attrition, no sensitivity analysis for this outcome after re-randomization in 1 RCT 1 level for imprecision • CI crosses over clinically meaningful change of 0.3%

Note. [a] Sample used in meta-analysis is smaller than total number randomized, although all continuous measures include full sample set according to publication; [b] Consistency not assessable with single study.
Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; LDL: low-density lipoprotein; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio; SBP: systolic blood pressure; SMD: standardized mean difference.

Detailed Findings

In a pooled analysis of 4 RCTs,[85,86,88,89] individuals randomized to naltrexone-bupropion had a small but significantly greater ***increase*** in SBP, in mmHg, compared to individuals randomized to placebo (MD, 1.54 mmHg; 95% CI, 0.91 to 2.17; Figure 71). All studies referenced the known pressor effect (increase in SBP of at least 30 mmHg) of bupropion as contributing to the initial increases in blood pressure observed across studies; although all reported SBP improved with treatment and was correlated with weight loss, the mean values did not return to baseline levels.[85,86,88]

Figure 71. Change in Systolic Blood Pressure (mmHg): Naltrexone-Bupropion vs. Placebo
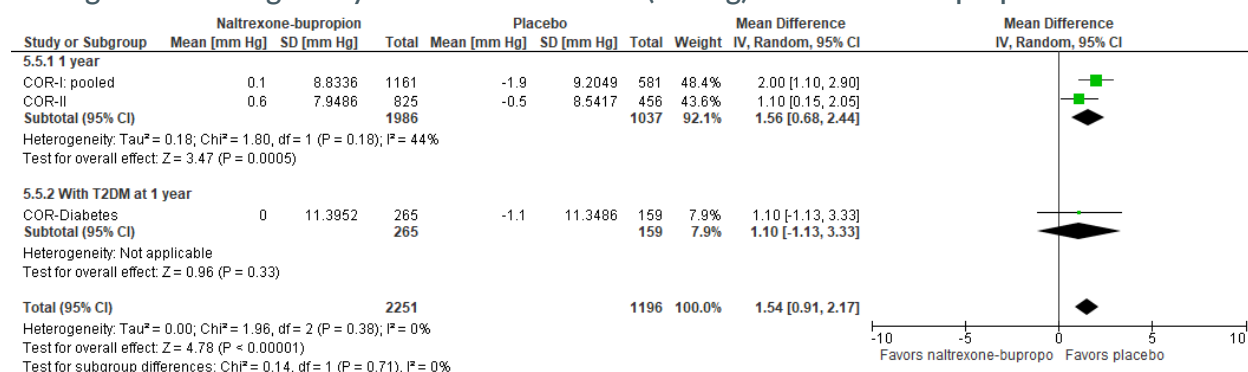
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

In a pooled analysis of 4 RCTs,[85,86,88,89] individuals randomized to naltrexone-bupropion experienced a significantly greater reduction in LDL cholesterol compared to individuals randomized to placebo (SMD, -0.09; 95% CI, -0.15 to -0.02; Figure 72). None of the improvements within studies were at levels considered clinically meaningful (at 1 mmol/L or 38.7 mg/dL).

The 26-week study by Halseth and colleagues[90] found no difference in LDL cholesterol levels between naltrexone-bupropion plus CLI and usual care groups (MD not reported; *P* = .97).

Figure 72. Change in LDL Cholesterol: Naltrexone-Bupropion vs. Placebo in Adults

Study or Subgroup	Naltrexone-bupropion Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.7.1 1 year								
COR-BMOD	7.1	31.2852	482	10	30.2868	193	15.0%	-0.09 [-0.26, 0.07]
COR-I: pooled	-0.105	0.6624	1161	-0.08	0.8054	581	42.2%	-0.04 [-0.13, 0.06]
COR-II	-6.2	23.8458	825	-2.1	27.7604	456	31.9%	-0.16 [-0.28, -0.05]
Subtotal (95% CI)			2468			1230	89.2%	-0.09 [-0.17, -0.01]

Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 2.23 (P = 0.03)

Study or Subgroup	Naltrexone-bupropion Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.7.2 With T2DM at 1 year								
COR-Diabetes	-1.4	30.9298	265	0	30.2628	159	10.8%	-0.05 [-0.24, 0.15]
Subtotal (95% CI)			265			159	10.8%	-0.05 [-0.24, 0.15]

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

Total (95% CI)			2733			1389	100.0%	-0.09 [-0.15, -0.02]

Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%

Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation; T2DM: type 2 diabetes.

Only the COR-Diabetes study reported change in HbA1c levels from baseline to 56 weeks. Individuals with T2DM randomized to naltrexone-bupropion experienced a significantly greater reduction in percent HbA1c compared to those randomized to placebo (MD, -0.5%; 95% CI, -0.8 to 0.2; Figure 73)[88]; the treatment effect is greater than what is considered clinically meaningful by at least 0.3%.

Figure 73. Change in HbA1c (%): Naltrexone-Bupropion vs. Placebo in Adults
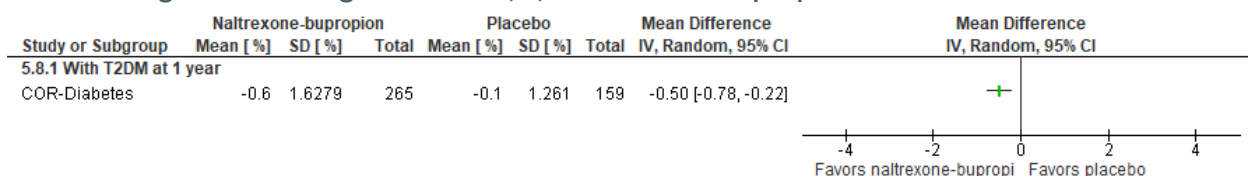
Study or Subgroup	Naltrexone-bupropion Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI
5.8.1 With T2DM at 1 year							
COR-Diabetes	-0.6	1.6279	265	-0.1	1.261	159	-0.50 [-0.78, -0.22]

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation; T2DM: type 2 diabetes.

Quality of Life Outcomes

Summary of Findings

Table 50. Certainty of Evidence (GRADE) for Quality of Life: Naltrexone-Bupropion in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Quality of life			
3 RCTs[86,88,89] N = 4,031	●●○○ Low	Participants randomized to naltrexone-bupropion experienced small but significant improvements in overall QoL compared to placebo at 1 year; the differences are likely not clinically meaningful	Downgraded: 2 levels for RoB • CoI, notable attrition

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

Three RCTs that compared naltrexone-bupropion with placebo in people without diabetes reported QoL[86,88,89] using the IWQoL-Lite survey total score; they also measured changes in food cravings or control of eating using a variety of tools. Overall, individuals randomized to naltrexone-bupropion experienced small but significant improvements in overall QoL compared to placebo.[86,88,89] With MDs ranging from 3.1 points (COR-BMOD)[89] to 4.5 points (pooled COR-II)[86], none reach levels considered clinically meaningful. QoL was not measure in the COR-Diabetes study in people with T2DM.

The 26-week study by Halseth and colleagues[87,90] also found that individuals randomized to naltrexone-bupropion plus CLI had significant improvements in QoL compared to the usual care group, based on the IWQoL-Lite total score; the authors reported that the MD of 17.4 points is clinically meaningful.

Safety Outcomes

Studies for naltrexone-bupropion included overall AEs, SAEs, mortality, and withdrawals due to AEs We only assessed CoE for withdrawals due to AEs.

Summary of Findings (GRADE)

Table 51. Certainty of Evidence (GRADE) for Safety Outcomes: Naltrexone-Bupropion in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
4 RCTs[85,86,88,89] N = 4,481[a]	●●●○ Moderate	Participants randomized to naltrexone-bupropion were significantly more likely to withdraw due to an AE compared to placebo RR, 1.92 (95% CI, 1.65 to 2.24); P < .001	Downgraded: 1 level for RoB • Author and funding CoI

Note. [a] Sample used in meta-analysis is smaller than total number randomized.

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest;

Detailed Findings

In a pooled analysis of 4 RCTs,[85,86,88,89] individuals randomized to naltrexone-bupropion were more likely to experience an AE that led to study withdrawal compared to individuals randomized to placebo (RR, 1.92; 95% CI, 1.65 to 2.24; Figure 74).

- The proportion of withdrawals due to AEs was 23.7% with naltrexone-bupropion and 12.2% with placebo across the 4 studies in the meta-analysis[85,86,88,89]

The 26-week study by Halseth and colleagues also found that more individuals who were randomized to naltrexone-bupropion plus CLI withdrew from the trial due to an AE (35 of 153, 22.9%) compared to usual care (1 of 86, 1.1%) at 26 weeks.

Figure 74. Proportion of Withdrawals Due to Adverse Events: Naltrexone-Bupropion vs. Placebo
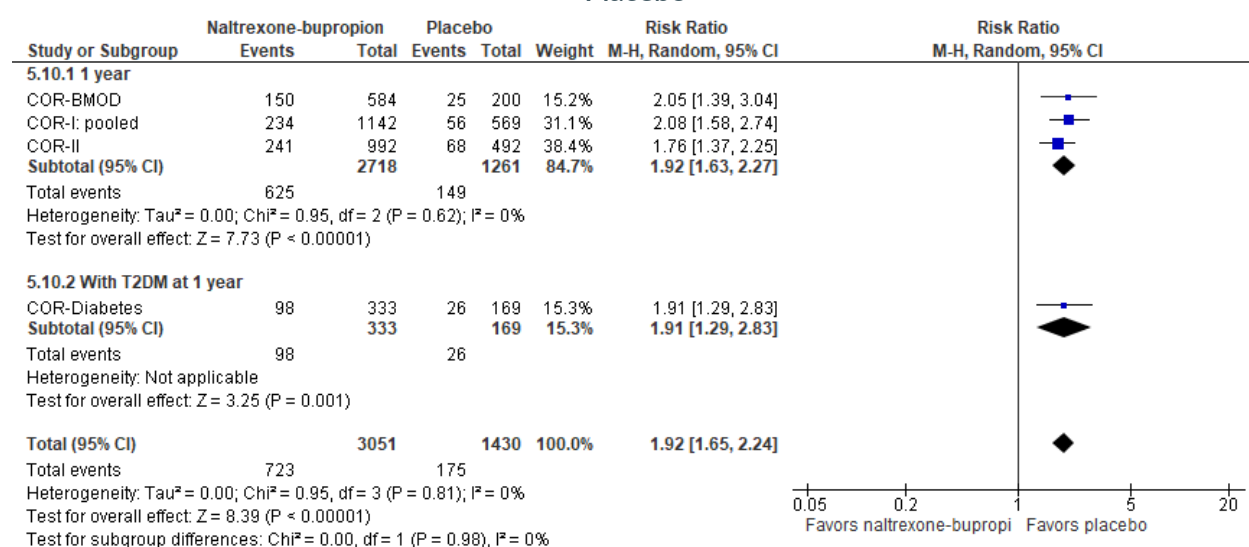
Abbreviations. AE: adverse event; CI: confidence interval; T2DM: type 2 diabetes.

In general, more people randomized to naltrexone-bupropion experienced an AE compared to those randomized to placebo,[85,86,88,89] while SAEs were more evenly distributed between groups (Table 52).[85,86,88-90] The most frequent AEs included nausea, constipation, headaches, and dizziness; all were more reported as occurring statistically more frequently in the naltrexone-bupropion groups across the 3 studies in people without diabetes[85,86,89] (no statistical tests in the COR-Diabetes study). See Appendix H, Tables H8 and H9, for details of AE outcomes for naltrexone-bupropion.

- The COR-BMOD study[89] did not report number of participants who experienced and AE, but rather, AEs with at least 5% incidence. Nausea, constipation, dizziness, dry mouth, tremor, upper abdominal pain, and tinnitus were reported as occurring significantly more frequently in the naltrexone-bupropion group compared to placebo.
- In studies of people without diabetes, the COR-I and COR-II studies described SAEs as mostly cardiovascular events that were considered not related to the study drug[85,86];

1 serious seizure was reported in a participant who received naltrexone-bupropion with no history of seizures.[86]

- The COR-BMOD study[89] reported cholecystitis as an SAE in 2 participants who received naltrexone-bupropion; both were considered possibly related to the study drug.
- There were no further descriptions of the SAEs experienced by individuals with T2DM in the COR-Diabetes trial.[88]
- In the study by Halseth and colleagues,[90] 1 participant who received naltrexone-bupropion plus CLI experienced an SAE within the 26-week randomized period deemed not related to the study drug (breast cancer diagnosis).

Table 52. Summary of Adverse Events and Serious Adverse Events: Naltrexone-Bupropion

Study Name Author, Year		Adverse Events n of N			Serious Adverse Events, % n of N		
		NalBup	Placebo	P Value	NalBup	Placebo	P Value
Adults							
COR-I[85] Greenway, 2010	32/360 mg	83.1% 476 of 573	68.5% 390 of 569	P < .05	1.6% a 9 of 1,145	1.4% 9 of 569	NS
	16/360 mg	80.0% 455 of 569	68.5% 390 of 569	P < .05			
COR-II[86] Apovian, 2013		85.2% 845 of 992	75.2% 370 of 492	NR	2.1% 21 of 992	1.4% 7 of 492	NS
COR-BMOD[89] Wadden, 2011		NR	NR	NR	2 of 591 possibly related to drug	NR	NR
COR-Diabetes[88] Hollander, 2013		90.4% 301 of 333	85.2% 144 of 169	NR	3.9% 13 of 333	4.7% 8 of 169	NR
		NalBup + CLI	Usual care		NalBup + CLI	Usual care	
Halseth, 2017[90]		NR	NR	NR	0.7% 1 in 153	0% 0 in 89	NR

Note. a Pooled doses.
Abbreviations. CLI: comprehensive lifestyle intervention; NalBup: naltrexone-bupropion; NR: not reported; NS: not significant.

One death was reported across all studies with naltrexone-bupropion. The COR-I study reported 1 death due to acute myocardial infarction in a participant randomized to 32/360 mg naltrexone-bupropion[85]; this individual was reported as having multiple cardiovascular risk factors prior to study enrollment.

Change in Medication Outcomes
The included studies for naltrexone-bupropion in adults did not report change in medication outcomes for obesity-related comorbidities.

Youth
No studies for naltrexone-bupropion in youth were identified for this report.

Phentermine-Topiramate

Summary of Included Studies

We identified 3 eligible RCTs in 6 publications that compared phentermine-topiramate with placebo (Table 53).[91-96] Two RCTs in 5 publications were in adults,[91-95] and 1 RCT was in adolescents.[96]

The 2 RCTs for phentermine-topiramate in adults were relatively similar in design, but there were some differences in study duration, doses included, and reporting of participant characteristics.

- The CONQUER[92-94] and EQUIP[91] RCTs followed participants for 56 weeks and included diet and exercise as background treatment; a subset of participants who completed the CONQUER trial (and had a BMI of at least than 23 kg/m^2) were followed for an additional 52 weeks on assigned treatment (SEQUEL extension study).[91,94,95]
  - After 56 weeks, 85.5% of participants in the 15/92 mg group continued in the SEQUEL extension trial, 79.4% of those in the 7.5/46 mg group continued, and 69.4% on placebo continued in the extension trial.[95]
- Both RCTs utilized a daily oral dose of 15 mg phentermine combined with 92 mg topiramate (15/92 mg); the comparator was placebo.
  - The CONQUER/SEQUEL study also included a lower-dose arm of 7.5/46 mg,[93] and the EQUIP study also included a lower-dose arm of 3.75/23 mg.[91]
- People with T2DM were not excluded from participating in either study, nor was it a required criterion.
  - In the CONQUER/SEQUEL study, approximately 15% of participants were diagnosed with T2DM; no lower limit of BMI was required with this diagnosis for study enrollment.[93]
  - The proportion of participants with T2DM was not reported in the EQUIP study.[91]

In the OB-403 study for phentermine-topiramate in adolescents,[96], participants with or without T2DM were eligible as long as treatment did not include any glucose-lowering medications (proportion with T2DM was not reported). Individuals were randomized to 1 of 2 doses of phentermine-topiramate (15/92 mg or 7.5/46 mg) or placebo and followed for 56 weeks.[96]

Table 53. Overview of Study Characteristics: Phentermine-Topiramate

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Condition
Adults								
CONQUER[92-94]/SEQUEL[94,95] Gadde, 2011 RCT Moderate RoB	Yes	56 + 104	Diet and exercise	2,487	• Oral PhenTop 15/92 mg daily • Oral PhenTop 7.5/46 mg daily • Placebo	With or without; ~15.5% T2DM	BMI 27 to 45 kg/m^2 (no lower limit if with T2DM) and ≥ 2 comorbidities	None

Study Name Author, Year Study Design RoB	Includes US	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Condition
EQUIP[91] Allison, 2011 RCT Moderate RoB	Yes	56	Diet and exercise	1,267	• Oral PhenTop 15/92 mg daily • Oral PhenTop 3.75/23 mg daily • Placebo	NR	BMI ≥ 35 kg/m^2	None
Adolescents								
OB-403[96] Kelly, 2022 RCT High RoB	Yes	56	Diet and exercise	223	• Oral PhenTop 15/92 mg daily • Oral PhenTop 7.5/46 mg daily • Placebo	NR	BMI ≥ 95th percentile	None

Abbreviations. BMI: body mass index; F/U: follow-up; PhenTop: phentermine-topiramate; RCT: randomized controlled trial; RoB: risk of bias; SC: subcutaneous; T2DM: type 2 diabetes.

We assessed the 2 RCTs in adults as moderate RoB, primarily for issues around high attrition rates (over 40% across both studies)[91,93] and author and funding conflicts of interest. We rated the OB-403 RCT in adolescents as having high RoB for limited reporting of methods, study and author conflicts of interest, and significant and disproportionate discontinuation of treatment (38.9% in 15/92 mg dose group, 27.8% in 7.5/46 mg dose group, 50% in the placebo group).[96]

Adults

The results for the 2 doses (15/92 mg and 7.5/46 mg) in the CONQUER/SEQUEL study were pooled for all outcomes unless otherwise stated. Results for the 3.75/23 mg dose group in the EQUIP study were not included in meta-analyses and GRADE assessments (see Appendix I, Tables I1 to I19, for detailed results of all doses).

Weight Outcomes

Summary of Findings (GRADE)

Table 54. Certainty of Evidence (GRADE) for Weight: Phentermine-Topiramate in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
2 RCTs[91,93] N = 3,513[a]	●●○○ Low	Participants randomized to phentermine-topiramate lost a significantly greater percentage of body weight compared to placebo; the overall effect is greater than what is considered clinically meaningful MD, -8.56% (95% CI, -9.93 to -7.19); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI 1 level for inconsistency • Substantial heterogeneity

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in weight (kg)			
1 RCT[93] N = 2,487[a]	●●●○ Moderate	Participants randomized to phentermine-topiramate lost significantly more body weight, in kg, compared to placebo MD, -8.10 kg (95% CI, -8.86 to -7.34); *P* < .001	Downgraded:[b] 1 level for RoB • Author and funding CoI
Change in BMI (kg/m²)			
Not reported			
Proportion with ≥ 5% weight loss			
2 RCTs[91,93] N = 3,444[a]	●●●○ Moderate	Participants randomized to phentermine-topiramate were more likely to lose at least 5% body weight compared to placebo RR, 3.47 (95% CI, 2.93 to 4.11); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI
Proportion with ≥ 10% weight loss			
2 RCTs[91,93] N = 3,444[a]	●●●○ Moderate	Participants randomized to phentermine-topiramate were more likely to lose at least 10% body weight compared to placebo RR, 6.12 (95% CI, 5.08 to 7.38); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI

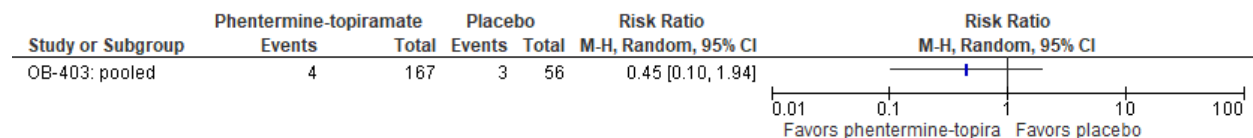*Notes. [a] Sample used in meta-analysis is smaller than total number randomized, although all continuous measures include full sample set according to publication; [b] Consistency not assessable with single study. Abbreviations. BMI: body mass index; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.*

Detailed Findings

In a pooled analysis of 2 RCTs,[91,93] individuals randomized to phentermine-topiramate lost significantly more percent body weight compared with individuals randomized to placebo (MD, -8.56%; 95% CI, -9.93 to -7.19; Figure 75). The overall treatment effect is more than what is considered a clinically meaningful loss of weight, of at least 5% weight loss.

Figure 75. Change in Body Weight (%): Phentermine-Topiramate vs. Placebo in Adults
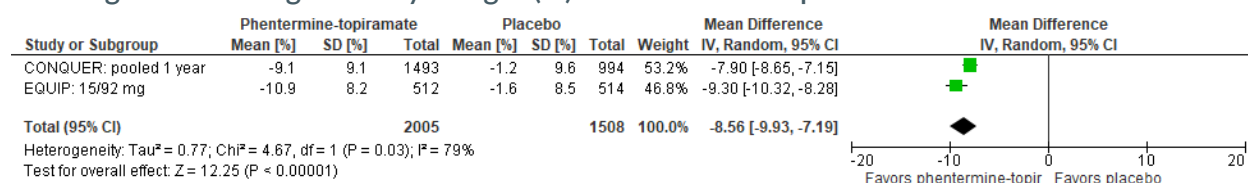
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In the CONQUER RCT,[93] the higher dose of daily 15/92 mg phentermine-topiramate resulted in a greater percent loss of body weight compared to placebo, than the lower dose of 7.5/46 mg phentermine-topiramate at 56 weeks (Figure 76); no statistical tests for differences were reported. Results for both doses are greater than what is considered clinically meaningful for loss of percent body weight.

Figure 76. Change in Weight (%) by Dose: Phentermine-Topiramate vs. Placebo in Adults

| Study or Subgroup | Phentermine-topiramate | | | Placebo | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
CONQUER: 1 year 15/92 mg	-9.8	9.5764	995	-1.2	9.5666	994	-8.60 [-9.44, -7.76]	
CONQUER: 1 year 7.5/46 mg	-7.8	7.8701	498	-1.2	9.5666	994	-6.60 [-7.51, -5.69]	

-10 -5 0 5 10
Favors phen-top Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In the CONQUER RCT,[93] individuals randomized to phentermine-topiramate lost significantly more body weight, as measured in kg, compared to individuals randomized to placebo (MD, -8.1 kg; 95% CI, -8.86 to -7.34; Figure 77); however, the impact of losing around 8.5 kg more than with placebo alone will vary depending on baseline weight and overall height. Correlated with percent change in body weight, this effect is also likely at clinically meaningful levels.

Figure 77. Change in Weight (kg): Phentermine-Topiramate vs. Placebo in Adults

| Study or Subgroup | Phentermine-topiramate | | | Placebo | | | Mean Difference | Mean Difference |
	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	IV, Random, 95% CI	IV, Random, 95% CI
CONQUER: pooled 1 year	-9.5	9.4	1493	-1.4	9.6	994	-8.10 [-8.86, -7.34]	

-10 -5 0 5 10
Favors phentermine-topir Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In a pooled analysis of 2 RCTs,[91,93] individuals randomized to phentermine-topiramate for 56 weeks were significantly more likely to lose at least 5% of their initial weight compared to individuals randomized to placebo (RR, 3.47; 95% CI, 2.93 to 4.11; Figure 78). The proportion of individuals who lost 5% or more body weight from baseline values baseline (which is considered a clinically meaningful level of weight loss) was 67.2% with phentermine-topiramate and 19.6% with placebo across the 2 RCTs.[91,93]

Figure 78. Proportion With at Least 5% Weight Loss: Phentermine-Topiramate vs. Placebo

| Study or Subgroup | Phentermine-topiramate | | Placebo | | | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CONQUER: pooled 1 year	990	1469	204	979	60.2%	3.23 [2.85, 3.67]	
EQUIP: 15/92 mg	332	498	86	498	39.8%	3.86 [3.15, 4.72]	
Total (95% CI)		1967		1477	100.0%	3.47 [2.93, 4.11]	
Total events	1322		290				

Heterogeneity: Tau² = 0.01; Chi² = 2.11, df = 1 (P = 0.15); I² = 53%
Test for overall effect: Z = 14.36 (P < 0.00001)

0.05 0.2 1 5 20
Favors placebo Favors phentermine-topir

Abbreviation. CI: confidence interval.

In a pooled analysis of 2 RCTs,[91,93] individuals randomized to phentermine-topiramate for 56 weeks were significantly more likely to lose at least 10% of their initial weight compared to individuals randomized to placebo (RR, 6.12; 95% CI, 5.08 to 7.38; Figure 79). The proportion of individuals who lost 10% or more body weight from baseline (clinically meaningful amount of weight loss) was 44.9% with phentermine-topiramate and 7.8% with placebo across the 2 RCTs.[91,93]

Figure 79. Proportion With at Least 10% Weight Loss: Phentermine-Topiramate vs. Placebo

Study or Subgroup	Phentermine-topiramate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
CONQUER: pooled 1 year	649	1469	72	979	66.5%	6.01 [4.77, 7.56]	
EQUIP: 15/92 mg	235	498	37	498	33.5%	6.35 [4.60, 8.78]	
Total (95% CI)		**1967**		**1477**	**100.0%**	**6.12 [5.08, 7.38]**	
Total events	884		109				

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 18.96 (P < 0.00001)

0.05 0.2 1 5 20
Favors placebo   Favors phentermine-topir

Abbreviation. CI: confidence interval.

The CONQUER/SEQUEL trial also had longer-term weight change data. The extension trial followed a smaller subgroup of individuals (fewer than 30% of original participants) randomized to phentermine-topiramate or placebo through 108 weeks.[93-95]

Individuals in the phentermine-topiramate group continued to lose weight after 1 year compared to those on placebo, although by a smaller amount, with an MD in change in percent body weight of -7.9% at 56 weeks and -9.2% at 108 weeks (Figure 80)[95]; the same weight loss pattern was reflected in the change in body weight, as measured in kg (Figure 81).

Figure 80. Change in Body Weight (%) Over Time: Phentermine-Topiramate vs. Placebo

Study or Subgroup	Phentermine-topiramate Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
CONQR/SEQL: 2 years	-11.7	21	448	-2.5	20.1	227	-9.20 [-12.46, -5.94]	
CONQUER: 1 year	-9.2	9.1	1492	-1.2	9.6	995	-8.00 [-8.75, -7.25]	

-20 -10 0 10 20
Favors phentermine-topir   Favors placebo
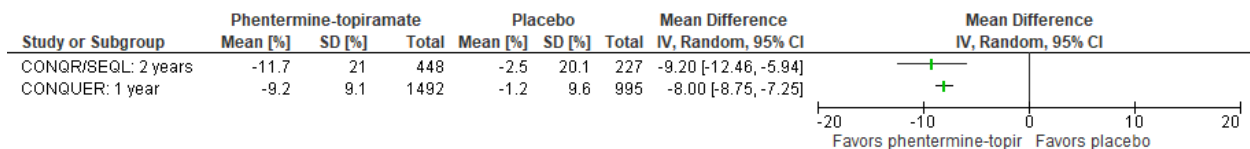
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

Figure 81. Change in Body Weight (kg) Over Time: Phentermine-Topiramate vs. Placebo
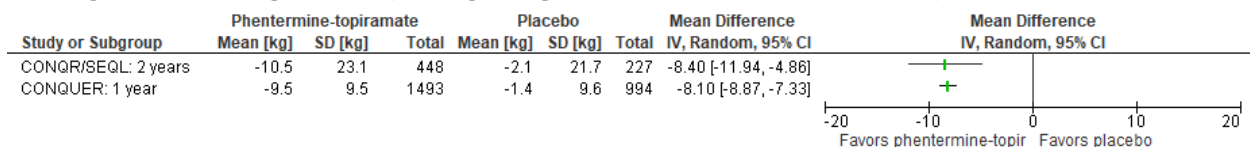
Study or Subgroup	Phentermine-topiramate Mean [kg]	SD [kg]	Total	Placebo Mean [kg]	SD [kg]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
CONQR/SEQL: 2 years	-10.5	23.1	448	-2.1	21.7	227	-8.40 [-11.94, -4.86]	
CONQUER: 1 year	-9.5	9.5	1493	-1.4	9.6	994	-8.10 [-8.87, -7.33]	

-20 -10 0 10 20
Favors phentermine-topir   Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

Comorbidity Risk Factor Outcomes

Summary of Findings (GRADE)

Table 55. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Phentermine-Topiramate in Adults

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
2 RCTs[91,93] N = 3,513	●●●○ Moderate	Participants randomized to phentermine-topiramate had a significantly greater reduction in SBP compared to placebo at 1 year; this difference is not considered clinically meaningful MD, -3.22 mmHg (95% CI, -4.14 to -2.31); *P* < .001	Downgraded: 1 level for RoB[a] • Author and funding CoI
Change in LDL cholesterol (%)			
2 RCTs[91,93] N = 3,513	●●●○ Moderate	Participants randomized to phentermine-topiramate had a small but significant reduction in in LDL cholesterol at 1 year compared to placebo; this difference is likely not clinically meaningful MD, -2.20% (95% CI, -3.82 to -0.57); *P* = .008	Downgraded: 1 level for RoB • Author and funding CoI
Change in HbA1c (%)			
1 RCT[93] N = 2,487	●●●○ Moderate	Participants randomized to phentermine-topiramate had a significant reduction in percent HbA1c at 1 year; this difference is not considered clinically meaningful MD, -0.17% (95% CI, -0.28 to -0.05); *P* = .004	Downgraded:[a] 1 level for RoB • Author and funding CoI

Note. [a] Consistency is not assessable with single study.

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; LDL: low-density lipoprotein; MD: mean difference; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of 2 RCTs,[91,93] individuals randomized to phentermine-topiramate had a significantly greater reduction in SBP, as measured in mmHg, compared to individuals randomized to placebo (MD, -3.22 mmHg; 95% CI, -4.14 to -2.31; Figure 82). This overall treatment effect is less than what is considered clinically meaningful (a decrease of at least 5.0 mmHg).

Figure 82. Change in SBP (mmHg): Phentermine-Topiramate vs. Placebo in Adults
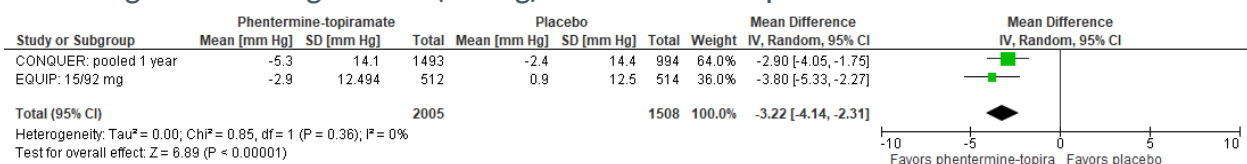
Study or Subgroup	Phentermine-topiramate Mean [mm Hg]	SD [mm Hg]	Total	Placebo Mean [mm Hg]	SD [mm Hg]	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
CONQUER: pooled 1 year	-5.3	14.1	1493	-2.4	14.4	994	64.0%	-2.90 [-4.05, -1.75]	
EQUIP: 15/92 mg	-2.9	12.494	512	0.9	12.5	514	36.0%	-3.80 [-5.33, -2.27]	
Total (95% CI)			**2005**			**1508**	**100.0%**	**-3.22 [-4.14, -2.31]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 6.89 (P < 0.00001)

Favors phentermine-topira   Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; SBP: systolic blood pressure.

In a pooled analysis of 2 RCTs,[91,93] individuals randomized to phentermine-topiramate had a significantly greater reduction in LDL cholesterol, as measured in percent change from baseline, compared to individuals randomized to placebo (MD, -2.20%; 95% CI, -3.82 to -0.57; Figure 83). With baseline LDL cholesterol levels of about 120 mg/dL in the EQUIP study and 124 mg/dL (reported as 3.2 mmol/L),[91] a reduction of about 2% is well under the less than the 38.7 mg/dL (or 1 mmol/L) considered a meaningful decrease, however baseline levels are only moderately elevated.

Figure 83. Change in LDL Cholesterol (%): Phentermine-Topiramate vs. Placebo in Adults
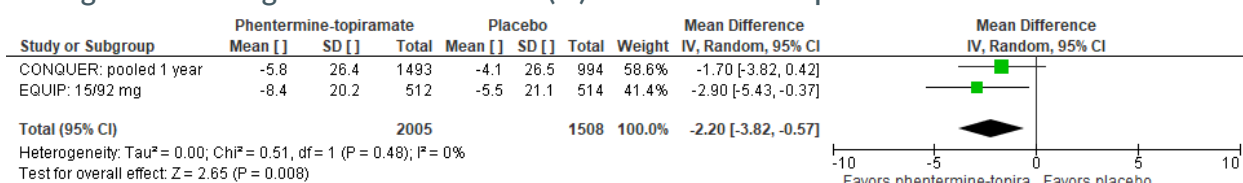
Study or Subgroup	Phentermine-topiramate Mean [ ]	SD [ ]	Total	Placebo Mean [ ]	SD [ ]	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
CONQUER: pooled 1 year	-5.8	26.4	1493	-4.1	26.5	994	58.6%	-1.70 [-3.82, 0.42]	
EQUIP: 15/92 mg	-8.4	20.2	512	-5.5	21.1	514	41.4%	-2.90 [-5.43, -0.37]	
Total (95% CI)			2005			1508	100.0%	-2.20 [-3.82, -0.57]	

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)

-10   -5   0   5   10
Favors phentermine-topira   Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation.

In the CONQUER study at 1 year,[93] the higher, 15/92 mg dose of phentermine-topiramate significantly reduced LDL cholesterol compared to placebo, while there was no difference with the lower 7.5/46 mg (Figure 84).

Figure 84. Change in LDL Cholesterol (%) by Dose: Phentermine-Topiramate vs. Placebo
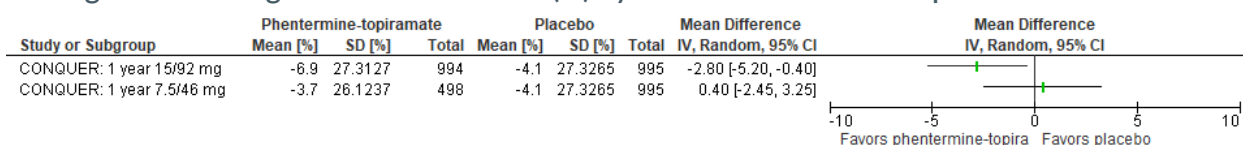
Study or Subgroup	Phentermine-topiramate Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
CONQUER: 1 year 15/92 mg	-6.9	27.3127	994	-4.1	27.3265	995	-2.80 [-5.20, -0.40]	
CONQUER: 1 year 7.5/46 mg	-3.7	26.1237	498	-4.1	27.3265	995	0.40 [-2.45, 3.25]	

-10   -5   0   5   10
Favors phentermine-topira   Favors placebo

Abbreviations. CI: confidence interval; IV: inverse variance; LDL: low-density lipoprotein; SD: standard deviation.

Only the CONQUER study reported change in percent HbA1c. This study included approximately 15.5% of individuals with T2DM; the average baseline percent HbA1c level was 5.9%, which is just above what is considered within normal limits (< 5.7%).[93,94] Individuals randomized to phentermine-topiramate experienced a significantly greater reduction in percent HbA1c compared to those randomized to placebo (MD, -0.17%; 95% CI, -0.28 to -0.05; Figure 85),[93,94] however this treatment effect is not considered clinically meaningful (a decrease of least a 0.3%).

Figure 85. Change in HbA1c (%): Phentermine-Topiramate vs. Placebo in Adults
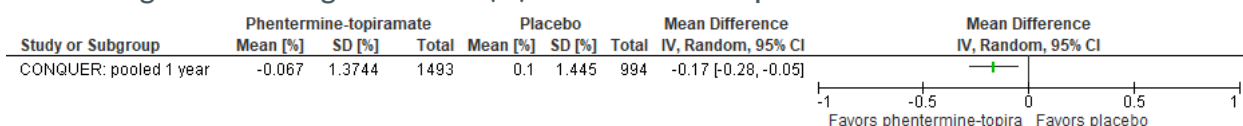
Study or Subgroup	Phentermine-topiramate Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
CONQUER: pooled 1 year	-0.067	1.3744	1493	0.1	1.445	994	-0.17 [-0.28, -0.05]	

-1   -0.5   0   0.5   1
Favors phentermine-topira   Favors placebo

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation.

The CONQUER/SEQUEL trial also had longer-term data for change in indirect measures for risk of comorbidities. The extension period followed a smaller subgroup of individuals (fewer than

30% of original participants) randomized to phentermine-topiramate or placebo through 108 weeks.[95]
- Change in SBP, as measured in mmHg, increased slightly from year 1 to year 2 with phentermine-topiramate, but did not return to baseline levels (Figure 86)[95]
- Percent HbA1c increased slightly from year 1 to year 2, but MD from placebo remained relatively stable over time (Figure 87)[94,95]

Figure 86. Change in SBP (mmHg) Over Time: Phentermine-Topiramate vs. Placebo in Adults
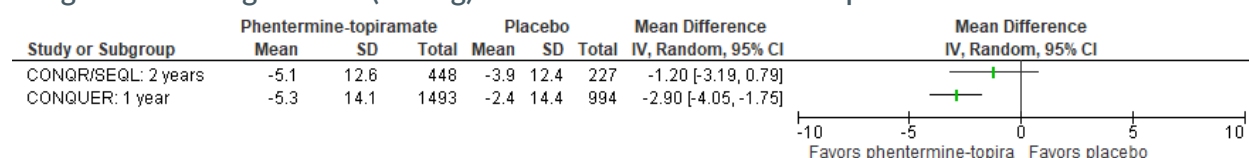
Study or Subgroup	Phentermine-topiramate			Placebo			Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
CONQR/SEQL: 2 years	-5.1	12.6	448	-3.9	12.4	227	-1.20 [-3.19, 0.79]	
CONQUER: 1 year	-5.3	14.1	1493	-2.4	14.4	994	-2.90 [-4.05, -1.75]	

Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; SBP: systolic blood pressure.

Figure 87. Change in HbA1c (%) Over Time: Phentermine-Topiramate vs. Placebo in Adults
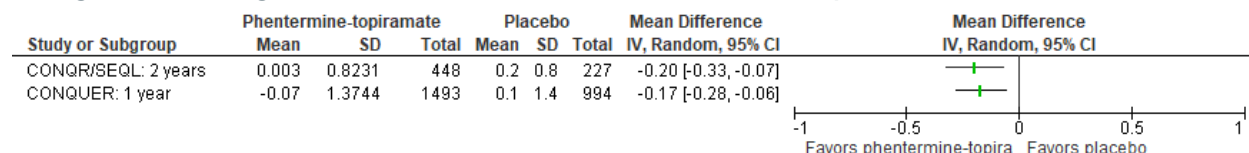
Study or Subgroup	Phentermine-topiramate			Placebo			Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
CONQR/SEQL: 2 years	0.003	0.8231	448	0.2	0.8	227	-0.20 [-0.33, -0.07]	
CONQUER: 1 year	-0.07	1.3744	1493	0.1	1.4	994	-0.17 [-0.28, -0.06]	

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c protein; IV: inverse variance; SD: standard deviation.

The SEQUEL extension of the CONQUER trial also measured annualized incidence rate of progression to T2DM after 108 weeks of treatment.
- In participants without diabetes at baseline, annualized incidence rate of progression to T2DM was 0.9 in the 15/92 mg group, 1.7 in the 7.5/46 mg group, and 3.7 in the placebo group, suggesting a 76% and 54% reduction, respectively, in the progression to T2DM compared to those in the placebo group.[95]
- In the subgroup with prediabetes or metabolic syndrome at initial enrollment, annualized incidence rate of progression to T2DM was 1.3 in the 15/92 mg group, 1.8 in the 7.5/46 mg group, and 6.1 in the placebo group, suggesting a 78.7% and 70.5% reduction, respectively, in the progression to T2DM compared to those in the placebo group.[94]

Quality of Life Outcomes
QoL was not reported in 1 study[93] ("data not shown"), and not measured in the other RCT that compared phentermine-topiramate with placebo in adults.

Safety Outcomes
The 2 RCTs for phentermine-topiramate in adults included overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed CoE for withdrawals due to AEs (Table 56).

Summary of Findings (GRADE)

Table 56. Certainty of Evidence (GRADE) for Safety: Phentermine-Topiramate vs. Placebo

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
2 RCTs[91,93] N = 3,713	●●●○ Moderate	Participants randomized to phentermine-topiramate were significantly more likely to withdraw due to an AE compared to placebo at 1 year RR, 1.88 (95% CI, 1.56 to 2.28); *P* < .001	Downgraded: 1 level for RoB • Author and funding CoI

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In a pooled analysis of 2 RCTs,[91,93] individuals randomized to phentermine-topiramate were more likely to experience an AE that led to study withdrawal compared to individuals randomized to placebo (RR, 1.88; 95% CI, 1.56 to 2.28; Figure 88). The proportion of withdrawals due to AEs was 16.6% with phentermine-topiramate and 8.8% with placebo across the 2 studies in the meta-analysis.

Figure 88. Proportion of Withdrawals Due to Adverse Events: Phentermine-Topiramate vs. Placebo
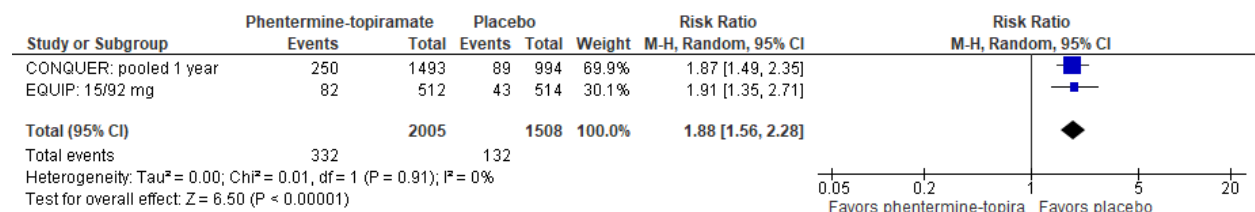
Abbreviations. AE: adverse event; CI: confidence interval.

In the CONQUER study at 1 year,[93] the higher, 15/92 mg, dose of phentermine-topiramate had more withdrawals attributed to AEs compared to the lower dose (19.2% and 11.6%, respectively; Figure 89). No test for statistical difference was reported.

Figure 89. Proportion of Withdrawals Due to Adverse Events by Dose: Phentermine-Topiramate vs. Placebo
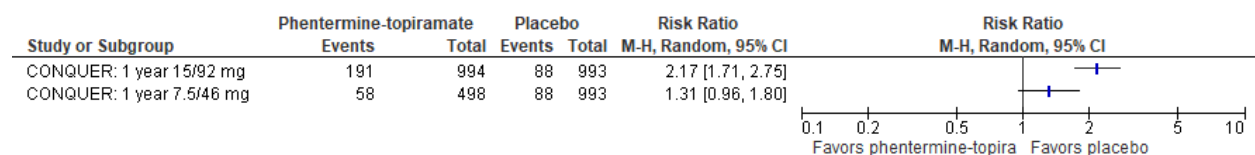
Abbreviations. AE: adverse event; CI: confidence interval.

In general, more people randomized to naltrexone-bupropion experienced an AE compared to those randomized to placebo (Table 57).[91,93]

Among the common AEs in the EQUIP trial,[91] paresthesia (i.e., tingling, burning sensation of the skin), dry mouth, constipation, and disordered taste were experienced statistically more frequently with 15/92 mg phentermine-topiramate compared to placebo.

The CONQUER study only reported number of specific AEs experienced during the trial, rather than number of participants who experienced an AE. Among the common AEs in the CONQUER trial,[93] paresthesia, dry mouth, constipation, disordered taste, insomnia, and dizziness were experienced statistically more frequently with all doses of phentermine-topiramate compared to placebo (see Appendix I, Tables I8 and I9, for details of AE outcomes for phentermine-topiramate).

Serious adverse events, however, were relatively infrequent and evenly distributed between groups across both studies (Table 57).
- The EQUIP study[91] reported 4 "drug related" SAEs: myelogenous leukemia 6 months after starting treatment with the 15/92 mg dose,[118] holelithiasis with the 7.5/46 mg dose, and chest pain and pulmonary embolism in the placebo group.
- There were no further descriptions of SAEs reported in the CONQUER/SEQUEL trials.[93,95]

Table 57. Summary of Adverse Events and Serious Adverse Events: Phentermine-Topiramate

Study Name Author, Year		Adverse Events, % n of N			Serious Adverse Events, % n of N		
		PhenTop	Placebo	P Value	PhenTop	Placebo	P Value
Adults							
EQUIP[a,91] Allison, 2011		84.5% 432 of 511	72.9% 374 of 513	NR	2.5% 13 of 511	2.5% 13 of 513	NR
CONQUER[92,93]/ SEQUEL[94,95] Gadde, 2011	56 weeks	NR	NR	NR	4.4%[b] 65 of 1,492	4.0% 40 of 993	NR
	56 to 108 weeks	NR	NR	NR	3.6%[b] 16 of 448	4.0% 9 of 227	NR

Notes. [a] For 15/92 mg dose only; [b] Results of pooled 15/92 mg and 7.5/46 mg doses.
Abbreviations. NR: not reported; PhenTop: phentermine-topiramate.

One death was reported in 1 of the 2 studies for phentermine-topiramate in adults. One participant treated with placebo died as a result of a cardiopulmonary arrest in the 56-week CONQUER trial.[93]

Change in Medication Outcomes
Only 1 study (SEQUEL/CONQUER)[92-95] of phentermine-topiramate measured changes in medication use for comorbidities (Table 58).

In general, more adults randomized to phentermine-topiramate decreased or stopped use of medications used to treat high blood pressure and dyslipidemia compared to placebo over

108 weeks of treatment, and fewer people increased use; no statistical tests for differences were reported.

In the same study, after 56 weeks of treatment, while more people randomized to phentermine-topiramate decreased or stopped use of oral glucose-lowering medications compared to placebo, the difference in percent who increased use was notable larger with placebo (about 4.5% increased use with phentermine-topiramate, and over 14% increased use with placebo).

Table 58. Summary of Changes in Concomitant Medication Use for Phentermine-Topiramate

Name Author, Year	Population	Decreased or Stopped Use		Increased Use		Between-Group Use Difference
		PhenTop	Placebo	PhenTop	Placebo	
Change in blood pressure medication						
CONQUER[92,93]/ SEQUEL[94,95] Gadde, 2011	15/92 mg at 108 weeks	15.6% 46 of 295	7.5% 17 of 227	5.8% 17 of 295	11.0% 25 of 227	NR
	7.5/46 mg at 108 weeks	13.1% 20 of 153		9.2% 14 of 153		NR
Change in lipid-lowering medication						
CONQUER[92,93]/ SEQUEL[94,95] Gadde, 201	15/92 mg at 108 weeks	5.8% 17 of 295	3.1% 7 of 227	10.5% 31 of 295	20.3% 46 of 227	NR
	7.5/46 mg at 108 weeks	5.9% 9 of 153		11.1% 17 of 153		NR
Change in glucose-lowering medication						
CONQUER[92,93]/ SEQUEL[94,95] Gadde, 2011	15/92 mg at 56 weeks; with T2DM	3.7% 6 of 164	2.5% 4 of 157	4.3% 7 of 164	14.6% 23 of 157	NR
	7.5/46 mg at 56 weeks; with T2DM	3.0% 2 of 67		4.5% 3 of 67		NR

Abbreviations. NR: not reported; PhenTop: phentermine-topiramate; T2DM: type 2 diabetes.

Youth

The results for the 2 doses (15/92 mg and 7.5/46 mg) in the OB-403 study were pooled for all outcomes unless otherwise stated.

Weight Outcomes

Summary of Findings (GRADE)

Table 59. Certainty of Evidence (GRADE) for Weight Outcomes: Phentermine-Topiramate in Adolescents

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in BMI z/SD score			
Not reported			

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in BMI (%)			
1 RCT[96] N = 223	●●○○ Low	Adolescents randomized to phentermine-topiramate had a statistically significantly, and clinically meaningful, reduction in percent BMI compared to placebo MD, -9.70% (95% CI, -12.93 to -6.47); P < .001	Downgraded:[a] 2 levels for RoB • Disproportionate attrition • Author and funding CoI
Change in BMI (kg/m^2)			
1 RCT[96] N = 223	●●○○ Low	Adolescents randomized to phentermine-topiramate had a significantly reduced change in BMI compared to placebo MD, -4.83 kg/m^2 (95% CI, -5.86 to -3.79); P < .001	Downgraded:[a] 2 levels for RoB • Disproportionate attrition • Author and funding CoI
Proportion with ≥ 5% weight loss			
Not reported			
Proportion with ≥ 10% weight loss			
Not reported			

Note. [a] Consistency is not assessable with single study.

Abbreviations. BMI: body mass index; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias; SD: standard deviation.

Detailed Findings

In 1 RCT,[96] adolescents randomized to phentermine-topiramate achieved a statistically significant reduction in percent BMI compared to those randomized to placebo (MD, 9.7%; -12.93 to -6.47; Figure 90). The treatment effect in this single study is above what is considered clinically meaningful of at least 5% difference in change in percent BMI.

Figure 90. Change in BMI (%): Phentermine-Topiramate vs. Placebo in Youth
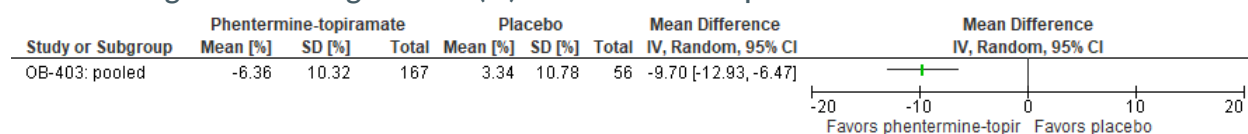
Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

The higher 15/92 mg dose contributed to a slightly larger decline in percent BMI compared to the lower dose (Figure 91) in the OB-403 study,[96] but the difference was not statistically significant (P = .12).

Figure 91. Change in BMI (%) by Dose: Phentermine-Topiramate vs. Placebo in Youth
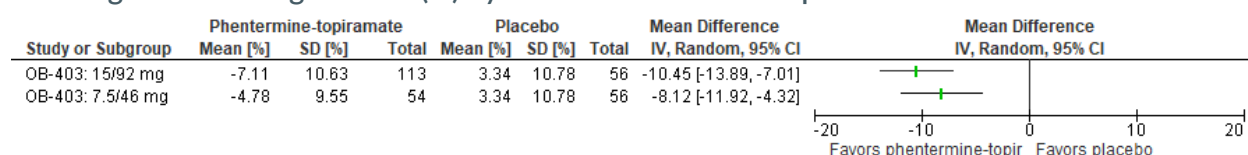
Study or Subgroup	Phentermine-topiramate Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Mean Difference IV, Random, 95% CI
OB-403: 15/92 mg	-7.11	10.63	113	3.34	10.78	56	-10.45 [-13.89, -7.01]
OB-403: 7.5/46 mg	-4.78	9.55	54	3.34	10.78	56	-8.12 [-11.92, -4.32]

Mean Difference IV, Random, 95% CI: scale from -20 to 20. Favors phentermine-topir / Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

In OB-403,[96] adolescents randomized to phentermine-topiramate achieved a statistically significant reduction in BMI, as measured in kg/m^2, compared to those randomized to placebo (MD, -4.83 kg/m^2; 95% CI, -5.9 to -3.8; Figure 92). Correlated with percent change in body weight, this effect is also likely at clinically meaningful levels.

Figure 92. Change in BMI (kg/m^2): Phentermine-Topiramate vs. Placebo in Youth
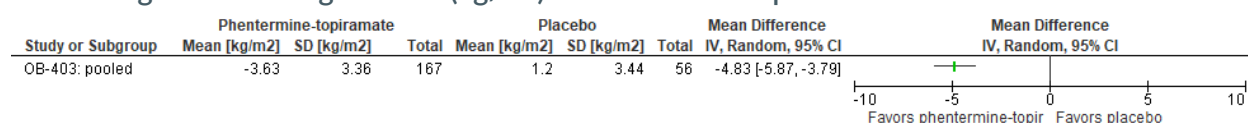
Study or Subgroup	Phentermine-topiramate Mean [kg/m2]	SD [kg/m2]	Total	Placebo Mean [kg/m2]	SD [kg/m2]	Total	Mean Difference IV, Random, 95% CI
OB-403: pooled	-3.63	3.36	167	1.2	3.44	56	-4.83 [-5.87, -3.79]

Mean Difference IV, Random, 95% CI: scale from -10 to 10. Favors phentermine-topir / Favors placebo

Abbreviations. BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation.

The OB-403 study also measured change in absolute body weight[96]; this measure demonstrated a similar effect as other weight measures reported above.

Comorbidity Risk Factor Outcomes

In the single study for phentermine-topiramate in youth, the only outcome of interest that included results for indirect measures of risk for comorbidities was change in blood pressure (Table 60).

Summary of Findings (GRADE)

Table 60. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Phentermine-Topiramate in Adolescents

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg)			
1 RCT[96] N = 223	●●○○ Low	The small improvement in mean SBP with phentermine-topiramate compared to placebo was not statistically significant in adolescents MD, -2.44 mmHg (95% CI, -6.03 to 1.15); P = .18	Downgraded:[a] 1 level for RoB • Disproportionate and large attrition, CoI 1 level for imprecision • CI crosses over clinically meaningful change of 5 mmHg
Change in LDL cholesterol			
Not reported			
Change in HbA1c			
Not reported			

Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; LDL: low-density lipoprotein; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In 1 RCT,[96] small improvements in SBP, as measured in mmHg, with phentermine-topiramate were not statistically different at 56 weeks compared with placebo in adolescents (MD, -2.44 mmHg; 95% CI, -6.0 to 1.2; Figure 93).

Figure 93. Change in Systolic Blood Pressure: Phentermine-Topiramate vs. Placebo in Youth

Study or Subgroup	Phentermine-topiramate Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
OB-403: pooled	0.36	11.05	167	2.8	12.12	56	-2.44 [-6.03, 1.15]

Favors phentermine-topira   Favors placebo
-10   -5   0   5   10
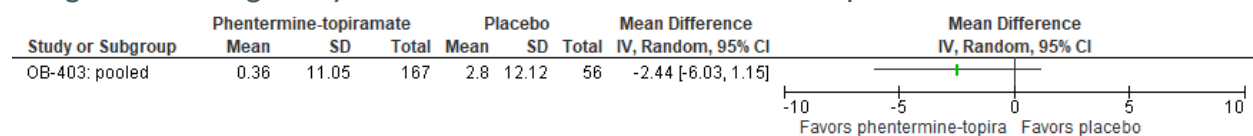
Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation.

In the body of the publication of the OB-403 study authors stated that change in LDL cholesterol at 56 weeks was not statistically different from placebo[96]; no other data or information about LDL cholesterol was reported.

Quality of Life Outcomes

QoL was measured as an exploratory end point only in the OB-403 study[96]; the data are not reported in this review.

Safety Outcomes

The OB-403 study reported overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed CoE for withdrawals due to AEs (Table 61).

Summary of Findings (GRADE)

Table 61. Certainty of Evidence (GRADE) for Safety Outcomes: Phentermine-Topiramate in Adolescents

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
1 RCT[96] N = 223	●○○○ Very low	No difference in withdrawals due to AEs between phentermine-topiramate and placebo groups at 1 year RR, 0.45 (95% CI, 0.10 to 1.94); *P* = .29	Downgraded:[a] 1 level for RoB - Disproportionate and large attrition, CoI 2 levels for imprecision - Very low number of events, low sample size from 1 study

Note. [a] Consistency is not assessable with single study.
Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RCT: randomized controlled trial; RoB: risk of bias; RR: risk ratio.

Detailed Findings

In the single OB-403 study,[96] there were very few withdrawals due to AEs overall, and no statistical difference between groups at 56 weeks (4 with phentermine-topiramate [2.4%] and 3 with placebo [5.3%]; Figure 94).

Figure 94. Proportion of Withdrawals Due to Adverse Events: Phentermine-Topiramate vs. Placebo

Study or Subgroup	Phentermine-topiramate Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
OB-403: pooled	4	167	3	56	0.45 [0.10, 1.94]

Risk Ratio M-H, Random, 95% CI — scale 0.01 to 100. Favors phentermine-topira / Favors placebo

Abbreviations. AE: adverse event; CI: confidence interval.

In the 1 RCT,[96] there were slightly fewer overall AEs with the lower dose of phentermine-topiramate, but relatively similar levels between the higher dose and placebo groups (Table 62). Two participants in the higher, 15/92 mg dose group experienced 3 SAEs over the course of the 56-week trial; 1 participant experienced a bile duct stone within 1 week after study completion, and the depression and suicide ideation experienced by another participant was considered unrelated to the study drug.[96] In general, frequently reported AEs were nervous system disorders (e.g., headaches) and gastrointestinal disorders (e.g., nausea, abdominal pain), but all were relatively equally dispersed across groups.[96] See Appendix I, Tables I8 and I9, for details of AE outcomes for phentermine-topiramate.

Table 62. Summary of Adverse Events and Serious Adverse Events: Phentermine-Topiramate

Study Name Author, Year		Adverse Events, % n of N			Serious Adverse Events, % n of N		
		PhenTop	Placebo	P Value	PhenTop	Placebo	P Value
Adolescents							
OB-403[96] Kelly, 2022	15/92 mg	52.2% 59 of 113	51.8% 29 of 53	NR	1.8% 2 of 113	0% 0 of 54	NR
	7.5/46 mg	37.0% 20 of 54		NR	0% 0 of 54		NR

Abbreviations. NR: not reported; PhenTop: phentermine-topiramate.

No deaths were reported in the OB-404 study[96] for phentermine-topiramate in youth.

Change in Medication Outcomes

The OB-403 study of phentermine-topiramate in youth did not report change in medication outcomes for obesity-related comorbidities.

Setmelanotide

Summary of Included Studies

We identified 3 studies in 5 publications[97-101] for daily 3.0 mg setmelanotide delivered subcutaneously in people with obesity caused by genetic variants; 1 is an RCT,[97] and 2 are single-arm trials (Table 63).[100,101]

- The 2022 RCT by Haqq and colleagues followed 38 individuals (mean age 20 years) with Bardet-Biedl (n = 32) or Alström (n = 6) syndrome randomized to setmelanotide or placebo for 14 weeks; at week 14, those on placebo were transitioned to setmelanotide, and all participants were followed during an open-label period for an additional 52 weeks.[97]
- The 2020 publication by Clement and colleagues included 2 trials in people aged 6 years or older[100]; one trial was in people with obesity caused by POMC deficiency (n = 10), and the other was in people with obesity cause by LEPR deficiency (n = 11).[100]
  - In people with POMC deficiency, 1 individual had T2DM, and 2 had T1DM; 3 individuals were on insulin and 2 were on metformin at enrollment[100]
  - In people with LEPR deficiency, 2 participants had T2DM, and none were on glucose-lowering medications at baseline[100]
  - After titration and 10 weeks of stable treatment, individuals who lost at least 5 kg (or at least 5% body weight in participants weighing < 100 kg at baseline) transitioned to an 8-week double-blind withdrawal phase where individuals setmelanotide for 4 weeks followed by placebo for 4 weeks (research staff were blinded to withdrawal phase sequence, although sequence was not randomized)[100]; open-label treatment was then resumed and continued for an additional 32 weeks.[100]
- The small (N = 10) single-arm study by Haws and colleagues included individuals with obesity caused by BBS (mean age 22.5 years)[101]; after 12 weeks, individuals who tolerated setmelanotide and were successful with weight loss (5 kg, or ≥ 5% of weight in those weighing less than 100 kg at baseline) continued to receive treatment for an additional 52 weeks[101]

Table 63. Overview of Study Characteristics: Setmelanotide

Author, Year Study Name Study Design RoB	Includes US?	Duration + F/U (weeks)	Background Therapy	N Randomized	Interventions, Comparators	Eligibility		
						Diabetes Status	Weight Criteria	Other Conditions
Clement, 2020[99,100] Single-arm High RoB	Yes	62	None	21	• SC setmelanotide 3.0 mg daily	With or without; 14% T2DM, 9.5% T1DM	BMI ≥ 30 kg/m^2 or weight > 95th percentile	Variant in POMC, PCSK1, or LEPR
Haqq, 2022[97,98] RCT + single-arm F/U High RoB	Yes	14 + 52	Nutrition counseling if < 12 years	38 + 12[a]	• SC setmelanotide 3.0 mg daily • Placebo	Not excluded; number with NR	BMI ≥ 30 kg/m^2 or weight > 97th percentile	With BBS or AS
Haws, 2020[101] Single-arm High RoB	Yes	12 + 52	None	10	• SC setmelanotide 3.0 mg daily	NR	BMI ≥ 30 kg/m^2 or weight > 97th percentile	With BBS

Note. [a] Supplemental cohort of participants added during the 14-week randomized period.
Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; BMI: body mass index; F/U: follow-up; LEPR:

leptin receptor; PCSK1: proprotein convertase subtilisin kexin type 1; POMC: proopiomelanocortin; RCT: randomized controlled trial; RoB: risk of bias; SC: subcutaneous; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

We assessed all 3 studies for setmelanotide as high RoB. The RCT included a small sample size, unclear reporting of results, and serious author and study funding conflicts of interest. The 2 single-arm studies were downgraded primarily because of no comparator.

Weight Outcomes

Summary of Findings (GRADE)

Table 64. Certainty of Evidence (GRADE) for Weight Outcomes: Setmelanotide

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in body weight (%)			
1 RCT[97] and 2 single-arm studies[100,101] N = 69	●○○○ Very low	Participants with BBS randomized to setmelanotide lost a significantly greater percentage of body weight compared to placebo at 14 weeks, but the pooled weight loss across participants with BBS and AS was not statistically different Change in percent body weight from baseline was significantly different in all populations at 12, 24 and 52 weeks, with most above clinically meaningful levels (range -5.5% to -25%)	Downgraded: 2 level for RoB • Funding and author CoI, no comparator in 2 studies, very short duration in RCT, small sample sizes 1 level for imprecision • Low sample size

Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MD: mean difference; RCT: randomized controlled trial; RoB: risk of bias.

Detailed Findings

In 1 RCT,[97] participants with BBS randomized to setmelanotide lost significantly more percent body weight compared to individuals with BBS randomized to placebo at 14 weeks (MD, -3.4%; 95% CI, -5.7 to −1.2), but the pooled effect that included participants with Alström syndrome (3 participants in each group) did not reach statistical significance (MD, -2.1%; 95% CI, -4.6 to 0.4; Table 65). Percent body weight loss continued during the extension phase where all individuals were transitioned to setmelanotide for an additional 52 weeks in the BBS and Alström syndrome cohort, and BBS subgroups.[97] In the 2 other single-arm trials, percent weight loss from baseline was statistically significant across all time points, and at 52 weeks, and ranged from -16.3% in the study by Haws and colleagues in participants with BBS,[101] to -25.6% in the study by Clement and colleagues in participants with the POMC genetic variant who were successful with at least 5% weight loss at 12 weeks.[100]

Other continuous measures of weight loss (change in body weight [as measured in kg] change in BMI, and percent change in BMI) were also reported in the 2 single-arm trials and during the single-arm extension period in the study by Haqq and colleagues (Table 65).[97,100,101] Nearly all results demonstrated significant weight loss from baseline. However, in the small study by

Clement and colleagues,[100] not all of the 4 participants with the POMC variant who were 18 years and older, responded to setmelanotide (*P* = .07).

In the single-arm extension portion of the study by Haqq and colleagues,[97] youth with BBS younger than 18 years significantly reduced their BMI z/SD score from baseline (mean change, -0.8; SD, 0.5); this decrease is considered clinically meaningful, of at least 0.15 SDs (Table 65).

Two single-arm studies reported the proportion who achieved at least 10% weight loss from baseline with setmelanotide at 52 weeks (Table 65).
- In the study by Clement and colleagues,[100] 80% of individuals with the POMC genetic variant, and 45% of individuals with the LEPR variant, lost at least 10% body weight.
- In the study by Haqq and colleagues,[97] 32% of individuals with BBS or Alström syndrome lost at least 10% body weight.

Table 65. Weight Outcomes for Setmelanotide

Author, Year	Time Point	Population, N	Difference
Placebo-controlled results			
Change in body weight (%)			**Mean CFB, % (SD)** **BG Difference, % (95% CI); *P* Value**
Haqq, 2022[97] RCT phase	14 weeks	[a] BBS and AS (N = 33)[b]	−2.4 (4.8) vs. −0.3 (2.3) MD, −2.1 (95% CI, −4.6 to 0.4); *P* = .052
		[c] BBS (N = 36)	−3.7 (4.2) vs. −0.2 (2.1) MD, −3.4 (95% CI, −5.7 to −1.2); *P* = .002
Single-arm results			
Change in body weight (%)			**Mean CFB, % (90% CI or SD); *P* value**
Clement, 2020[100]	52 weeks	POMC variant, successful with weight loss at 12 weeks (N = 9)	−25.6% (9·9; 90% CI, −28.8 to −22.0); *P* < .001
		LEPR variant, successful with weight loss at 12 weeks (N = 7)	−12.5% (8.9; 90% CI, −16.1 to −8.8); *P* < .001
Haqq, 2022[97] Single-arm extension phase	52 weeks	BBS and AS ≥ 12 years (N = 31)	−5.2 (7.9); *P* < .001
		BBS only ≥ 12 years (N = 28)	−6.5 (7.0); *P* < .001
		BBS only ≥ 18 years (N = 15)	−7.6 (−7.1); *P* < .001
Haws, 2020[101]	12 weeks	BBS (N = 8)	−5.5 (90% CI, −9.3 to −1.6); *P* = .02
	24 weeks	BBS (N = 8)	−11.3 (90% CI, −15.5 to −7.0); *P* < .001
	52 weeks	BBS (N = 7)	−16.3 (90% CI, −19.9 to −12.8); *P* < .001
Change in body weight (kg)			**Mean CFB, kg (SD); *P* value**
Haqq, 2022[97] Single-arm extension phase	52 weeks	BBS and AS ≥ 12 years (N = 31)	−5.9 (9.3); *P* < .001
	52 weeks	BBS only ≥ 12 years (N = 28)	−7.4 (8.2); *P* < .001

Author, Year	Time Point	Population, N	Difference
	52 weeks	BBS only ≥ 18 years (N = 15)	−9.4 (9.4); P < .001
Change in BMI (%)			**Mean CFB, % (90% CI or SD); P value**
Clement, 2020[100]	52 weeks	POMC variant, successful with weight loss at 12 weeks (N = 9)	−27.8 (9.9; 90% CI, −31.7 to −23.7); P < .001
		LEPR variant, successful with weight loss at 12 weeks (N = 7)	−13.1 (9.4; 90% CI, −16.9 to −9.6); P < .001
Haws, 2020[101]	12 weeks	BBS (N = 8)	−5.5 (5.6); P = .01
	24 weeks	BBS (N = 8)	−11.1 (6.3); P < .001
	52 weeks	BBS (N = 7)	−16.2 (5.3); P < .001
Change in BMI (kg/m^2)			**Mean CFB, % (90% CI or SD); P value**
Clement, 2020[100]	52 weeks	POMC variant, ≥ 18 years (N = 4)	−9.3 (6.9; 90% CI, −17.4 to −1.2); P = .07
		LEPR variant, ≥ 18 years (N = 7)	−5.2 (3.9; 90% CI, −8.1 to −2.3); P = .013
Haqq, 2022[97] Single-arm	52 weeks	BBS only ≥ 18 years (N = 15)	−3.4 (2.1); P, NR
Change in BMI z/SD score			**Mean CFB, SDs (SD); P value**
Haqq, 2022[97] Single-arm	52 weeks	BBS only, < 18 years	-0.8; 0.5; P < .05
Proportion with ≥ 10% weight loss			**n of N (%; 95% CI); P Value**
Clement, 2020[100]	52 weeks	POMC variant (N = 10)	8 of 10 (80)
		LEPR variant (N = 9)	4 of 9 (45)
Haqq, 2022[97] Single-arm	52 weeks	BBS and AS ≥ 12 years (N = 31)	10 of 31 (32.3; 95% CI, 16.7 to 51.4); P < .001

Notes. [a] Pivotal cohort includes all enrolled individuals at the time of planned enrollment; [b] Individuals randomized to placebo were at least 12 years of age; [c] Pivotal plus supplemental cohort.
Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; BG: between-group; BMI: body mass index; CFB: change from baseline; CI: confidence interval; CoE: certainty of evidence; LEPR: leptin receptor; NR: not reported; POMC: proopiomelanocortin; RCT: randomized controlled trial; SD: standard deviation.

Comorbidity Risk Factor Outcomes

Summary of Findings (GRADE)

The single RCT did not report changes in indirect measures of risks for obesity-related comorbid conditions during the 14-week placebo-controlled period. Our GRADE assessments include single-arm data only (Table 66).

Table 66. Certainty of Evidence (GRADE) for Comorbidity Risk Factors: Setmelanotide

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Change in systolic blood pressure (mmHg) from baseline			
3 studies of single-arm data[97,100,101] N = 69	●○○○ Very low	No difference in SBP from baseline across all	Downgraded:[a] 1 level for RoB • CoI, no comparator

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
		populations and time points	1 level for inconsistency • Some increased, some decreased 1 level for imprecision • Low overall sample size
Change in LDL cholesterol from baseline			
3 studies of single-arm data[97,100,101] N = 69	●○○○ Very low	In general, there was no difference in LDL cholesterol levels from baseline with setmelanotide, at 52 weeks, but may depend on genetic condition	Downgraded:[a] 1 level for RoB • CoI, no comparator, small sample sizes 1 level for imprecision • Low overall sample size
Change in HbA1c (%) from baseline			
1 single-arm study[100] N = 21	●○○○ Very low	No difference in percent change in HbA1c from baseline with setmelanotide in people with POMC or LEPR genetic variants	Start at low with NRSs Downgraded:[a,b] 1 level for RoB • CoI, no comparator 1 level for imprecision • Low sample size

Note. [a] Nonrandomized studies start at low CoE; [b] Consistency not assessable with 1 study.
Abbreviations. CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; HbA1c: hemoglobin A1c; LDL: low-density lipoprotein; NRS: nonrandomized studies; RoB: risk of bias; SBP: systolic blood pressure.

Detailed Findings

In 3 studies of single-arm data,[97,100,101] there were no differences in change in SBP from baseline to 52 weeks across all populations studied (Table 67). Baseline blood pressure levels were reported as normal in the study by Haws and colleagues,[101] below normal (mean, 111.5 mmHg) and borderline (mean 121.7 mmHg) in POMC and LEPR populations in the study by Clement and colleagues,[100] and not reported in the study by Haqq and colleagues.

Table 67. Change in Systolic Blood Pressure from Baseline: Setmelanotide

Author, Year	Time Point	Population	MC from Baseline
Clement, 2020[100]	52 weeks	POMC variant (N = 10)	% mmHg (SD): -1.4% (5.1; 90% CI, −4.3 to 1.6); *P* = .42
		LEPR variant (N = 11)	% mmHg (SD): -3.8% (9.9; 90% CI, −9·9 to 2·4); *P* = ·29
Haqq, 2022[97]	52 weeks	BBS and AS (N = 38)	mmHg (SD): -2.4 (16.1); *P* > .05
Haws, 2020[101]	12 weeks	BBS (N = 8)	% mmHg: 8.9 (90% CI, −0.2 to 17.9); *P* > .05
	52 weeks	BBS (N = 7)	% mmHg: 8.9 (90% CI, −1.0 to 18.8); *P* > .05

Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; CI: confidence interval; LEPR: leptin receptor; NR: not reported; MC: mean change; POMC: proopiomelanocortin; RCT: randomized controlled trial; SD: standard deviation.

In general, in 3 studies of single-arm data,[97,100,101] there was no difference in change in LDL cholesterol from baseline to 52 weeks across all populations studied (Table 68). In the study by Clement and colleagues,[100] participants with the LEPR genetic variant reduced LDL cholesterol by 10.0% (SD, 12.1; 90% CI, −17.5 to −2.5), which was a significant decrease from baseline.

Table 68. Change in LDL Cholesterol From Baseline: Setmelanotide

Author, Year	Time Point	Population	MC from Baseline
Clement, 2020[100]	52 weeks	POMC variant (N = 10)	% of mg/dL (SD): −7.6 (23.1; 90% CI, −21.1 to 5.8); P = .32
		LEPR variant (N = 11)	% of mg/dL (SD): −10.0 (12.1; 90% CI, −17.5 to −2.5); P = .04
Haqq, 2022[97]	52 weeks	BBS and AS (N = 36)	mmol/L (SD): −0.2 (0.4); P > .05 % change of mmol/L (SD): -8.8% (16.2)
		BBS only (N = 31)	mmol/L (SD): −0.2 (0.4); P > .05 % change of mmol/L (SD): -7.8 (16.8); P > .05
Haws, 2020[101]	12 weeks	BBS (N = 9)	% of mg/dL: −10.1 (90% CI, −20.8 to 0.7)
	24 weeks	BBS (N = 8)	% of mg/dL: −9.0 (90% CI, −24.6 to 6.6)
	52 weeks	BBS (N = 7)	% of mg/dL: −1.9 (90% CI, −17.6 to 13.8)

Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; CI: confidence interval; LDL: low-density lipoprotein; LEPR: leptin receptor; NR: not reported; MC: mean change; POMC: proopiomelanocortin; SD: standard deviation.

The single-arm study by Clement and colleagues measured percent change in HbA1c[100]; individuals with POMC or LEPR genetic variant had reduced percent HbA1c levels from baseline with 52 weeks of setmelanotide , but not at significantly lower levels (Table 69). At enrollment, 1 individual was with T2DM, and 2 were with T1DM in the POMC variant group, and 2 were with T2DM in the LEPR group; baseline HbA1c levels were not reported.[100]

Table 69. Change in Percent HbA1c From Baseline: Setmelanotide

Author, Year	Time Point	Population	MC from Baseline
Clement, 2020[100]	52 weeks	POMC variant (N = 10)	−4.0 (SD, 10.5; 90% CI, −10.1 to 2.1); P = .26
		LEPR variant (N = 11)	−4.9 (SD, 7.8; 90% CI, -12.3 to 2.6); P = .24

Abbreviations. CI: confidence interval; HbA1c: hemoglobin A1c; LEPR: leptin receptor; MC: mean change; POMC: proopiomelanocortin; SD: standard deviation.

Quality of Life Outcomes
Summary of Findings

Table 70. Certainty of Evidence (GRADE) for Quality of Life: Setmelanotide

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
2 studies of single-arm data[97-100] N = 59	●○○○ Very low	In general, QoL improved with setmelanotide from baseline levels, likely at clinically meaningful levels	Downgraded:[a] 1 level for RoB • Col, no comparator, very small sample size 1 level for imprecision • Small sample size

Detailed Findings

Two RCTs reported survey results of the IWQoL-Lite total score and the IWQoL-Lite physical function component score in adults, and the PedsQL total score in children and adolescents (Table 71).[97-100] QoL scores were improved across measures in the populations studied (individuals with BBS, POMC variant, and LEPR variant). Statistical tests were not completed for any mean change value, but all mean values were reported as clinically meaningful improvements (increases of at least 7.7 points of IWQoL-Lite and 4.4 points for PedsQL).[97-100]

In the study by Haqq and colleagues,[97,98] change in QoL was significantly correlated with weight loss (based on IWQoL-Lite total score) in adults, but not in children or adolescents (Table 71).

Table 71. Quality of Life Measures: Setmelanotide

Author, Year	Time Point	Population	MC from Baseline
Change in IWQoL-Lite: total score (SD) from baseline			
Clement, 2020[99,100]	52 weeks	≥ 18 years; POMC and LEPR variants	24.2 (12.1); *P* value NR
Haqq, 2022[97,98]	52 weeks	≥ 18 years with BBS	12.0 (10.3); *P* value NR
Change in IWQoL-Lite: physical function score (SD) from baseline			
Clement, 2020[99,100]	52 weeks	≥ 18 years; POMC and LEPR variants	18.0 (13.6); *P* value NR
Haqq, 2022[97,98]	52 weeks	≥ 18 years with BBS	15.3 (11.6); *P* value NR
Change in PedsQL score (SD) from baseline			
Clement, 2020[99,100]	52 weeks	8 to 12 years; POMC variant (n = 2)	15.8 (17.7); *P* value NR
		13 to 17 years; POMC variant (n = 4)	5.8 (18.3); *P* value NR
Haqq, 2022[97,98]	52 weeks	< 18 years with BBS	Total score: 11.2 (14.3); *P* value NR
			Physical function score: 14.0 (27.7); *P* value NR

Safety Outcomes

Studies for setmelanotide reported overall AEs, SAEs, mortality, and withdrawals due to AEs. We only assessed the CoE for withdrawals due to AEs using GRADE (Table 72).

Summary of Findings

Table 72. Certainty of Evidence (GRADE) for Safety Outcomes: Setmelanotide vs. Placebo

Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Withdrawals due to AEs			
1 RCT[97] and 2 single-arm studies[100,101] N = 69	●○○○ Very low	Fewer participants assigned to setmelanotide experienced withdrawals due to AEs compared to placebo at 14 weeks in 1 study, but this was not statistically significant RR, 0.33 (95% CI, 0.04 to 2.93); *P* = .32 An additional 5 participants withdrew due to an AE across all single-arm study periods	Downgraded: 1 level for RoB • Funding and author CoI, RCT with short study duration 2 levels for imprecision • Very few events and very wide CIs

Abbreviations. AE: adverse event; CI: confidence interval; CoE: certainty of evidence; CoI: conflict of interest; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RR: risk ratio.

In 1 RCT in people with BBS or Alström syndrome, fewer in the setmelanotide group withdrew because of an AE compared to placebo, over 14 weeks,[97] but this difference was not statistically significant (RR, 0.33; 95% CI, 0.04 to 2.93; Figure 95); 4 additional participants withdrew due to an AE during the 52 week single-arm phase of this study by Haqq and colleagues.

There was only 1 other withdrawal due to an AE across the 2 single-arm trials; grade 1 hypereosinophilia in a participant with a LEPR genetic variant was considered as possibly related to setmelanotide, and resolved following discontinuation[100]

Figure 95. Proportion of Withdrawals Due to Adverse Events: Setmelanotide vs. Placebo

Study or Subgroup	Setmelanotide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Haqq 2020	1	19	3	19	100.0%	0.33 [0.04, 2.93]
Total (95% CI)		19		19	100.0%	0.33 [0.04, 2.93]
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						

Risk Ratio M-H, Random, 95% CI — scale: 0.01 — 0.1 — 1 — 10 — 100; Favors setmelanotide / Favors placebo
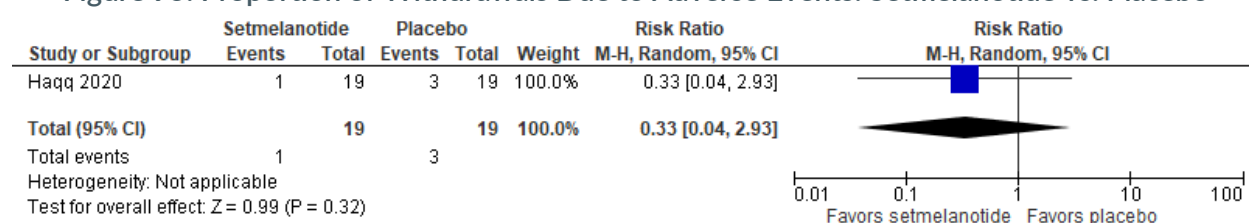
Abbreviations. AE: adverse event; CI: confidence interval.

In the 1 RCT, there were similar rates of AEs experienced by both groups (94.7% each) at 14 weeks.[97] Nearly all of the 69 participants who received setmelanotide in the 3 trials experienced at least 1 AE, and most were reported as generally mild and transient, and rarely led to discontinuation of setmelanotide.[97,100,101] Nine SAEs were reported across all single-arm studies for setmelanotide, and none were considered related to treatment.[97,100,101] See Table 73 for number of participants with AEs and SAEs.

The majority of participants who received setmelanotide experienced injection site reactions[97,100,101]; however, the rates were relatively similar between setmelanotide and placebo groups during 14-week randomized phase of the 1 RCT.[97] Other common AEs included nausea and vomiting.[97,100,101] One notable side effect of setmelanotide is the hyperpigmentation, or discoloration, of the skin, which worsens up to a point, and then stabilizes. Setmelanotide works by activating melanocortin receptors that also have a role in the synthesis of melanin in the skin.[116] Hyperpigmentation occurred in:

- 100% of the individuals with POMC variant, and 45.5% with LEPR variant in the study by Clement and colleagues[100]
- 67% of the individuals with BBS or Alström syndrome in the study by Haqq and colleagues[97]
- 80% of the individuals with BBS in the study by Haws and colleagues[101]

No participants withdrew from the study because of hyperpigmentation.

Table 73. Summary of Adverse Events and Serious Adverse Events: Setmelanotide

Author, Year	Time Point	Population	Adverse Events, % n of N		Serious Adverse Events, % n of N	
			Setmelanotide	Placebo	Setmelanotide	Placebo
Placebo-controlled results						
Haqq, 2022[97]	14 weeks	BBS and AS	94.7% 18 of 19	94.7% 18 of 19	0% 0 of 19	10.5% 2 of 19
Single-arm results						
Clement, 2020[100]	52 weeks	POMC variant	100% 10 of 10	N/A	40% 4 of 10	N/A
		LEPR variant	100% 11 of 11		27% 3 of 11	
Haqq, 2022[97]	52 weeks	BBS and AS	94.7% 18 of 19	N/A	5%[a] 2 of 38	N/A
Haws, 2020[101]	52 weeks	BBS	100% 10 of 10	N/A	10% 1 of 10	N/A

Note. [a] Includes the 2 in placebo group during 14-week randomized period.
Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; LEPR: leptin receptor; N/A: not applicable; POMC: proopiomelanocortin.

One death was reported across all 3 studies; the death was unrelated to the study drug or trial.

Change in Medication Outcomes
The included studies for setmelanotide did not report change in medication outcomes for obesity-related comorbidities.

Off-Treatment Outcomes

Studies for liraglutide, semaglutide, and setmelanotide included some outcomes for off-treatment periods.

- We did not identify any results for off-treatment measurements in our included studies for naltrexone-bupropion or phentermine-topiramate.
- The Combat-JUDO study for exenatide in children and adolescents[83] followed participants for an additional 2 weeks off treatment, but no results were reported for that time period.

- The single head-to-head trial of weekly semaglutide compared with daily liraglutide followed participants for an additional 7 weeks off treatment for safety outcomes only; adverse events were only reported for the final time point which included both on- and off treatment events.[55]
- The single study for tirzepatide[81] included a 4-week off-treatment safety period in the published methods and protocol but did not include any results from that phase. Future reporting of these results is likely given the study protocol indicates a subgroup will be followed through 176 weeks.

Liraglutide

Four studies for liraglutide measured outcomes after discontinuing treatment; the SCALE Obesity and Prediabetes and SCALE Maintenance studies were in adults without diabetes,[56,62] the SCALE Diabetes study was in adults with T2DM,[57] and 1 RCT was in adolescents[60] See Appendix C for full evidence tables including off-treatment outcomes.
- In the SCALE Obesity and Prediabetes study,[56] at the end of the primary trial (56 weeks), patients in the liraglutide group who did not have prediabetes at screening (n = 959) were randomly assigned to continue receiving liraglutide or switch to placebo for 12 weeks. Participants with prediabetes were followed for an additional 2 years, maintaining their assigned liraglutide or placebo treatment, and at the end of the extension period, were followed for an additional 12 weeks off treatment.
- In the SCALE Maintenance[62] and SCALE Diabetes[57] studies, participants were followed for an additional 12 weeks off treatment after 56 weeks on 3.0 mg liraglutide or placebo.
- In the study by Kelly and colleagues,[60] adolescents were followed for an additional 26 weeks off treatment after 56 weeks on 3.0 mg liraglutide or placebo; lifestyle therapy continued during the off treatment period.

In general, more weight was regained after discontinuation of liraglutide compared to the discontinuation of the placebo in adults and adolescents, but weight did not reach baseline levels within the duration of the off-treatment phases, ranging from 12 to 26 weeks.[56,57,60,62]
- In the SCALE Obesity and Prediabetes study,[56] individuals who continued with liraglutide from week 56 to week 68 also regained some weight, but those who transitioned to placebo regained more weight.

The SCALE Obesity and Prediabetes[56] and SCALE Diabetes[57] trials also measured change in SBP during the off-treatment study phases. SBP rebounded in a similar pattern as weight outcomes.

Semaglutide

The study designs of some of the STEP trials for weekly 2.4 mg semaglutide were more robust for off-treatment follow-up compared to most other studies in this report. Authors concluded that the findings of weight regain and rebounding of metabolic improvements with the discontinuation of semaglutide provides evidence of obesity as a chronic disease and supports the benefits of continued treatment in order to sustain weight loss.[79] The cost-effectiveness study by Kim and colleagues[117] (included in this report, below), emphasized that the off-treatment follow-up in the STEP series provided a unique dataset for cost-effectiveness estimates that could include estimates of weight rebound after drug discontinuation.

Five studies of semaglutide reported off-treatment follow-up outcomes including anthropometric and other effectiveness measures in their methods section.[74,76-79] However, only 3 studies reported off-treatment results (see Appendix D for full evidence tables including off-treatment outcomes):

- The extension of the STEP 1 trial[77] followed a subgroup of adults without diabetes for an additional 52 weeks off treatment.
- The STEP 4 trial[74] was a discontinuation study that followed adults without diabetes who were randomized to semaglutide or placebo for 48 weeks after a 20-week run-in period on semaglutide.
- The STEP TEENS trial[78] followed adolescents for 7 weeks after discontinuing treatment.

In the STEP 4 trial,[74] participants lost, on average 10.6% (SD, 4.7) body weight during the 20-week run-in with semaglutide; individuals who continued with semaglutide lost an additional 7.9% (95% CI, -8.6 to -7.2) over 48 weeks, while those who switched to placebo regained weight and were at 6.9% (95% CI, 5.8 to 7.9) overall loss of body weight. In the STEP 1 extension trial,[77] baseline mean weight loss values after 68 weeks of treatment were 17.3% (SD, 9.3) with semaglutide and 2.0% (SD, 6.1) with placebo; after 52 weeks of treatment withdrawal, those who discontinued semaglutide regained an average of 11.6% (SD, 7.7) body weight, and those who discontinued placebo regained 1.9% (SD, 4.8) body weight.

- In both STEP 1 and STEP 4 trials,[74,77] participants who stopped semaglutide regained just over one-third of their body weight back after 52 weeks (STEP 1) and 48 weeks (STEP 2) off treatment, irrespective of ongoing diet and exercise background therapy.
- In the STEP 4 study,[74] this pattern of rebound was similar for SBP, LDL cholesterol, and HbA1c outcome measures; however in the STEP 1 study, some indirect measures of comorbidity risk factors reverted to towards baseline levels after 52 weeks off treatment.

In the STEP TEENS study, more weight was regained after discontinuation of semaglutide compared to the discontinuation of the placebo adolescents, but weight did not reach baseline levels after 7 weeks off treatment.[78]

Setmelanotide

Two small single-arm studies for setmelanotide in 1 publication, in people with POMC or LEPR variants, included an 8-week double-blind, placebo-controlled withdrawal sequence for participants who lost at least 5% body weight after 10 weeks of setmelanotide (see Appendix J for full evidence tables including off-treatment outcomes).[100] All but 1 participant started with 4 weeks of setmelanotide, followed by 4 weeks of placebo (the single participant experienced the reverse order of treatment).[100] Changes in hunger scores and weight were measured during this off-treatment phase; we only included changes in weight in this report.

- In both trials of genetic variants, individuals regained all the lost weight and gained more weight at the end of the placebo period, from the weight lost during the 4 weeks on setmelanotide.[100] To note, individuals had lost more weight on setmelanotide prior to starting the 4-week placebo-controlled period on setmelanotide, so the weight regained after placebo did not reach baseline levels at study enrollment.[100]

Ongoing Studies

For KQ4, we identified 47 ongoing studies (42 RCTs and 5 nonrandomized; Table 74). Study sizes range from 12 to 17,500 and are in enrolling individuals aged 2 years and older. Of the 31 studies that provide eligibility details related to diabetes status, 17 (55%) explicitly exclude individuals with T1DM or T2DM,[118-128] [129-134] while the remainder accept participants with diabetes; only 3 studies are exclusively enrolling individuals with T2DM.[135-137] All studies report weight change or BMI; most also report outcomes related to cardiovascular health (e.g., LDL), QoL, or adverse events. No ongoing studies for exenatide, dulaglutide, or lixisenatide were identified. Further details of characteristics of ongoing study are available in Appendix L. Briefly, we identified:

Head-to-head studies:
- 3 RCTs, 2 of which compare at least 3 interventions of interest; primary completion dates from August 2022 to December 2024.[130,134,137]
  - Study sizes range from 69 to 700 participants.
  - All studies are at least 52 weeks, enrolling participants aged 18 years and older with a BMI of ≥ 27 or ≥ 30 kg/m^2, and include US participants.
  - EMPOWER-T2D exclusively enrolled individuals with T2DM; this study completed in August 2022, but no publications could be identified.[137]

Liraglutide[118,120,138-142]:
- 7 RCTS comparing liraglutide to placebo with primary completion dates ranging from February 2021 to December 2025; no publications were identified for completed studies.
  - Study sizes range from 48 to 392 participants; 3 of 7 studies include US participants.
  - Most studies (6 of 7) have a minimum duration of 52 weeks; 1 study has a duration of 26 weeks.
  - 3 studies are enrolling individuals who have been authorized or have had bariatric surgery[118,138,142], 1 is enrolling individuals with T2DM.[142]
  - 1 study is enrolling children aged 6 to 12 with a BMI ≥ 95th percentile for their age.[141]

Semaglutide[119,143,123,124,125-128,144,131,132,136,145-147,148,149]:
- 17 studies were identified (14 RCTs and 3 nonrandomized studies) with primary completion dates ranging from January 2023 to October 2032
  - Study sizes range from 16 to 17,500 participants; 11 of 17 studies will include participants from the US.
  - 6 placebo-controlled RCTs are enrolling adults aged 18 and older.[126,132,136,143-146]
  - 2 placebo-controlled RCTs are enrolling individuals of any age with a BMI of ≥ 25 or ≥ 30.[125,127]
  - A 72-week RCT will compare semaglutide with placebo in adults aged 18 years and older with T2DM and a BMI ≥ 30.[136]
  - A small RCT (N=16) is comparing a single dose of 1 mg per week with the standard of care in adults aged 65 years and older with a BMI ≥ 30.[131]
  - The SELECT placebo-controlled RCT enrolled adults (N = 17,500) aged 45 years and older with a BMI ≥ 27 for 236 weeks; a nonrandomized extension study, SELECT-LIFE, will enroll 12,450 former SELECT participants to examine outcomes of long-term treatment for up to 10 years.[124]

- o SWEET is enrolling adults aged 18 to 45 with a BMI ≥ 25 and a history of gestational diabetes to compare semaglutide with placebo for 26 weeks.[123]
- o BARI-STEP (N=70) will enroll individuals aged 18 to 65 years with poor weight loss following bariatric surgery.[128]
- o STEP Young is enrolling children and adolescents between the ages of 6 and 18 years who have a BMI in the 85th percentile with a weight-related comorbidity or 95th percentile and comparing semaglutide to placebo for 130 weeks.[147]
- o A 52-week nonrandomized study, SEMASEARCH (N=1,000) is examining long-term effects in adults aged 18 years and older.[149]
- o 1 nonrandomized study is enrolling overweight or obese pregnant people (N=728) aged 15 to 45 years with at least 1 weight-related comorbid condition and were exposed to at least 1 dose of semaglutide during pregnancy, or were completely unexposed, to measure pregnancy-related outcomes (e.g., malformations, preterm delivery).[148]

Tizepatide[121,122,129,133,135,150,151]:
- 6 placebo-controlled RCTs with completion dates ranging from March 2023 to October 2027.
  - o Study sizes range from 261 to 15,000 participants; the majority (5 of 6) of the studies include US participants.
  - o 4 studies are part of the SURMOUNT trial series with a minimum of 72 weeks duration; a joint protocol and baseline characteristics paper was published in December 2022.[121,122,135,151]
  - o SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4 are enrolling adults aged 18 years and older with a BMI ≥ 27; SURMOUNT-2 is enrolling individuals with T2DM.[121,122,135,151]
  - o SURMOUNT-J is being conducted in Japan and enrolling adults aged 20 and older with a BMI ≥ 27.[129]
  - o SUMMIT is a 52 week RCT with 78 weeks follow-up enrolling individuals with heart failure with preserved ejection fraction who are aged 40 years and older with a BMI ≥ 30.[150]
  - o The largest tirzepatide study (N=15,000) is enrolling adults aged 40 years and older with a BMI ≥ 27 and cardiovascular disease or risk factors for up to 260 weeks of treatment.[133]

Naltrexone-bupropion[152-156,157-160]:
- 9 RCTs comparing naltrexone-bupropion with placebo, cognitive behavioral therapy, or a lifestyle intervention with completion dates ranging from December 2021 to January 2027.
  - o Study sizes range from 38 to 214 participants; 7 of 10 studies include US participants.
  - o Most studies (8 of 10) are 12 to 26 weeks duration; 7 of these studies include an additional follow-up period of 26 to 52 weeks.
  - o 2 studies have a duration of 52 weeks.
  - o All studies are enrolling adults aged 18 years and older with a minimum BMI of ≥ 25; 4 studies did not specify BMI but require participants to be overweight or obese.
  - o 4 studies are enrolling participants with binge-eating disorder.[152-155]
  - o 4 studies are enrolling participants who have had bariatric surgery.[156,158-160]

Phentermine-topiramate[161,162]:

- 2 placebo-controlled RCTs with 52 weeks treatment with primary completion dates in June 2022 and November 2023.
  - o 1 study included participants (N = 80) from the US aged 18 years or older with a BMI of ≥ 30; this study completed in June 2022, but no publications were identified; however, the researchers published data to ClinicalTrials.gov.[161]
  - o The other study is enrolling adults (N = 301) aged 19 to 70 with a BMI ≥ 25; no US participants will enrolled.[162]

Setmelanotide[163-165]:

- 3 studies (2 nonrandomized, 1 RCT) in individuals with BBS or *POMC, PCSK1, LEPR, NCOA1,* or *SH2B1*; all studies have a minimum duration of 52 weeks and include pediatric populations and completion dates in September 2023 or December 2024.
  - o Study sizes range from 12 to 400 individuals.
  - o A small single-arm study (N = 12) is enrolling children between the ages of 2 and 6 years with a BMI in the 97th percentile; primary completion is expected in September 2023.[163]
  - o A nonrandomized study, with up to 260 weeks duration, is enrolling individuals aged 2 years and older with obesity-related LEPR.[164]
  - o EMANATE is a placebo-controlled RCT enrolling individuals aged 6 to 65 with a BMI ≥ 30 or the ≥ 95th percentile[165]; a protocol has been published.[166]

Table 74. Ongoing Studies

Study Name Trial Number	Study Details				Eligibility Criteria				Outcomes					Primary Completion Date
	Includes US	Duration + Follow-up, Weeks	N Enrolled	Interventions	Age, Years	Accepts Diabetes?	BMI, kg/m^2	Required Conditions	Blood Pressure	LDL	HbA1c	AEs	QoL	
Head-to-head studies														
EMPOWER-T2D[137] NCT04531176	√	52 + 52	69	• Liraglutide • NalBup • Orlistat • PhenTop • Lifestyle • SOC	≥ 18	√	≥ 30	T2DM	√	√	√	X	√	August 2022
NCT05579249[130]	√	52	500	• Liraglutide • NalBup • Orlistat • PhenTop • Semaglutide	≥ 18	No	≥ 30	NR	X	X	X	X	√	November 2024
SURMOUNT-5[134] NCT05822830	√	72	700	• Semaglutide • Tirzepatide	≥ 18	No	≥ 27[a] or ≥ 30	NR	X	X	X	X	X	December 2024
Liraglutide														
ACTRN12617001613392[138]	X	52	48	• Liraglutide • Placebo	20 to 65	NR	NR	Post-bariatric surgery without sufficient weight loss	X	√	√	√	√	February 2021
NCT03048578[140] US	√	52	132	• Liraglutide • Placebo	≥ 18	√[b]	≥ 27[a] or ≥ 30	Post-bariatric weight regain ≥ 10%	X	X	X	X	X	March 2021
STRIVE[139,167] NCT03036800	X	52 + 52	392	• Liraglutide • Placebo	≥ 18	√[b]	≥ 35	Prediabetes, T2DM, hypertension,	√	√	√	√	√	June 2022

Study Name Trial Number	Study Details				Eligibility Criteria				Outcomes					Primary Completion Date
	Includes US	Duration + Follow-up, Weeks	N Enrolled	Interventions	Age, Years	Accepts Diabetes?	BMI, kg/m²	Required Conditions	Blood Pressure	LDL	HbA1c	AEs	QoL	
								or obstructive sleep apnea						
NCT05285397[142]	X	26	60	• Liraglutide • SOC	Any	√	> 35	Secondary bariatric surgery due to weight regain	√	√	√	X	X	September 2022
NCT03115424[118]	√	132	75	• Liraglutide • Placebo	20 to 65	No	NR	Authorized for bariatric surgery	√	√	X	X	X	July 2023
SCALE KIDS[141] NCT04775082	√	56 + 26	78	• Liraglutide • Placebo	6 to 12	√[b]	≥ 95th percentile	NR	√	X	√	√	X	July 2023
RESETTLE[120] EudraCT: 2019-002274-31	X	52	150	• Liraglutide • Placebo	18 to 25	No	> 30	NR	X	X	X	X	X	December 2025
Semaglutide														
STEP 10[126] NCT05040971	X	52	201	• Semaglutide • Placebo	≥ 18	No	≥ 30	Prediabetes	√	√	√	X	X	January 2023
OASIS 1[144] NCT05035095	√	68	667	• Semaglutide • Placebo	≥ 18	NR	≥ 27[a] or ≥ 30	NR	√	√	√	√	√	March 2023
NCT05302596[131]	√	16	16	• Semaglutide • SOC	≥ 65	No	≥ 30	NR	X	X	X	X	X	March 2023
STEP-HfpEF[143,168] NCT04788511	√	52 + 52	516	• Semaglutide • Placebo	≥ 18	NR	≥ 30	HfpEF	√	X	X	√	X	April 2023
SELECT[119,169 170] NCT03574597	√	236	17,500	• Semaglutide • Placebo	≥ 45	No	≥ 27	CV disease	√	√	√	√	X	June 2023
NCT05064735[127]	√	68	407	• Semaglutide • Placebo	Any	No	≥ 30	Knee osteoarthritis	X	X	X	X	√	July 2023

Study Name Trial Number	Study Details				Eligibility Criteria				Outcomes					Primary Completion Date
	Includes US	Duration + Follow-up, Weeks	N Enrolled	Interventions	Age, Years	Accepts Diabetes?	BMI, kg/m^2	Required Conditions	Blood Pressure	LDL	HbA1c	AEs	QoL	
OASIS 2[145] NCT05132088	X	68	198	• Semaglutide • Placebo	≥ 18	√	≥ 27 or ≥ 30	≥ 1 weight-related comorbidities for BMI ≥ 30	√	√	√	√	√	July 2023
NCT04998136[125]	X	44	150	• Semaglutide • Placebo	Any	No	≥ 25	Both parents of Asian descent	√	√	X	X	X	November 2023
SWEET[123] NCT04873050	√	26	102	• Semaglutide • Placebo	18 to 45	No	≥ 25	History of gestational diabetes	X	X	√	X	X	February 2024
BARI-STEP[128] NCT05073835	X	68	70	• Semaglutide • Placebo	18 to 65	No	NR	Post-bariatric surgery with poor weight loss	√	X	√	X	√	March 2024
OASIS 4[146] NCT05564117	√	64 + 7	281	• Semaglutide • Placebo	≥ 18	NR	≥ 27[a] or ≥ 30	NR	√	√	√	√	√	March 2024
STEP UP[132] NCT05646706	√	72	1,407	• Semaglutide • Placebo	≥ 18	No	≥ 30	NR	X	y	√	√	X	October 2024
NCT05649137[136]	√	72	513	• Semaglutide • Placebo	≥ 18	√	≥ 30	T2DM	X	√	√	√	X	October 2024
[c]SEMASEARCH[149] NCT05897398	X	52	1,000	• Semaglutide	≥ 18	NR	≥ 40	≥ 1 weight-related comorbidity	X	X	X	X	X	September 2025
STEP Young[147] NCT05726227	√	130	210	• Semaglutide • Placebo	6 to 18	√[b]	≥ 85th[c] or ≥ 95th per-centile	NR	√	√	√	X	X	November 2025

Study Name Trial Number	Study Details				Eligibility Criteria				Outcomes					Primary Completion Date
	Includes US	Duration + Follow-up, Weeks	N Enrolled	Interventions	Age, Years	Accepts Diabetes?	BMI, kg/m^2	Required Conditions	Blood Pressure	LDL	HbA1c	AEs	QoL	
[c]SELECT-LIFE[124] NCT04972721	√	Up to 520	12,450	• Semaglutide	≥ 45	No	≥ 27	Participated in SELECT	√	X	X	√	√	April 2032
[a]NCT05872022[148]	NR	Up to 52	728	• Semaglutide	15 to 45	NR	NR	≥ 1 weight-related comorbidity and exposed to 0 or ≥ 1 dose of semaglutide, during recent or current pregnancy	X	X	X	√[d]	X	October 2032
Tirzepatide														
SURMOUNT-2[135, 151] NCT04657003	√	72	938	• Tirzepatide • Placebo	≥ 18	√[b]	≥ 27	T2DM	√	√	√	X	√	March 2023
SURMOUNT-3[121, 151] NCT04657016	√	72	806	• Tirzepatide • Placebo	≥ 18	No	≥ 27[a] or ≥ 30	NR	√	√	√	N	√	April 2023
SURMOUNT-4[122, 151] NCT04660643	√	88	783	• Tirzepatide • Placebo	≥ 18	No	≥ 27[a] or ≥ 30	NR	√	√	√	X	√	April 2023
SURMOUNT-J[129] NCT04844918	X	72	261	• Tirzepatide • Placebo	≥ 20	No	≥ 27[e] or ≥ 35	≥ 1 weight-related comorbidity	√	√	√	X	√	June 2023
SUMMIT[150] NCT04847557	√	52 + 78	700	• Tirzepatide • Placebo	≥ 40	√	≥ 30	HfpEF	√	X	X	√	X	June 2024
NCT05556512[133]	√	Up to 260	15,000	• Tirzepatide • Placebo	≥ 40	No	≥ 27	CV disease or ≥ 2 risk factors	√	X	√	√	√	October 2027

Study Name Trial Number	Study Details				Eligibility Criteria				Outcomes					Primary Completion Date
	Includes US	Duration + Follow-up, Weeks	N Enrolled	Interventions	Age, Years	Accepts Diabetes?	BMI, kg/m^2	Required Conditions	Blood Pressure	LDL	HbA1c	AEs	QoL	
Naltrexone-bupropion														
NCT03047005[152]	√	16 + 26	68	• NalBup • Placebo	≥ 18	NR	NR	Obesity + BED	X	X	X	X	X	December 2021
NCT03063606[153]	√	16 + 26	38	• NalBup • CBT	≥ 18	NR	NR	Obesity + BED	X	X	X	X	X	December 2021
NCT03539900[154]	√	12 + 52	200	• NalBup • Placebo	≥ 18	NR	≥ 25	BED	X	X	X	X	X	April 2022
COR-WM[157] NCT04589130	X	52	214	• NalBup • Placebo	≥ 18	√	≥ 27	≥ 1 weight-related comorbidity	X	√	√	√	√	November 2022
COR-WR[156] NCT04587843	X	52	200	• NalBup • Placebo	≥ 18	√	≥ 27[a] or ≥ 30	Post-bariatric surgery	√	√	√	√	√	May 2023
NCT03946111[155]	√	12 + 52	40	• NalBup • Placebo	18 to 64	√	≥ 27	BED	X	X	X	X	X	July 2024
NCT04902625[159]	X	22 + 26	116	• NalBup • Lifestyle intervention	≥ 18	NR	≥ 35 prior to bariatric surgery	Post-bariatric weight regain ≥ 5%	X	X	X	√	X	March 2025
NCT04605081[158]	√	12 + 52	100	• NalBup • Placebo	≥ 18	√	NR	Post-bariatric surgery	X	X	X	X	X	May 2026
NCT05157698[160]	√	26 + 52	160	• NalBup • Lifestyle • Placebo	18 to 64	√	≥ 27[a] or ≥ 30 to < 50	Post-bariatric surgery	X	√	√	X	X	January 2027

Study Name Trial Number	Study Details				Eligibility Criteria				Outcomes					Primary Completion Date
	Includes US	Duration + Follow-up, Weeks	N Enrolled	Interventions	Age, Years	Accepts Diabetes?	BMI, kg/m^2	Required Conditions	Blood Pressure	LDL	HbA1c	AEs	QoL	
Phentermine-topiramate														
NCT04408586[161]	√	52	80	• PhenTop • Placebo • Online support	18 to 75	NR	≥ 30	NR	X	X	X	X	√	June 2022
NCT05378503[162]	X	52	301	• PhenTop • Placebo	19 to 70	√	≥ 25	NR	√	√	√	X	X	November 2023
Setmelanotide														
[c]NCT04966741[163]	√	52	12	• Setmelan-otide	2 to 5	NR	≥ 97th per-centile	Bardet-Biedl syndrome, POMC, PCSK1, or LEPR	X	X	X	X	X	September 2023
[c]NCT03651765[164]	√	Up to 260	300	• Setmelan-otide	≥ 2	NR	NR	LEPR	X	X	X	√	X	December 2024
EMANATE[165,166] NCT05093634	√	52	400	• Setmelan-otide • Placebo	6 to 65	NR	≥ 30 or 95th per-centile	POMC, PCSK1, NCOA1, or SH2B1	X	X	X	X	X	December 2024

Notes. All studies report outcomes related to weight or BMI. Shaded rows indicate studies that include pediatric populations. [a] Participants with a BMI between 27 and 29.9 are required to have ≥ 1 weight-related comorbidity. [b] Participants with T1DM are excluded from participation. [c] This is a nonrandomized study. [d] NCT05872022 aims to examine pregnancy-related outcomes (e.g., malformations, preterm delivery). [e] Participants with a BMI between 27 and 34.9 are required to have ≥ 2 weight-related comorbidities.

Abbreviations. AE: adverse event; BED: binge-eating disorder; BMI: body mass index; CBT: cognitive-behavioral therapy; CV: cardiovascular; HbA1c: hemoglobin A1c; HfpEF; heart failure with preserved ejection fraction; LDL: low-density lipoprotein; LEPR: leptin receptor; POMC: proopiomelanocortin; NalBup: naltrexone/bupropion; NR: not reported; PhenTop: phentermine/topiramate; QoL: quality of life; SAE: serious adverse event; T2DM: type 2 diabetes.

Cost-Effectiveness of Pharmacologic Agents for Weight Management

Summary of Study Characteristics for Included Studies

We identified 8 eligible economic modeling studies evaluating costs or cost-effectiveness of the weight management agents of interest in the US from a health care payer perspective (Table 75).[117,171-177] Six of these studies were cost-effectiveness modeling studies[117,171,173-176] and the other 2 modeled cost comparisons.[172,177] Each of the cost-effectiveness studies had no treatment or usual care as the primary comparator but made comparisons among multiple interventions performing incremental cost-effectiveness calculations based on effectiveness findings from separate trials. Five drugs, liraglutide (3.0 mg, daily), phentermine-topiramate (7.5/46 mg, daily), naltrexone-bupropion (32/360 mg, daily), semaglutide (2.4 mg, weekly), and tirzepatide were studied in multiple economic studies. The economic studies were mostly for populations with obesity with the exception of 1 study that was for the population of people with T2DM.[172] We rated 2 of the 8 studies low RoB[171,174], 4 as moderate RoB[117,172,173,176], and 2 as high RoB.[175,177]

Table 75. Summary of Study Characteristics of Included Economic Studies

Author, Date RoB	Population	Intervention	Comparators	Economic Analytic Method
Atlas et al., 2022[171] Low	People without pre-existing T2DM, and a BMI ≥ 30 or ≥ 27 kg/m² with ≥ 1 weight-related comorbidity	• Semaglutide (2.4 mg, weekly) • Liraglutide (3 mg, daily) • Phentermine-topiramate (7.5/46 mg to 15/92 mg, daily) • Naltrexone-bupropion (32/360 mg, daily)	• Usual care alone, which included standard diet and activity and lifestyle recommenda-tions	Cost-effectiveness analysis (Markov state transition model) US payer perspective
Azuri et al., 2023[172] Moderate	People with T2DM	• Tirzepatide (15 mg, weekly)	• Semaglutide (2.4 mg, weekly)	Cost needed to treat US payer perspective
Finkelstein et al., 2019[173] Moderate	People with BMI ≥ 30 kg/m²	• Weight Watchers Online • Weight Watchers Meetings • Jenny Craig • Intragastric balloon system (Orbera) • Orlistat (180 mg, weekly) • Orlistat (360 mg, weekly) • Phentermine-topiramate (7.5/46 mg, daily) • Naltrexone-bupropion (32/360 mg, daily) • Liraglutide (3 mg, daily) • Lorcaserin (20 mg, daily)	• No treatment	Cost-effectiveness analysis US payer perspective
Gomez Lumbreras et al., 2023[174] Low	People with obesity and no comorbidities	• Tirzepatide • Semaglutide (2.4 mg, weekly) • Phentermine-topiramate	• No treatment	Cost-effectiveness analysis (Markov state transition model)

Author, Date RoB	Population	Intervention	Comparators	Economic Analytic Method
		• Naltrexone-bupropion • Liraglutide (3.0 mg, daily)		US payer perspective
Hu et al., 2022[175] High	People with obesity	• Liraglutide (1.8 mg, daily) • Semaglutide (1.0 mg, weekly) • Dulaglutide (1.5 mg, weekly) • Exenatide (10 μg, twice daily)	• No treatment	Cost-effectiveness analysis (Decision tree model) US payer perspective
Kim et al., 2022[117] Moderate	People with BMI ≥ 30 kg/m^2, or BMI 27 to 29.9 kg/m^2 and at least 1 weight-related comorbidity	• Semaglutide (2.4 mg, weekly)	• No treatment • Diet and exercise • Liraglutide (3 mg, daily) • Phentermine-topiramate • Naltrexone-bupropion	Cost-effectiveness analysis (Markov state transition model) US payer perspective
Lee et al., 2020[176] Moderate	People with BMI 30 to 35 kg/m^2	• Intensive lifestyle intervention • Phentermine-topiramate (7.5/46 mg, daily) • Liraglutide (3.0 mg, daily) • Semaglutide (0.4 mg, daily) • Orlistat (120 mg, 3-times per day) • Lorcaserin (10 mg, 2-times per day) • Phentermine (37.5 mg, daily)	• No treatment	Cost-effectiveness analysis (Microsimulation model) US payer perspective
Nuijten et al., 2018[177] High	People with BMI ≥ 30 kg/m^2	• OPTIFAST	• No treatment • Liraglutide (3 mg, daily) • Naltrexone-bupropion	Cost-comparison, cost-effectiveness analysis (decision tree model) US payer perspective

Abbreviations. BMI: body mass index; RoB: risk of bias; T2DM: type 2 diabetes.

Atlas and colleagues[171] evaluated the cost-effectiveness of semaglutide (2.4 mg, weekly), liraglutide (3 mg, daily), phentermine-topiramate (7.5/46 mg to 15/92 mg, daily), and naltrexone-bupropion (32/360 mg, daily) for weight management for adults who have no pre-existing T2DM and with either a BMI of at least 30 kg/m^2 or at least 27 kg/m^2 with 1 or more weight-related comorbidities. We assessed this study as being at low RoB.

Azuri and colleagues[172] assessed the cost needed to achieve a 1% reduction in body weight using tirzepatide (15 mg, weekly) versus semaglutide (2.4 mg, weekly) among people with T2DM. We assessed this study as being at moderate RoB because the costs of treatment-related adverse

events were not included in the estimates and there was a lack of clarity on some modeling choices.

Finkelstein and colleagues[173] assessed the cost-effectiveness of all evidence-based non-surgical weight loss interventions that were commercially available at the time of the study for adults with a BMI of at least 30 kg/m^2. The interventions they evaluated were 2 lifestyle modification programs (Weight Watchers Online and Weight Watchers Meetings), a food replacement program (Jenny Craig), an intragastric balloon system (Orbera), and 6 pharmaceuticals products including low- and high-dose orlistat (180 mg, weekly, and 360 mg, weekly), phentermine-topiramate (7.5/46 mg, daily), naltrexone-bupropion (32/360 mg, daily), liraglutide (3 mg, daily), and lorcaserin (20 mg, daily). We assessed this study as being at moderate RoB because the costs associated with comorbidities and treatment-related adverse events were not included in the estimates and there was a lack of clarity on some modeling choices.

Gomez Lumbreras and colleagues[174] evaluated the cost-effectiveness of semaglutide (2.4 mg, weekly), liraglutide (3 mg, daily), phentermine-topiramate (7.5/46 mg to 15/92 mg, daily), naltrexone-bupropion (32/360 mg, daily), and tirzepatide for weight management among adults with obesity and no comorbidities. We assessed this study as being at low RoB.

Hu and colleagues[175] evaluated the cost-effectiveness of low-dose semaglutide (1.0 mg, weekly), low-dose liraglutide (1.8 mg, daily), dulaglutide (1.5 mg, weekly), and exenatide (10 µg, twice daily) for weight management. We assessed this study as being at high RoB because of failure to include costs associated with comorbidities and treatment-related adverse events, lack of clarity on some aspects of effectiveness studies chosen, and some concerns about the interpretation of the model findings.

Kim and colleagues[117] evaluated the cost-effectiveness of semaglutide (2.4 mg, weekly), liraglutide (3 mg, daily), phentermine-topiramate, and naltrexone-bupropion (32/360 mg, daily) for weight management for adults with either a BMI of at least 30 or at least 27 with 1 or more weight-related comorbidities. We assessed this study as being at moderate RoB due to lack of clarity on the selection and inclusion criteria for effectiveness studies chosen and conflict of interest.

Lee and colleagues[176] compared cost-effectiveness of 7 weight loss strategies relative to no treatment. These strategies included intensive lifestyle intervention, semaglutide (0.4 mg, daily), liraglutide (3 mg, daily), phentermine-topiramate (7.5/46 mg, daily), orlistat (120 mg, 3-times per day), lorcaserin (10 mg, 2-times per daily), and phentermine (37.5 mg, daily) for weight management for people with a BMI between 30 and 35 kg/m^2. We assessed this study as being at moderate RoB due to failure to include costs associated with comorbidities and treatment-related adverse events and potential conflict of interest.

Nuijten and colleagues[177] assessed the cost of a medically supervised weight loss program, OPTIFAST, compared to no treatment and 2 weight management drugs including liraglutide (3 mg, daily) and naltrexone-bupropion. We assessed this study as being at high RoB due to lack of important details about cost-effectiveness modeling, lack of sensitivity analyses, and conflict of interest.

Cost-Effectiveness Findings

We reviewed 8 eligible economic modeling studies evaluating costs or cost-effectiveness of the weight management treatments of interest.[117,171-177] Although all economic studies included in our review considered costs from a health care payer perspective in the US, there were wide variations across these studies in terms of other modeling choices and assumptions. Three of the cost-effectiveness studies had a long-term (at least 30 years) time horizon[117,171,174] while the others focused on cost-effectiveness in a short- to medium-term time horizon. There were other differences regarding critical model components such as treatment duration, post-treatment weight rebound, and adjustment of costs and utilities for treatment harms and adverse effects and weight-related complications and comorbidities. When there are such structural and methodological differences across economic studies, a meta-analysis of costs or cost-effectiveness ratios (CERs) is inappropriate and the review of economic evaluations should take a narrative approach that aims to explain the implications of these differences.[178]

While it may be problematic to combine cost and CER estimates across studies calculated in different time horizons with different underlying model assumptions, it may be informative to compare how interventions are ranked in terms of their costs and cost-effectiveness within each study. Figure 96 shows the rankings among 5 weight management drugs that were compared in multiple studies.[117,171-174,176,177] When included in comparisons against other interventions, phentermine-topiramate ranked most favorably with the lowest cost per quality-adjusted life year (QALY) gained. Phentermine-topiramate was followed by naltrexone-bupropion, tirzepatide, semaglutide (2.4 mg, weekly), and liraglutide (3 mg, daily) in terms of cost-effectiveness. This ranking was highly consistent across studies.

Figure 96. Ranking of Weight Management Drugs in Terms of Cost or Cost-Effectiveness

	Phentermine-topiramate	Naltrexone-bupropion	Tirzepatide	Semaglutide	Liraglutide		
Gomez-Lumbreras et al.	1	2	3	4	5	1	Ranked 1st
Atlas et al.	1	2		3	4	2	Ranked 2nd
Kim et al.	1	2		3	4	3	Ranked 3rd
Finkelstein et al.	1	2			3	4	Ranked 4th
Lee et al.	1				2	5	Ranked 5th
Azuri et al.*			1	2			Not studied
Nuijten et al.*		1			2		

* Cost studies

The studies that reported CERs relative to no treatment or usual care indicated that phentermine-topiramate is likely a cost-effective intervention (Figure 97).[117,171,173,176] Although the estimated costs and QALY gains varied widely due to underlying modeling choices, the resulting average CER estimates for phentermine-topiramate were consistently below the conventional cost-effectiveness threshold of $100,000 per QALY regardless of the time horizon and other differences in the model assumptions. [117,171,173,176] The CER estimates for naltrexone-bupropion were higher than the CERs for phentermine-topiramate in all studies that included a comparison between these 2 interventions.[117,171,173] However, naltrexone-bupropion may still potentially be within the cost-effective range for higher willingness-to-pay (WTP) thresholds of $150,000 and $200,000 per QALY. One of the 2 studies that evaluated cost-effectiveness of semaglutide relative to usual care indicated that it was cost-effective at $150,000 WTP

threshold 82% of the time[117] while the other study[171] found that it was cost-effective at $150,000 WTP threshold only 1% of the time. Finally, the CER estimates for liraglutide were consistently greater than $400,000 per QALY above any conventional WTP threshold for cost-effectiveness.[117,171,173,176]

Figure 97. Cost-Effectiveness Ratios for Weight Management Drugs Relative to No Treatment or Usual Care
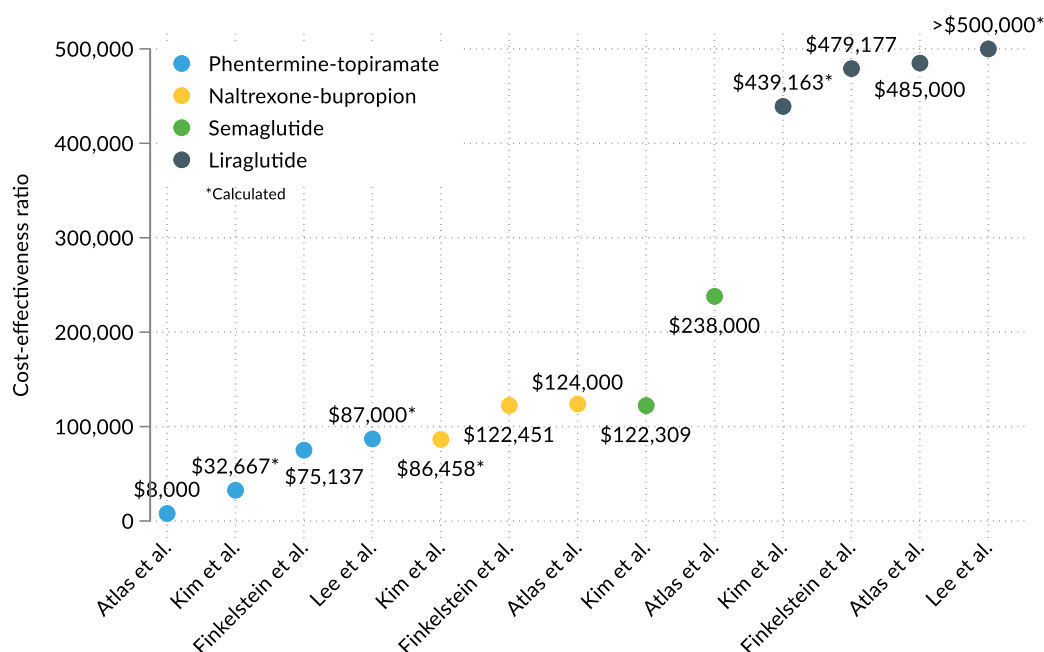
Summary of Findings for Cost-Effectiveness

Table 76. Certainty of Evidence (GRADE) for Cost-Effectiveness

Number of Studies	Findings	Certainty of Evidence	Rationale
Phentermine-topiramate vs. usual care			
Outcome: Cost-effectiveness			
5 economic modeling studies[117,171,173,174,176]	Phentermine-topiramate was assessed as being cost-effective at a WTP threshold of $150,000	●●●○ Moderate	Downgraded 1 level for RoB
Naltrexone-bupropion vs. usual care			
Outcome: Cost-effectiveness			
3 economic modeling studies[117,171,173]	Naltrexone-bupropion is likely to be cost-effective at a higher WTP threshold of $200,000	●●○○ Low	Downgraded 1 level for RoB 1 level for inconsistency
Outcome: Cost			
1 economic modeling study[177]	Total 3-year drug and non-drug costs of naltrexone-bupropion is $12,589 for people with class I or II obesity,	●●○○ Low	Downgraded 2 levels for RoB

Number of Studies	Findings	Certainty of Evidence	Rationale
	$19,057 people with class III obesity and $38,712 for people with class I or II obesity and T2DM		
Semaglutide (2.4 mg, weekly) vs. usual care			
Outcome: Cost-effectiveness			
2 economic modeling studies[117,171]	Semaglutide is unlikely to be cost-effective at a WTP threshold of $150,000 but may be cost-effective at a higher WTP threshold of $200,000	●●○○ Low	Downgraded 1 level for RoB 1 level for inconsistency
Outcome: Cost			
1 economic modeling study[172]	Total cost needed to treat per 1% of body weight reduction with semaglutide is $1,351 for 52-week treatment and $1,845 for 68-week treatment	●●○○ Low	Downgraded 1 level for RoB 1 level for indirectness
Liraglutide (3.0 mg daily) vs. usual care			
Outcome: Cost-effectiveness			
2 economic modeling studies[117,171]	Liraglutide was assessed as being not cost-effective even at a higher WTP threshold of $200,000	●●●○ Moderate	Downgraded 1 level for RoB
Outcome: Cost			
1 economic modeling study[177]	Total 3-year drug and non-drug costs of liraglutide is $21,216 for people with class I or II obesity, $27,643 people with class III obesity and $47,370 for people with class I or II obesity and T2DM	●●○○ Low	Downgraded 2 levels for RoB

Abbreviations. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RoB: risk of bias; T2DM: type 2 diabetes; WTP: willingness-to-pay.

Detailed Findings

The first cost-effectiveness study by Atlas and colleagues[171] of the Institute for Clinical and Economic Review compared cost-effectiveness of 4 pharmaceutical interventions, semaglutide (2.4 mg, weekly), liraglutide (3 mg, daily), phentermine-topiramate (7.5/46 mg to 15/92 mg, daily), and naltrexone-bupropion (32/360 mg, daily) added to usual care compared to usual care alone, which included standard diet and activity and lifestyle recommendations. The time horizon was 40 years with all costs discounted at a 3% annual discount rate. The reference year for the cost estimates was not reported.

The patients were assumed to continue to receive the intervention throughout the model time horizon with discontinuation due to non-response considered in the first year of treatment. For each intervention, the treatment effectiveness estimates were obtained from all relevant clinical trials identified in a rigorous systematic review and combined in a meta-analysis. Costs and disutility associated with treatment-related harms and AEs, and weight-related complications and comorbidities were included in the models. Treatment costs consisted of drug costs, which

were based on net price (pricing after rebates) information obtained from US Department of Veterans Affairs Federal Supply Schedule Service.

Total discounted lifetime costs (including drug and non-drug costs) were lowest for phentermine-topiramate at $182,600, followed by naltrexone-bupropion at $207,300, liraglutide at $377,000, and semaglutide at $392,100. The CER, indicated as cost per QALY gained relative to lifestyle modification only, was lowest for phentermine-topiramate at $8,000 per QALY. Naltrexone-bupropion, semaglutide, and liraglutide had higher CERs of $124,000, $238,000, and $485,000, respectively.

Probabilistic sensitivity analyses indicated that phentermine-topiramate was cost-effective 94.9%, 92.5%, 87%, and 67.4% of the time at $200,000, $150,000, $100,000, and $50,000 per QALY WTP thresholds, respectively, while naltrexone-bupropion was cost-effective 59%, 38.4%, 12.4%, and 1.1% of the time at the same WTP thresholds. Semaglutide was cost-effective 8.7% of the time at a WTP of $200,000 per QALY and was never cost-effective at $50,000 or $100,000 per QALY thresholds. Liraglutide was never cost-effective at any of the 4 threshold levels.

One-way sensitivity analyses evaluated sensitivity to disutility per BMI change, baseline HbA1c level, cost of diabetes management, baseline BMI, weight-lowering effect of treatments and change in HbA1c with treatment. Semaglutide and liraglutide were most sensitive to disutility per BMI change, while, for phentermine-topiramate, the cost of diabetes was most impactful. Varying the effectiveness of each treatment and the baseline HbA1c had a considerable influence across all 4 treatment options.

Another cost-effectiveness study with a long-term time horizon by Gomez Lumbreras and colleagues[174] compared 5 weight management drugs, the same 4 evaluated by Atlas and colleagues[171], semaglutide (2.4 mg, weekly), liraglutide (3 mg, daily), phentermine-topiramate (15/92 mg, daily), and naltrexone-bupropion (32/360 mg, daily), plus one additional drug, tirzepatide. The time horizon in this study was also 40 years with all costs discounted at a 3% annual discount rate and 2021 as the reference year.

Similar to Atlas and colleagues[171], Gomez Lumbreras and colleagues[174] assumed that the patients continued to receive the intervention throughout the model time horizon. They considered discontinuation in all years with discontinuing patients maintaining their weight the first year followed by a yearly BMI increase. The treatment effectiveness estimates for each intervention were obtained from all relevant clinical trials with a duration of at least 20 weeks. Costs and utilities were adjusted for SAEs with an average side effect duration of 2 months and for some weight-related complications and comorbidities including cardiovascular events and T2DM. Treatment costs consisted of drug costs only, which were based on wholesale acquisition costs discounted by 30% to account for manufacturer rebates and discounts.

Total discounted lifetime costs (including drug and non-drug costs) were again lowest for phentermine-topiramate at $118,900, followed by naltrexone-bupropion at $126,957, tirzepatide at $234,084, liraglutide at $252,146, and semaglutide at $308,767. These prices are lower compared to those estimated by Atlas and colleagues[171] likely due to the fact that non-drug costs in Atlas and colleagues'[171] models included costs associated with a more

comprehensive list of weight-related complications and comorbidities. However, the ranking of the drugs in terms of their lifetime costs is consistent across these 2 studies[171].

Gomez Lumbreras and colleagues[174] did not evaluate the CERs of the interventions relative to no treatment. Instead they calculated incremental CERs relative to the least costly intervention, phentermine-topiramate. Compared to phentermine-topiramate, naltrexone-bupropion was dominated (less effective, costlier). Semaglutide and liraglutide were slightly more effective than phentermine-topiramate but came at a much higher cost. Even tirzepatide, which was found to have the highest QALY gain, had an incremental CER relative to phentermine-topiramate of $355,616 per QALY.

One-way sensitivity analyses indicated that the findings were most sensitive to the disutility of obesity followed by the drug prices and to a lesser extent cost of obesity and obesity-related complications. Probabilistic sensitivity analyses indicated that phentermine-topiramate was the optimal choice across WTP threshold values up to $400,000.

Kim and colleagues[117] assessed cost-effectiveness of semaglutide (2.4 mg, weekly) relative to no treatment, diet and exercise, and 3 other pharmaceutical interventions, namely liraglutide (3 mg, daily), phentermine-topiramate, and naltrexone-bupropion. The time horizon in this study was 30 years with all costs discounted at a 3% annual discount rate and 2021 as the reference year.

Unlike the other 2 long-term cost-effectiveness studies described above, in this study, patients were assumed to continue to receive the intervention for 2 years with discontinuation due to non-response within those 2 years considered in the models. Weight loss benefits were assumed to diminish post-treatment at a higher rebound rate than natural weight gain until patients' BMI return to baseline levels. The patients were assumed to receive treatment in conjunction with diet and exercise, which is assumed to continue after the drug treatment ends for the entire duration of the time horizon. The treatment effectiveness estimates for each intervention were obtained from their respective Phase 3 trials. Costs and disutility associated with treatment-related harms and adverse events and weight-related complications and comorbidities were included in the models.

The ranking of the total discounted lifetime costs (drug and non-drug costs) assuming 2-year treatment was similar to the rankings emerged in the other 2 studies. Phentermine-topiramate had the lowest cost at $109,078, followed by naltrexone-bupropion at $109,977, liraglutide at $126,786, and semaglutide at $130,040. These prices are lower compared those estimated by Atlas and colleagues[171] and Gomez Lumbreras and colleagues[174] likely due to the short-term nature of treatment.

Kim and colleagues[117] focused on assessing cost-effectiveness of semaglutide and did not evaluate the CERs for the other interventions. Semaglutide was estimated to be cost-effective relative to diet and exercise only with an incremental CER of $122,549. Semaglutide was also estimated to be cost-effective relative to no treatment and other pharmaceutical interventions including phentermine-topiramate, naltrexone-bupropion, and liraglutide, with incremental CERs ranging from $27,113 (relative to no treatment) to $144,296 (relative to phentermine-topiramate).

Scenario analyses exploring alternative treatment discontinuation assumptions, maximum treatment durations, bariatric surgery consideration, time horizons, discount rates, treatment discontinuation rates, baseline utilities by BMI, and natural weight-gain rates resulted in incremental CERs for semaglutide ranging from $30,540 to $253,206 compared to diet and exercise only. The model was most sensitive to maximum treatment duration and time horizon, followed by regimen after treatment discontinuation, weight-rebound rate, and drug efficacy on BMI.

Subgroup analysis by patient obesity class revealed that semaglutide was particularly cost-effective for patients with obesity class III (incremental CERs ranging from $8,094 relative to liraglutide 3 mg to $85,024 relative to phentermine-topiramate). Incremental CERs for semaglutide was higher for the patients with type 2 diabetes (ranging from $87,211 relative to liraglutide to $225,171 relative to phentermine-topiramate).

Probabilistic sensitivity analyses revealed that at a WTP threshold of $150,000 per QALY, semaglutide was cost-effective 82% of the time relative to diet and exercise, 98% of the time relative to liraglutide, 64% of the time relative to phentermine-topiramate, 74% of the time relative to naltrexone-bupropion, and 100% of the time relative to no treatment.

Finkelstein and colleagues[173] compared cost-effectiveness of all commercially available, evidence-based, non-surgical weight loss interventions for people with excess weight including 2 lifestyle modification programs (Weight Watchers Online and Weight Watchers Meetings), a food replacement program (Jenny Craig), an intragastric balloon system (Orbera), and 6 pharmaceuticals products including low- and high-dose orlistat (180 mg, weekly, and 360 mg, weekly), phentermine-topiramate (7.5/46 mg, daily), naltrexone-bupropion (32/360 mg QD), liraglutide (3 mg, daily), and lorcaserin (20 mg, daily). The time horizon was 4 years with all costs discounted at a 3.5% annual discount rate. The reference year for the cost estimates was not reported.

The patients were assumed to continue to receive the intervention for 12 months with linear decay of weight loss benefits over the next 3-year period. The treatment effectiveness estimates were obtained from separate clinical trials for each intervention identified in a rigorous systematic review. The attrition rates from respective effectiveness studies were built into the models. QoL gains associated with weight loss were based on previously published estimates of the relationship between weight loss and QoL change that controls for gender, age, baseline BMI and baseline QALY. Cost of treatment included program fees and food costs for commercial programs, medication costs and physician costs for pharmaceutical products, and for intragastric balloon, the balloon costs as well as insertion and removal costs. Medical costs associated with comorbidities or costs and disutility associated with treatment-related harms and adverse events were not accounted for.

Cost per QALY gained, or CER, at 4 years relative to no treatment was lowest for Weight Watcher Meetings at $30,071, followed by orlistat (180 mg) at $56,422, and phentermine-topiramate at $75,167. Jenny Craig, naltrexone-bupropion, and lorcaserin had higher CERs, $102,516, $122,451, and $185,874, respectively, but would still be considered cost-effective at a higher $200,000 per QALY WTP threshold. Other interventions including intragastric balloon system, high-dose orlistat, and liraglutide (3 mg, daily) had CERs ranging between $300,000 and

$500,000, higher than any conventional WTP thresholds. When the duration of benefits changed from linear decay over 3 years to linear decay over 1 year all CERs nearly doubled.

Lee and colleagues[176] compared cost-effectiveness of 6 pharmaceutical interventions and intensive lifestyle intervention relative to no treatment in patients with BMI between 30 and 35. These pharmaceutical interventions were phentermine-topiramate (7.5/46 mg, daily), liraglutide (3.0 mg, daily), low-dose semaglutide (0.4 mg, daily), orlistat (120 mg, 3 times daily), lorcaserin (10 mg, twice daily), and phentermine (37.5 mg, daily). The authors calculated CERs in 3 different time horizons, 1, 3, and 5 years, with 2019 as the reference year. In the analyses with 3-year and 5-year time horizons, all costs were discounted at a 3% annual discount rate.

The patients were assumed to continue to receive the intervention for the duration of the model time horizon with discontinuation included in the first year of treatment. The treatment effectiveness estimates were obtained from separate clinical trials for each intervention. For any intervention with more than one published clinical trial, the findings of the trial with the longest duration were used. The authors noted that all clinical trials for the pharmaceutical interventions included lifestyle modification counseling in addition to the intervention. The weight loss gains were converted into QALY gains based on QoL constants used in previous studies assuming a unit of BMI loss leads to a gain of 0.0056 QALYs. The cost of pharmaceutical interventions included drug costs and cost of 2 doctor visits. There were no cost or QoL adjustments for treatment harms and adverse events or for costs associated with weight-related comorbidities.

In all time horizons, phentermine (37.5 mg, daily) had the lowest CERs at $46,258, $20,157, and $17,880 in 1-, 3-, and 5-year horizons, respectively. Although the weight loss in the first year was the greatest on phentermine, this weight loss was not sustained with patients returning to baseline weight by year 5. Patients on semaglutide (0.4 mg, daily), on the other hand, maintained significant weight loss throughout the 5-year time horizon making semaglutide (0.4 mg, daily) the most effective strategy in the longer term. However, semaglutide (0.4 mg, daily) was not cost-effective with incremental CERs higher than $500,000 per QALY even in the longest time horizon.

When phentermine was excluding from the analysis, intensive lifestyle intervention was the most cost-effective strategy with CERs of $82,733, $41,265, and $39,219 in 1-, 3-, and 5-year horizons, respectively. Semaglutide (0.4 mg, daily) remained cost-ineffective even with phentermine excluded from the analysis. In scenario analyses with higher QoL constant of 0.017 QALYs gained per BMI unit lost, semaglutide (0.4 mg, daily) approached cost-effectiveness in 3- and 5-year time horizons with an incremental CERs of $127,062 and $106,873, respectively.

The authors did not report CERs for phentermine-topiramate (7.5mg/46 mg, daily) or liraglutide (3.0 mg, daily) as these interventions were dominated by phentermine. However, the incremental QALY gains and costs relative to no treatment reported for these interventions suggest that the CERs for phentermine-topiramate (7.5mg/46 mg, daily) were below $100,000 WTP threshold for 3-year and 5-year time horizons making it a potentially cost-effective treatment option, and the CERs for liraglutide (3.0 mg, daily) were over $1,000,000 in all time horizons indicating that this treatment option is unlikely to be cost-effective under conventional WTP thresholds.

Finally, Hu and colleagues[175] focused on a different set of treatments than the other economic studies and compared cost-effectiveness of liraglutide (1.8 mg, daily), semaglutide (1.0 mg, weekly), dulaglutide (1.5 mg, weekly), and exenatide (10 µg, twice daily) for weight loss in adult patients with obesity. The time horizon was 6 months with 2019 as the reference year for the cost estimates.

The patients were assumed to continue to receive the intervention for the 6-month. The treatment effectiveness estimates were obtained from 4 separate clinical trials, one for each treatment. Similar to Lee and colleagues[176], the authors converted weight loss gains into QALY gains based on QoL constants used in previous studies assuming a gain of 0.0056 QALYs per BMI unit lost. The cost of treatment included drug costs, cost of 2 doctor visits and the cost of injection needles. Possible discontinuation of treatment, treatment-related harms and adverse events, and costs associated with weight-related comorbidities were not included in the models.

The findings indicate that none of the treatments evaluated were cost-effective compared to no treatment. Exenatide had the smallest CER at $982,032, which is above any conventional WTP threshold.

In addition to these cost-effectiveness studies there were 2 cost-comparison studies. The first one was a cost-needed-to-treat study by Azuri and colleagues[172] estimating and comparing the cost needed to achieve 1% body weight loss using tirzepatide (15 mg, weekly) versus semaglutide (2.4 mg, weekly) among patients with T2DM. They estimated the costs for each drug in a 1-year time horizon, as well as in time horizons that mimic the follow-up period in the respective clinical trials, 68 weeks for semaglutide and 72 weeks for tirzepatide. All costs were discounted at a 3% annual discount rate for time horizons that are longer than a year and were represented in 2022 US dollars.

The patients were assumed to continue to receive the intervention for the duration of the time horizon with an assumption of a linear decline in body weight during the treatment period. Treatment effectiveness estimates were from 2 separate clinical trials (STEP-1 trial for semaglutide and SURMONT-1 trial for tirzepatide). The cost of treatment included drug costs only. Possible discontinuation of treatment, treatment-related harms and adverse events, and costs associated with weight-related comorbidities were not included in the models.

The total cost needed to treat per 1% of body weight reduction with tirzepatide in 72-week time horizon was $955 compared with $1,845 with semaglutide in 68-week time horizon. Over a 1-year time horizon, the total cost of 1% of body weight reduction was $683 for tirzepatide and $1,351 for semaglutide.

In another cost-comparison study, Nuijten and colleagues[177] estimated cost savings associated with a medically supervised weight loss program, OPTIFAST, relative to no treatment, naltrexone-bupropion, liraglutide (3.0 mg, daily), and bariatric surgery in people with class I or II obesity, class III obesity, and class I or II obesity and T2DM. They also evaluated cost-effectiveness of OPTIFAST relative to no treatment. The time horizon was 3 years with all costs discounted at a 5% annual discount rate. The reference year for the cost estimates was 2016.

The patients receiving liraglutide or naltrexone-bupropion were assumed to continue the intervention for the duration of the time horizon with discontinuation due to non-response included in the models in accordance with the discontinuation rates in the clinical trials. The cost of pharmaceutical interventions included drug costs and cost of 2 doctor visits. The model also took into consideration the costs associated with a comprehensive list of obesity-related and T2DM-related complications and comorbidities were included in the model as well as the costs of treatment harms and adverse events.

Compared to no treatment, after accounting for cost savings associated with reduced comorbidities and complications, the additional cost of naltrexone-bupropion was estimated to be $3,207 for people with class I or II obesity and $2,962 for people with class III obesity in 3-years. For people with class I or II obesity and T2DM, naltrexone-bupropion was estimated to result in $14,170 worth of savings to the payer. Liraglutide (3.0 mg, daily), on the other hand, was estimated to cost an additional $11,834 for people with class I or II obesity and $11,548 for people with class III obesity relative to no treatment after accounting for potential cost savings associated with reduced comorbidities and complications. The potential cost savings with liraglutide for people with class I or II obesity and T2DM were smaller at $5,512.

Scenario analyses with longer time horizons of 5 and 10 years indicated lower additional costs or net cost savings for all interventions for people with class I or II obesity. The additional costs of naltrexone-bupropion and liraglutide were lower at $1,992 and $10,693, respectively, in 5-year time horizon compared to additional costs in 3-year time horizon. In 10-year time horizon, naltrexone-bupropion resulted in net cost savings of $3,415 relative to no treatment while liraglutide had an additional cost of $8,145.

Although the study estimated an incremental CER for OPTIFAST relative to no treatment, the cost-effectiveness of other interventions was not evaluated.

Policy Findings

These findings are related to key questions 5 (public and private payer policies for managing weight management drugs including coverage criteria and prior authorization (PA) and reauthorization) and 6 (place in the treatment pathway for weight management drugs). For KQ5, we begin an overview of FDA information to provide context, then examine 5 state Medicaid programs' policies and lessons learned, and end with analysis of 3 non-Medicaid payer policies. For KQ6, we begin with context from some recent guidelines, all of which were published or updated in 2022 or 2023 and which include newer weight management drugs and expanded approvals. We then present findings from interviews with subject matter experts.

FDA Approvals Are Key Context for Use of Weight Management Drugs

FDA-Approved Indications, Usage, and Contraindications Inform Prior Authorization Criteria

The FDA's approvals of weight management drugs are important context for payers' PA requirements. Table 77 provides a snapshot of the FDA's approved indications, usage and contraindications for these drugs, all directly quoted from the FDA-approved package inserts. For most of these drugs (Saxenda, Wegovy, Contrave, and Qsymia), the indications relate either to obesity or to overweight (BMI of 27 or greater) with a weight-related comorbidity.

Table 77. FDA-Approved Indications, Usage, Contraindications for Weight Management Drugs

Drug	Indications and Usage	Contraindications
Saxenda (liraglutide)[179]	Saxenda is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in: Adult patients with an initial body mass index (BMI) of • 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes, or dyslipidemia) Pediatric patients aged 12 years and older with: • body weight above 60 kg and • an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cutoffs Limitations of Use: • Saxenda contains liraglutide and should not be coadministered with other liraglutide-containing products or with any other GLP-1 receptor agonist • The safety and effectiveness of Saxenda in pediatric patients with type 2 diabetes have not been established • The safety and efficacy of Saxenda in combination with other products intended for weight loss have not been established	• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Hypersensitivity to liraglutide or any excipients in Saxenda • Pregnancy

Wegovy (semaglutide)[180]	Wegovy is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:
	• Adult patients with an initial body mass index (BMI) of:
	  o 30 kg/m^2 or greater (obesity) or
	  o 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes, or dyslipidemia)
	• Pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity)
	
	Limitations of Use:
	• Wegovy should not be used in combination with other semaglutide-containing products or any other GLP-1 receptor agonist
	• The safety and efficacy of coadministration with other products for weight loss have not been established
	• Wegovy has not been studied in patients with a history of pancreatitis
		• Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2
		• Known hypersensitivity to semaglutide or any of the excipients in Wegovy

Drug	Indications and Usage	Contraindications
Contrave (bupropion and naltrexone)[181]	Contrave is a combination of naltrexone, an opioid antagonist, and bupropion, an aminoketone antidepressant, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m^2 or greater (obese) or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia) Limitations of Use: • The effect of Contrave on cardiovascular morbidity and mortality has not been established • The safety and effectiveness of Contrave in combination with other products intended for weight loss, including prescription and over-the-counter drugs, and herbal preparations, have not been established	• Uncontrolled hypertension • Seizure disorders, anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs • Use of other bupropion-containing products • Chronic opioid use • During or within 14 days of taking monoamine oxidase inhibitors (MAOI) • Known allergy to any of the ingredients in Contrave

Qsymia (phentermine and topiramate)[182]	Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:
	• Adults with an initial body mass index (BMI) of:
	  ○ 30 kg/m^2 or greater (obese) or
	  ○ 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes, or dyslipidemia
	• Pediatric patients aged 12 years and older with BMI in the 95th percentile or greater standardized for age and sex
	
	Limitations of Use:
	• The effect of Qsymia on cardiovascular morbidity and mortality has not been established
	• The safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over-the-counter drugs, and herbal preparations, have not been established
		• Pregnancy
		• Glaucoma
		• Hyperthyroidism
		• Taking or within 14 days of stopping monoamine oxidase inhibitors
		• Known hypersensitivity to any component of Qsymia or idiosyncrasy to sympathomimetic amines

Imcivree (setmelanotide)[183]	Imcivree is a melanocortin 4 (MC4) receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to: • Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)	None

Drug	Indications and Usage	Contraindications
	• Bardet-Biedl syndrome (BBS) Limitations of Use: Imcivree is not indicated for the treatment of patients with the following conditions as Imcivree would not be expected to be effective: • Obesity due to suspected POMC, PCSK1, or LEPR deficiency with POMC, PCSK1, or LEPR variants classified as benign or likely benign • Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity	
Xenical (orlistat)[184]	• Xenical is a reversible inhibitor of gastrointestinal lipases indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet • Xenical is also indicated to reduce the risk for weight regain after prior weight loss	• Pregnancy • Chronic malabsorption syndrome • Cholestasis • Known hypersensitivity to Xenical or to any component of this product

Abbreviations. FDA: US Food and Drug Administration; kg: kilogram; m: meter.

As shown in the table above, pregnancy is not a highlighted contraindication for some of these drugs; however, additional prescribing information addresses these drugs' use during pregnancy:
- Wegovy should be not be used during pregnancy and, given its long half-life, should be discontinued at least 2 months before a planned pregnancy.[180]
- Contrave should not be used during pregnancy.[181]
- Imcivree should not be used during pregnancy unless potential risks to the fetus are outweighed by the drug's therapeutic benefits.[183]

Challenges in Defining Behavioral Interventions as a Component of Weight Management

As shown in Table 77 above (FDA-Approved Indications, Usage, and Contraindications for Weight Management Drugs), all of the weight management drugs except for Imcivree (setmelanotide) are indicated for use adjunct to diet and exercise. Behavioral interventions are foundational to obesity treatment, but these interventions are not consistently defined and, in actual clinical practice, may range from unstructured, patient-reported efforts to participation in an established treatment program.[185] Many behavioral weight loss programs have not been rigorously evaluated.[186] For children, the US Preventive Services Task Force (USPSTF) notes that effective intensive behavioral interventions involve at least 26 contact hours over 2 months to 1 year and often include work with both parents and children, information about food choices and exercise, problem solving and strategies to avoid obesogenic triggers, and some sessions of guided physical activity. [187] For adults with obesity, USPSTF recommends intensive, multicomponent behavioral interventions, which commonly last for 1 to 2 years, with at least 12 sessions in the first year.[188]

The FDA also has approved warnings and precautions for these drugs, which are quoted in Table 78.

Table 78. FDA-Approved Warnings and Precautions for Weight Management Drugs

Drug	Boxed Warning	Warnings and Precautions
Saxenda (liraglutide)[179]	WARNING: RISK OF THYROID C-CELL TUMORS *See full prescribing information for complete boxed warning.* • Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined • Saxenda is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2. Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors	• *Thyroid C-cell Tumors*: See Boxed Warning • *Acute Pancreatitis*: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed • *Acute Gallbladder Disease*: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated • *Hypoglycemia*: Can occur in adults when Saxenda is used with an insulin secretagogue (e.g., a sulfonylurea) or insulin. The risk may be lowered by a reduction in the dose of concomitantly administered insulin secretagogues or insulin. In the pediatric clinical trial, patients did not have type 2 diabetes. Hypoglycemia occurred in Saxenda-treated pediatric patients. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia • *Heart Rate Increase*: Monitor heart rate at regular intervals • *Renal Impairment*: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Saxenda in patients with renal impairment • *Hypersensitivity Reactions*: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue Saxenda and other suspect medications and promptly seek medical advice • *Suicidal Behavior and Ideation*: Monitor for depression or suicidal thoughts. Discontinue Saxenda if symptoms develop
Wegovy (semaglutide)[180]	WARNING: RISK OF THYROID C-CELL TUMORS *See full prescribing information for complete boxed warning.* • In rodents, semaglutide causes thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Wegovy causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in	• *Thyroid C-cell Tumors*: See Boxed Warning • *Acute Pancreatitis*: Has occurred in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed • *Acute Gallbladder Disease*: Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated • *Hypoglycemia*: Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia.

Drug	Boxed Warning	Warnings and Precautions
	humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined • Wegovy is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2. Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors	Reducing the dose of insulin secretagogue or insulin may be necessary. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia • *Acute Kidney Injury*: Has occurred. Monitor renal function when initiating or escalating doses of Wegovy in patients reporting severe adverse gastrointestinal reactions or in those with renal impairment reporting severe adverse gastrointestinal reactions • *Hypersensitivity Reactions*: Anaphylactic reactions and angioedema have been reported postmarketing. Discontinue Wegovy if suspected and promptly seek medical advice • *Diabetic Retinopathy Complications in Patients with Type 2 Diabetes*: Has been reported in trials with semaglutide. Patients with a history of diabetic retinopathy should be monitored • *Heart Rate Increase*: Monitor heart rate at regular intervals • *Suicidal Behavior and Ideation*: Monitor for depression or suicidal thoughts. Discontinue Wegovy if symptoms develop
Contrave (bupropion and naltrexone)[181]	WARNING: SUICIDAL THOUGHTS AND BEHAVIORS *See full prescribing information for complete boxed warning* • Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders • Monitor for worsening and emergence of suicidal thoughts and behaviors • Contrave has not been studied in pediatric patients.	• *Suicidal Behavior and Ideation*: Monitor for depression or suicidal thoughts. Discontinue Contrave if symptoms develop • *Neuropsychiatric Adverse Events During Smoking Cessation*: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients taking Contrave for the occurrence of such symptoms and instruct them to discontinue Contrave and contact a healthcare provider if they experience such adverse events • Risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding coadministration with high-fat meal • *Increase in Blood Pressure and Heart Rate*: Monitor blood pressure and heart rate in all patients, especially those with cardiac or cerebrovascular disease • *Hepatotoxicity*: Cases of hepatitis and clinically significant liver dysfunction observed with naltrexone exposure • *Angle-closure glaucoma*: Angle-closure glaucoma has occurred in patients with untreated

Drug	Boxed Warning	Warnings and Precautions
		anatomically narrow angles treated with antidepressant • *Use of Antidiabetic Medications*: Weight loss may cause hypoglycemia. Monitor blood glucose
Qsymia (phentermine and topiramate)[182]	None	• *Embryo-Fetal Toxicity:* Can cause fetal harm. In patients who can become pregnant, a negative pregnancy test is recommended before initiating Qsymia and monthly during therapy; advise use of effective contraception. Qsymia is available through a limited program under a Risk Evaluation and Mitigation Strategy (REMS) • *Increase in Heart Rate*: Monitor heart rate, especially in those with cardiac or cerebrovascular disease • *Suicidal Behavior and Ideation*: Monitor for depression or suicidal thoughts. Discontinue Qsymia if symptoms develop • *Risk of Ophthalmologic Adverse Reactions*: Acute myopia and secondary angle-closure glaucoma have been reported. Immediately discontinue Qsymia if symptoms develop. Consider Qsymia discontinuation if visual field defects occur • *Mood and Sleep Disorders*: Consider dosage reduction or discontinuation for clinically significant or persistent mood or sleep disorder symptoms • *Cognitive Impairment*: May cause disturbances in attention or memory, or speech/language problems. Caution patients about operating automobiles or hazardous machinery when starting treatment • *Slowing of Linear Growth*: Consider dosage reduction or discontinuation if pediatric patients are not growing or gaining height as expected • *Metabolic Acidosis*: Measure electrolytes before and during treatment. If persistent metabolic acidosis develops, reduce dosage or discontinue Qsymia • *Decrease in Renal Function*: Measure creatinine before and during treatment. For persistent creatinine elevations, reduce dosage or discontinue Qsymia • *Serious Skin Reactions*: Qsymia should be discontinued at the first sign of a rash, unless the rash is clearly not drug related
Imcivree (setmelanotide)[183]	None	• *Disturbance in Sexual Arousal*: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting

Drug	Boxed Warning	Warnings and Precautions
		longer than 4 hours to seek emergency medical attention • *Depression and Suicidal Ideation*: Depression and suicidal ideation have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing Imcivree if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur • *Skin Pigmentation and Darkening of Pre-Existing Nevi*: Generalized increased skin pigmentation and darkening of pre-existing nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions • *Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants*: Imcivree is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs
Xenical (orlistat)[184]	None	• Xenical has drug interactions and can decrease vitamin absorption • Take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition • Rare cases of severe liver injury with hepatocellular necrosis or acute hepatic failure have been reported • Patients may develop oxalate nephrolithiasis and oxalate nephropathy following treatment with Xenical. Monitor renal function in patients at risk for renal insufficiency. Discontinue Xenical if oxalate nephropathy develops • Substantial weight loss can increase the risk of cholelithiasis • Exclude organic causes of obesity (e.g., hypothyroidism) before prescribing Xenical • Gastrointestinal events may increase when Xenical is taken with a diet high in fat (> 30% total daily calories from fat

Qsymia Is Subject to a Risk Evaluation and Mitigation Strategy Program

Qsymia (phentermine and topiramate) also is subject to a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of congenital malformations if a person taking Qsymia becomes pregnant.[189] Pharmacies dispensing Qsymia must enroll in the REMS program, ensure that staff are appropriately trained, and take steps so patients receive warnings each time the drug is

dispensed.[189] Wholesale distributors must ensure that Qsymia is distributed only to pharmacies that have been certified as participating in the REMS program.[189]

Weight Management Drugs Covered by State Medicaid Programs

State Medicaid programs that have elected to cover this optional class of medications differ in how long they have covered weight management drugs. Coverage began recently in some states (e.g., Mississippi in July 2023, and Michigan in February 2022) and many years ago in others (e.g., Wisconsin over 17 years ago) (Medicaid staff: Mississippi, Michigan, Wisconsin, personal communication).[190] Even for programs with long-standing coverage policies, the landscape has shifted recently as new, higher-cost drugs became available, Medicaid enrollment increased, and the COVID-19 pandemic caused program disruptions (Wisconsin Medicaid staff, personal communication).

Which Weight Management Drugs Do State Medicaid Programs Cover?

As previously noted, state Medicaid programs may restrict or exclude coverage of outpatient drugs "when used for anorexia, weight loss, or weight gain."[46] The Medicaid programs profiled in this report—California, Michigan, Mississippi, and Wisconsin—have opted to cover different combinations of weight loss medications. All of the state Medicaid programs interviewed cover the weight management drugs as part of their pharmacy benefit (Medicaid staff: California, Michigan, Mississippi, Wisconsin, personal communication).

Box 1. Commercial Payers and Off-label Use

Some private payers reportedly are taking additional steps to prevent off-label use of glucagon-like peptide 1 (GLP-1) receptor agonists that are indicated for treatment of diabetes. Recently, some Anthem plans that do not cover GLP-1s for weight management wrote to a number of clinicians who apparently had prescribed Ozempic (semaglutide) to patients without diabetes and threatened to report suspected inappropriate prescribing behaviors to state or federal authorities.[191]

News reports also cite examples of private payers, driven by budget concerns, that are ending coverage of weight management drugs or limiting to patients with severe obesity.[192] The University of Texas, for example, ended coverage of Wegovy and Saxenda after that its costs for those drugs more than tripled (from $1.5 million to $5 million per month) over the course of a year and a half.[192]

None of these programs routinely cover off-label use of tirzepatide (Mounjaro) for weight loss. In California, tirzepatide is not included in the Medicaid preferred drug list (PDL).[193] California Medicaid requires PA for medications such as tirzepatide that are not on the PDL or that are prescribed for an off-label purpose, such as weight loss; approval of PA requests is based on medical necessity (California Medicaid staff, personal communication). In Michigan, Mississippi, and Wisconsin, tirzepatide is covered as a nonpreferred agent for diabetes.[194-196] These Medicaid programs do not cover drugs used off label (Medicaid staff: Michigan, Wisconsin, personal communication). State Medicaid programs often rely on PA to ensure drugs are not being used off label (Medicaid staff: Michigan, Mississippi, Wisconsin, personal communication).

Table 79. Weight Management Drugs Covered in State Medicaid Programs

Medicaid Program	Saxenda (liraglutide)	Wegovy (semaglutide)	Contrave (bupropion and naltrexone)	Qsymia (phentermine and topiramate)	Imcivree (setmelanotide)	Xenical (orlistat)
California	PDL	PDL	Only if medical necessity shown in PA	Only if medical necessity shown in PA	Only if medical necessity shown in PA	Only if medical necessity shown in PA
Michigan	PDL	PDL	PDL	No	Not on PDL but may be requested with non-formulary PA[a]	PDL
Mississippi	PDL	PDL	PDL	No	No	PDL (non-preferred)
Wisconsin	Yes, not on PDL but may be covered with PA	Yes, not on PDL but may be covered with PA	No	No	Yes, not on PDL but may be covered with PA[b]	Yes, not on PDL but may be covered with PA

Notes. [a] Although setmelanotide (Imcivree) is not on Michigan's PDL, it may be approved with a nonformulary PA request; in the Michigan Medicaid PA criteria, setmelanotide is not grouped with the antiobesity agents (Magellan Rx Management[197(p107, p96)]; Michigan Department of Health and Human Services[198]). [b] Similarly, Wisconsin Medicaid PA criteria for setmelanotide are separate from the antiobesity agents criteria. Sources. California Department of Health Care Services[193]; Michigan Department of Health and Human Services[194]; Mississippi Division of Medicaid[195]; State of Wisconsin Department of Health Services.[196,199] Abbreviations. PDL: preferred drug list; PA: prior authorization.

Some state Medicaid programs also cover weight management drugs that are not included interventions for this report. In addition to the drugs listed in Table 79, Michigan Medicaid includes several additional antiobesity agents on its PDL: Adipex-P (phentermine), Didrex (benzphetamine), diethylpropion, Lomaira (phentermine), phendimetrazine, and phentermine.[194] Wisconsin Medicaid also covers benzphetamine, diethylpropion, phendimetrazine, phentermine, and Evekeo.[199]

How Do State Medicaid Programs Manage Use of Weight Management Drugs?

With the exception of California, the state Medicaid programs we interviewed used PA requirements to manage the utilization of weight management drugs. Table 80 summarizes the requirements related to initial PA and reauthorization, as well as limits on the duration of use.

The state Medicaid programs we interviewed do not require a specialist to prescribe weight management drugs (Medicaid staff: California, Michigan, Mississippi, Wisconsin, personal communication). For Imcivree, however, Wisconsin Medicaid requires the prescription is written by an endocrinologist or geneticist or through an endocrinology or genetics consultation (Wisconsin Medicaid staff, personal communication) For Mississippi Medicaid, the PA criteria were written in consultation with specialists in obesity with the hope of guiding primary care

providers and encouraging them to feel comfortable prescribing these drugs when needed for patients with severe obesity (Mississippi Medicaid staff, personal communication).

In Mississippi Medicaid's PA process, treatment is divided into 3 phases[200]:

- *Initial authorization*, which involves evaluation and determination of whether the patient meets clinical criteria for weight management drugs therapy and development of a treatment plan. The treatment plan includes the patient's current BMI, the goal BMI to be reached in 6 months, other goals unrelated to weight, and the expected duration of the treatment plan. This initial authorization period may be 3-6 months, depending on the drug; Table 80 details the authorization period for each drug.
- *Reauthorization*, which occurs if the patient is adhering to treatment, tolerating the recommended dosage, and making ongoing progress on weight loss or improvement in weight-related comorbidities. In this reauthorization phase, goals are set for the next reauthorization period, and the patient is counseled on diet and physical activity. If the patient did not meet the goal from the initial treatment plan, then clinical justification must be provided to continue the same treatment. This reauthorization period may be 3-6 months, depending on the drug and the progress being made; Table 80 contains more details. The PA policy does not set a fixed limit on the number of reauthorizations required or allowed before the patient moves on to the maintenance phase.
- *Maintenance*, when the patient is at their goal and is maintaining a body weight within 15% of their goal BMI. The maintenance reauthorization may continue to be approved for 6-month periods if the patient continues to tolerate the recommended dose, adhere to treatment, and be counseled on physical activity and diet.

Table 80. Example Utilization Management Criteria Used in State Medicaid Programs

Drug(s)[a]	Initial PA	Reauthorization PA	Duration Limits
California			
Saxenda, Wegovy	Not required	Not required	None
Michigan			
Saxenda, Wegovy, Contrave, Xenical	6 months	6 months if member maintains loss of at least 5% from baseline weight (adults) or member has maintained or improved from baseline weight (adolescents)	None
Mississippi			
Saxenda, Wegovy	6 months	Reauthorization: • 6 months if member lost at least 5% of body weight • 3 months may be approved if member lost 1-4% of body weight with either delayed titration (intolerance, hospitalization, illness) or progress on other goals unrelated to weight Maintenance reauthorization: 6 months	None

Drug(s)[a]	Initial PA	Reauthorization PA	Duration Limits
Contrave	3 months	Reauthorization: • 6 months if member lost at least 5% of body weight • If member lost less weight, reauthorization is denied and another covered agent is considered Maintenance reauthorization: 6 months	None
Wisconsin			
Saxenda, Wegovy	180 days	Additional 180 days if member loses at least 5% of body weight. PA cannot be renewed if BMI falls under 24.	12 continuous months and then must wait 6 months to request another PA. Maximum 2 lifetime attempts with each drug (i.e., a member could have 2 attempts with Saxenda and 2 attempts with Wegovy).
Xenical	180 days	Additional 180 days if member loses at least 10 lb from baseline in first 6 months; if member remains below baseline weight, additional 180-day renewals. PA cannot be renewed if BMI falls under 24.	24 continuous months and then must wait 6 months to request another PA. Maximum 2 lifetime attempts with Xenical.

Notes. [a] *Saxenda (liraglutide), Wegovy (semaglutide), Contrave (bupropion and naltrexone), Qsymia (phentermine and topiramate), Xenical (orlistat).*

Sources. *California Department of Health Care Services[193]; California Medicaid staff, personal communication; Michigan Department of Health and Human Services,[194] Magellan Rx Management[197]; Mississippi Division of Medicaid[200]; State of Wisconsin Department of Health Services.[199]*

Abbreviations. *BMI: body mass index; lb: pound; PA: prior authorization.*

Among the state Medicaid programs interviewed, California is the only state that does not require clinical PA for weight management drugs. Medications on California Medicaid's PDL, called Medi-Cal Contract Drugs List (CDL), do not require PA if use is consistent with the drugs' FDA-approved indications; medications that are not on the Medi-Cal CDL or those used off label do require PA, which is then based on medical necessity (California Medicaid staff, personal communication).[201] Saxenda and Wegovy are included in the Medi-Cal CDL for chronic weight management, subject to quantity limits of 1 box per prescription fill for a 28-day supply, and limited to Novo Nordisk NDC labeler code products (00169).[193] Quantity limits decrease the risk of loss; for example, if a person misplaces or improperly stores their medication, there would be a larger loss if they had a 3-month supply versus a 1-month supply (California Medicaid staff, personal communication). Prescriptions must be consistent with the FDA-approved indications, such as BMI thresholds (California Medicaid staff, personal communication). Prescribers must document in the patient's chart the diagnosis or condition that meets the criteria set in the Medi-Cal CDL.[193,202] If clinicians prescribe other drugs for weight loss, such as off-label uses of diabetes drugs, those prescriptions would require PA to show medical necessity (California Medicaid staff, personal communication).

As of January 2022, California Medicaid carved all pharmacy benefits out of managed care into the fee-for-service program, Medi-Cal Rx, to deliver pharmacy benefits for all Medicaid members.[201] The state contracts with a pharmacy benefit administrator (PBA) to perform claims

management, including PA, utilization management, and other pharmacy services for Medi-Cal Rx.[201] Under a state law, California Medicaid must process and respond to PA requests within 24 hours.[201,203] Because of challenges in the transition to the contracted PBA, PA requirements for all medications were suspended from early 2022 through September 2022 (California Medicaid staff, personal communication). PA requirements have since been reinstated (California Medicaid staff, personal communication).

Michigan Medicaid began covering weight management drugs effective February 1, 2022,[190] and uses a single PDL for pharmacy benefits across managed care and fee-for-service (Michigan Medicaid staff, personal communication).[198] Managed care plans must cover drugs on the common PDL, including weight management drugs, with the same PA criteria as fee-for-service (Michigan Medicaid staff, personal communication). Because the PA criteria are published and familiar to prescribers, most PA requests for weight management drugs meet the criteria and are approved (Michigan Medicaid staff, personal communication). Denials most typically occur for Medicaid members with BMIs between 27 and 30 with no risk factors or no prior attempt at weight loss in the past year (Michigan Medicaid staff, personal communication).

Prior Authorization and Reauthorization Criteria

As reflected in Table 77 above (FDA Indications, Usage, and Contraindications), the indications for Saxenda (liraglutide), Wegovy (semaglutide), Contrave (bupropion and naltrexone), and Qsymia (phentermine and topiramate) depend on age, BMI, and (for adults with overweight but not obesity) comorbidities. Indications for Imcivree (setmelanotide) are related to specific genetic factors, while indications for Xenical (orlistat) are related to weight loss and management without BMI or risk factor criteria.[183,184] Table 81 illustrates where indications overlap for these medications.

Table 81. Summary of FDA Indications for Saxenda, Wegovy, Contrave, and Qsymia[a]

Age range for medications	BMI	Comorbidities	Additional Indication
Adults: • Saxenda • Wegovy • Contrave • Qsymia	BMI of 30 or more (obesity)	Not applicable	Adjunct to reduced-calorie diet and increased physical activity
	BMI of 27 or more (overweight)	At least 1 weight-related comorbidity (e.g., hypertension, type 2 diabetes, dyslipidemia)	
Adolescents 12 and older: • Saxenda • Wegovy • Qsymia	Obesity, variously defined as: • BMI corresponding to 30 for adults and weight over 60 kg (Saxenda) • BMI at the 95th percentile or higher for age and sex (Wegovy and Qsymia)	Not applicable	

Note. [a] Saxenda (liraglutide), Wegovy (semaglutide), Contrave (bupropion and naltrexone), Qsymia (phentermine and topiramate).
Source. US Food and Drug Administration.[179,180,182]
Abbreviations. BMI: body mass index; kg: kilogram.

Those indications underlie many PA criteria, which typically relate to the member's age and BMI, comorbidities for overweight, lifestyle modifications related to diet and physical activity, and

listed contraindications. State Medicaid programs cite a variety of comorbidities and risk factors in their PA criteria, as summarized in Table 82.

Table 82. Comorbidities Used in Initial PA for Adults with BMI of at Least 27

State Medicaid Program	Drugs to Which Criteria Apply[a]	Comorbidities or Risk Factors Criteria
Michigan	Contrave Saxenda Wegovy Xenical	**At least 1 risk factor:** • Coronary heart disease • Diabetes • Dyslipidemia • Hypertension • Sleep apnea
Mississippi	Contrave Saxenda Wegovy	**At least 1 weight-related comorbidity:** • Hypertension • Hyperlipidemia • Glucose dysregulation (diabetes with history of glucose-lowering medications or prediabetes) • Obstructive sleep apnea • Cardiovascular disease (coronary artery disease, heart failure, prior heart attack or cerebrovascular accident) • Non-alcoholic liver disease • Other (with detailed clinical justification)
Wisconsin	Saxenda Wegovy Xenical	**2 or more risk factors:** • Coronary heart disease • Dyslipidemia • Hypertension • Sleep apnea • Type 2 diabetes

Note. [a] Saxenda (liraglutide), Wegovy (semaglutide), Contrave (bupropion and naltrexone), Xenical (orlistat).
Sources. Magellan Rx Management[197]; Mississippi Division of Medicaid[200]; State of Wisconsin Department of Human Services.[199]
Abbreviations. PA: prior authorization; BMI: body mass index.

State Medicaid programs set a variety of requirements for documentation needed for PA for weight management drugs. In Wisconsin, prescribers or their designees may request Pas by phone, portal, fax, or mail.[199] Medical records are not required as part of the PA process, which functions like an attestation by the provider (Wisconsin Medicaid staff, personal communication). All of the pharmacy benefits are carved out of managed care to fee-for-service, and a high volume of Pas are approved by phone (Wisconsin Medicaid staff, personal communication). Michigan Medicaid requires providers to attest that the requirements for PA are met (Michigan Medicaid staff, personal communication). Similarly, in Mississippi, the prescribing provider must sign the form, certifying that the information provided in the form is accurate and appropriately documented in the patient's medical record.[200]

Reimbursement Approaches

All state Medicaid programs opt to provide outpatient prescription drug coverage.[204] Typically, programs must cover the FDA-approved medications produced by drug makers that participate in the Medicaid Drug Rebate Program (MDRP) as long as the medications are used as medically indicated.[205] State Medicaid programs may use management tools such as PA and quantity limits

and may negotiate for supplemental rebates in exchange for putting specific drugs on the PDL.[205] Because this drug category is optional, state Medicaid programs may choose whether to cover weight management drugs at all.[204] Figure 98 depicts the flow of payments for prescription drugs in Medicaid.

NOTES: This figure is a simplified depiction of the payment and drug supply chain in the Medicaid prescription drug benefit provided through a fee-for-service setting. WAC is Wholesale Acquisition Cost. While WAC is publicly available, the negotiated amount is not. AAC is Actual Acquisition Cost which can be based on a published schedule such as NADAC or determined through other benchmarks. MAC is the state Maximum Allowable Cost and FUL is the Federal Upper Limit; both programs establish ceilings for what Medicaid will pay for certain multiple-source drugs.

Source. Dolan, R.[206]
Abbreviations. AAC: actual acquisition cost; CMS: Centers for Medicare & Medicaid Services; FUL: federal upper limit; MAC: maximum allowable cost; PBM: pharmacy benefit manager; PDL: prescription drug list; Rx: prescription; WAC: wholesale acquisition cost.

State Medicaid programs' payments for outpatient drugs incorporate the ingredient cost calculation (the cost of buying the drug) and a dispensing fee (the pharmacy's overhead and professional services).[204] The total payment must be consistent with Centers for Medicare & Medicaid Services (CMS) payment limits.[204] State Medicaid programs typically reimburse providers at the lowest amount, based on one of these methodologies[204]:

- Actual acquisition cost (AAC), which the state Medicaid program may base on a state survey of retail pharmacies, the national average drug acquisition cost (NADAC) survey, or the average manufacturer price (AMP)
- Federal upper limit (FUL), which CMS sets based on monthly AMP data and the most recent NADAC
- State maximum allowable cost (MAC), which most state Medicaid programs use to set the maximum price they will pay for drugs
- The usual and customary charge to the pharmacy's customers

The wholesale acquisition cost (WAC) is the amount that a wholesaler pays when buying from the drug maker, and it may be used as a benchmark when calculating supplemental rebates.[204]

Table 83. State Medicaid Programs' Weight Management Agents Reimbursement Approaches

State Medicaid Program	Basis for reimbursement	Supplemental rebate?	MCOs required to follow state's UM policies?
California	NADAC if available; if not, then WAC	Yes	Not applicable; pharmacy benefits are carved out of MCO contracts and handled through FFS
Michigan	Lesser of NADAC, WAC, or MAC	Yes	Yes
Mississippi	NADAC if available; if not, then WAC	Yes	Yes
Wisconsin	NADAC if available; if not, then WAC	No, not on PDL	Not applicable; pharmacy benefits are carved out of MCO contracts and handled through FFS

Source. Medicaid staff: California, Michigan, Mississippi, Wisconsin personal communication.
Abbreviations. FFS: fee-for-service; MAC: maximum allowable cost; MCO: managed care organization; NADAC: national average drug acquisition cost; UM: utilization management; WAC: wholesale acquisition cost.

Mississippi's Medicaid program began covering weight management drugs effective July 1, 2023 (Mississippi Medicaid staff, personal communication). In the state plan amendment, the program sought and received approval from CMS to cover "select" weight management drugs, allowing flexibility to choose specific drugs within the class to cover (Mississippi Medicaid staff, personal communication). As data become available, Mississippi Medicaid staff would like to evaluate numbers of prescriptions, rates of adherence, and success in meeting treatment goals, and any corresponding changes in other health care costs, but do not yet know details about the frequency or detail that will be included in these reviews (Mississippi Medicaid staff, personal communication). After the program evaluation, Mississippi Medicaid might undertake additional provider outreach, education, and feedback, including identification of members with a diagnosis of obesity who have not received weight management treatment (Mississippi Medicaid staff, personal communication).

Weight Management Drug Coverage Lessons Learned

Among the state Medicaid programs we interviewed, some have a longer history of coverage for weight management drugs, while others have begun coverage recently. These longer-term programs have identified lessons learned and areas of program management limitations.

- Most of the state Medicaid programs we interviewed were using PA criteria to manage use of these medications, but often did not receive much information from the PA submissions that would support program evaluation.
  - In Wisconsin, the PA approval process for drugs that are not on the PDL (including the covered weight management drugs) typically involves a phone call from staff in the prescriber's office to pharmacy technicians in a call center (Wisconsin Medicaid staff, personal communication). These requests usually are resolved without submission of a written PA request, which results in the state Medicaid program receiving less detailed PA data (Wisconsin Medicaid staff, personal communication). Changing to an entirely

written PA process, however, would be a large effort (Wisconsin Medicaid staff, personal communication).

- o In California, PA is not required for the weight management drugs on the PDL (California Medicaid staff, personal communication). In addition, Pas were lifted for much of 2022, so PA data were unavailable for that period (California Medicaid staff, personal communication).

- State Medicaid programs often rely on provider attestations rather than submission of clinical information in the PA process (Michigan, Wisconsin Medicaid staff, personal communication).
  - o Although the FDA-approved indications call for these drugs to be used as adjunct to diet and exercise, as a practical matter, data are not readily available to monitor actual diet or physical activity (California, Wisconsin Medicaid staff, personal communication).
  - o Michigan Medicaid includes in the PA criteria a recommendation that providers consider whether the diabetes prevention program may benefit the patient for whom weight management drugs are requested (Michigan Medicaid staff, personal communication).
  - o In the future, California Medicaid may explore ways to assess activities such as creating nutrition and physical activity goals for Medicaid members, potentially addressing the issue through value-based payment arrangements (California Medicaid staff, personal communication).
- When considering placing weight management drugs on the PDL and receiving supplemental rebates, state Medicaid programs should consider what PA criteria they will use. In exchange for supplemental rebates, some manufacturers limit state Medicaid programs' ability to clinically edit and set PA criteria (Wisconsin Medicaid staff, personal communication).
- State Medicaid programs also are tightening their PA criteria for diabetes drugs that are apparently being prescribed off label for weight management. In Wisconsin, for example, a diagnosis code will be required for coverage of diabetes drugs that are among the preferred drugs on the PDL (Wisconsin Medicaid staff, personal communication).

Taking a pragmatic view of the value and limitations that patients may place on weight management drugs, a pharmacist observed that people typically do not like to give themselves injections (California Medicaid staff, personal communication). Patients' willingness and adherence to injected weight management drugs, past the initial period of induction and dose titration when they also may experience their most significant side effects such as nausea and vomiting, may function as an indicator that patients find the drugs provide meaningful results (California Medicaid staff, personal communication). Although state Medicaid agencies are encouraged that weight management drugs seem to have few risks compared to older weight loss drugs, they are monitoring the possibility that adverse effects might surface over time, with

longer use among a larger and more diverse population than has been formally studied (California Medicaid staff, Mississippi Medicaid staff, personal communication).

Other Payers' Coverage Approaches for Weight Management Drugs

To provide other perspectives on coverage approaches, we reviewed policies of federal and state employers and a commercial payer.

Office of Personnel Management

The US Office of Personnel Management (OPM) is the federal human resources agency that manages employee benefits, including health insurance, for over 8 million federal employees and retirees and their families.[210] In recent years, OPM has required carriers to include coverage of some FDA-approved weight management drugs, with requirements growing more specific over time.[211,212]

For the 2023 contract year, OPM set out requirements for plan proposals to address access to antiobesity drugs as part of a comprehensive package of services.[213] Carriers were asked to address coverage of FDA-approved medications, drug tiering, utilization management, and clinical criteria for determining medical necessity.[213] OPM explained that carriers could not have a benefit exclusion that applied to all weight management drugs.[211] OPM required carriers to "have adequate coverage of FDA-approved antiobesity medications on their formulary to meet patient needs."[211,213] In addition to coverage, carriers were asked to address how they would communicate with members and providers about available benefits and how they would improve billing and coding for obesity screening, diagnoses, and treatment.[213]

For 2024, OPM's requirements are becoming more stringent and specific. In a carrier letter in early 2023, OPM noted progress in coverage of weight management drugs and emphasized that all carriers should provide sufficient coverage of these drugs.[214] In guidance to carriers submitting proposals for 2024, OPM stressed that coverage for obesity prevention and treatment remains a high priority.[215] In addition to comprehensive benefits for nutrition and physical activity, carriers are required to cover at least one GLP-1 antiobesity drug and at least 2 oral antiobesity drugs[215,216] Coverage must include medications that are approved for use by adolescents.[212] Carriers are also expected to review and update their formularies when the FDA approves new drugs to treat obesity.[214]

Cigna

Cigna has PA policies for each of the weight management drugs of interest for this report, but it is difficult to discern who may be covered, as the policies warn that specific benefit plan documents might exclude coverage.[217-219] Cigna's PA policy for GLP-1s is specific to Saxenda (liraglutide) and Wegovy (semaglutide) only, as summarized in Table 84; other GLP-1s, which lack FDA-approved indications for weight loss, are not covered by the policy.[217] A separate PA policy covers other weight loss medications, including Contrave (bupropion and naltrexone), Qsymia (phentermine and topiramate), and Xenical (orlistat),[218] which are summarized in Table 85. Imcivree (setmelanotide) is addressed in yet another PA policy, specifically targeting use for metabolic disorders.[219] The PA criteria for Imcivree include a requirement that an endocrinologist, geneticist, or physician specializing in metabolic disorder either prescribe or provide consultation.[219]

Cigna may cover tirzepatide (Mounjaro) as an antihyperglycemic therapy, with requirements that the patient has a type 2 diabetes diagnosis and first tries metformin unless contraindicated.[220] The PA criteria emphasize that tirzepatide is not FDA-approved as a treatment for weight management.[221]

Table 84. Cigna Prior Authorization Criteria for Saxenda and Wegovy

Applicability of Criteria	Approval Criteria	Saxenda Approval Periods	Wegovy Approval Periods

Initial for adults	If patient:
	• Tried at least 3 months of behavior modification and dietary restriction *and*
	• Is engaged in behavior modification and reduced-calorie diet *and*
	• Has either:
	  o BMI of 30 or more
	  o BMI of 27 or more and at least 1 of these weight-related comorbidities: hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, or cardiovascular disease
		4 months	7 months

Initial for 12- to 17-year-olds	If patient: • Tried at least 3 months of behavior modification and dietary restriction *and* • Is engaged in behavior modification and reduced-calorie diet *and* • Has BMI in at least 95th percentile for age and sex	4 months	7 months

Reauthorization for adults	If patient:
	• Had baseline BMI of at least 30 or at least 27 with comorbidities and
	• Meets required weight loss from baseline *and*
	• Is engaged in behavior modification and reduced-calorie diet *and*
	• Meets required toleration for drug
		1 year
		• Required weight loss: at least 4%
		• Required toleration: Maintenance dose of 3 mg daily
			• Required weight loss: at least 5%
			• Required toleration:
			  o Maintenance dose of 2.4mg weekly → 1 year *or*
			  o On drug less than 12 consecutive months and continuing titration → up to 5 months (to total 12 consecutive months of therapy)

Reauthorization for 12- to 17-year-olds	If patient: • Had baseline BMI in at least 95th percentile for age and sex *and*	1 year • Required toleration: Maintenance dose of	• Required toleration: o Maintenance dose of 1.7 or 2.4 mg weekly → 1 year *or*

Applicability of Criteria	Approval Criteria	Saxenda Approval Periods	Wegovy Approval Periods
	• Reduced BMI at least 1% from baseline *and* • Is engaged in behavior modification and reduced-calorie diet *and* • Meets required toleration for drug	2.4 mg or 3 mg daily	○ On drug less than 12 consecutive months and continuing titration → up to 5 months (to total 12 consecutive months of therapy)

Source. Cigna.[217]
Abbreviations. BMI: body mass index; mg: milligram.

Cigna's quantity limits policy for Wegovy allows for 8 pens each of the 4 strengths used to titrate up (0.25mg, 0.5mg, 1mg, and 1.7mg) per 365 days; at the full dose of 2.4mg (or 1.7mg as an alternative maintenance dose for adolescents), the quantity limit is 4 pens per 28 days retail or 12 pens per 84 days home delivery.[222] One-time overrides of the titration doses may be approved if the patient has missed more than 2 consecutive doses and needs to reinitiate treatment.[222] In addition, adults may receive a one-time override for 4 doses at 1.7mg as a temporary dose reduction; if after 4 weeks at a reduced dose of 1.7mg an adult patient cannot tolerate the full 2.4mg dose, then Wegovy should be discontinued for that patient.[222]

Table 85. Cigna Prior Authorization Criteria for Contrave, Qsymia, and Xenical

Applicability of Criteria	Approval Criteria	Contrave	Qsymia	Xenical

Initial for adults	If patient:
	• Tried at least 3 months of behavior modification and diet *and*
	• Is engaged in behavior modification and diet *and*
	• Has:
	  ○ BMI of at least 30 *or*
	  ○ BMI of at least 27 with comorbidities such as diabetes, impaired glucose tolerance, dyslipidemia, hypertension, sleep apnea, or cardiovascular disease *or*
	  ○ For Xenical only, is maintaining weight loss from initial BMI of at least 30 or initial BMI of at least 27 with comorbidities
		4 months	6 months	3 months

Initial for 12- to 17-year-olds	If patient: • Tried at least 3 months of behavior modification and diet *and* • Is engaged in behavior modification and diet *and* • Has BMI in at least the 95th percentile for age and sex	Not approved for this age group	4 months	3 months
Reauthorization for adults	If patient: • Had initial BMI of at least 30 or of at least 27 with comorbidities *and* • Has lost at least 5% of baseline weight *and* • Is engaged in behavior modification and reduced-calorie diet	1 year	1 year	1 year

Applicability of Criteria	Approval Criteria	Contrave	Qsymia	Xenical
Reauthorization for 12- to 17-year-olds	If patient: • Had initial BMI in at least the 95th percentile for age and sex *and* • Has reduced at least 5% from baseline BMI *and* • Is engaged in behavior modification and diet	Not approved for this age group	1 year	1 year

Source. Cigna.[218]
Abbreviation. BMI: body mass index.

Commonwealth of Massachusetts Group Insurance Commission

The Massachusetts Group Insurance Commission (GIC) manages benefits, including health insurance, for Massachusetts state employees and retirees and their families, a total of 460,0000 members.[223] GIC uses CVS Caremark as the PBA for Massachusetts state employees' health care.[224] The CVS formulary includes 3 antiobesity drugs: Saxenda (liraglutide), Wegovy (semaglutide), and Qsymia (phentermine and topiramate),[225] and uses PA criteria to assess eligibility for coverage (Table 86).

Table 86. CVS Prior Authorization Criteria for Qsymia, Saxenda, and Wegovy

Applicability of Criteria	Qsymia	Saxenda	Wegovy

Initial for adults	• Patient has at least 6 months' participation in comprehensive weight management program[a] *and*
	• Patient has either:
	   ○ BMI of 30 or more
	   ○ BMI of 27 or more and at least 1 weight-related comorbidity
		• Patient has at least 6 months' participation in comprehensive weight management program[a] *and*
		• Patient has either:
		   ○ BMI of 30 or more
		   ○ BMI of 27 or more and at least 1 weight-related comorbidity
		• Drug will be used with reduced-calorie diet and increased physical activity
			• Patient has at least 6 months' participation in comprehensive weight management program[a] *and*
			• Patient has either:
			   ○ BMI of 30 or more
			   ○ BMI of 27 or more and at least 1 weight-related comorbidity
			• Drug will be used with reduced-calorie diet and increased physical activity

Initial for 12- to 17-year-olds	• Patient has BMI in 95th percentile or higher standardized for age and sex	• Patient has body weight over 60 kg and initial BMI corresponding to 30 or more for adults *and* • Drug will be used with reduced-calorie diet and increased physical activity *and* • Patient has at least 6 months' participation in comprehensive	• Patient has initial BMI in 95th percentile or higher standardized for age and sex *and* • Drug will be used with reduced-calorie diet and increased physical activity *and* • Patient has at least 6 months' participation in comprehensive

Applicability of Criteria	Qsymia	Saxenda	Wegovy
		weight management program	weight management program
Reauthorization for adults	After at least 12 weeks on 15 mg/92 mg: • Lost at least 5% of baseline body weight *or* • Maintained initial 5% weight loss *or* After at least 12 weeks on 7.5 mg/46 mg: • Lost at least 3% of baseline body weight *or* • Maintained initial loss of 3% body weight *or* • Has not lost or maintained % and has been escalated to 11.25 mg/69 mg and will follow the appropriate dose escalation	After at least 16 weeks of therapy, patient has: • Lost at least 4% of baseline body weight *or* • Maintained initial 4% weight loss	After at least 3 months of therapy at stable maintenance dose, patient has: • Lost at least 5% of baseline body weight *or* • Maintained initial 5% weight loss
Reauthorization for 12- to 17-year-olds	After at least 12 weeks on 15mg/92 mg: • Reduced BMI at least 5% from baseline *or* • Maintained initial 5% reduction in BMI *or* After at least 12 weeks on 7.5 mg/46 mg: • Reduced BMI at least 3% from baseline *or* • Maintained initial 3% reduction in BMI *or* • Has not reduced or maintained 3% reduction in baseline BMI and has been escalated to 11.25 mg/69 mg and will follow the appropriate dose escalation	After at least 12 weeks of therapy, patient has: • Reduced BMI 1% from baseline *or* • Maintained initial 1% reduction in BMI	Patient has successfully titrated to stable maintenance dose and either: • Had a reduction from baseline BMI *or* • Maintained their reduction in BMI
Additional criteria – all patients	• Patient is not using fenfluramine • Drug will be used with reduced-calorie diet and increased physical activity		

Note. [a] The PA criteria refer to a comprehensive weight management program that encourages changes in behavior, diet, and physical activity and includes a minimum of 6 months' continuing follow-up.
Source. CVS Caremark.[226-228]
Abbreviation. BMI: body mass index.

Place in Obesity Treatment for Weight Management Drugs

Guidelines for the treatment of overweight and obesity are evolving. This report does not involve a full review of guidelines or assessment of methodologies used to develop guidelines. Rather, we provide brief summaries of some recent guidelines that discuss weight management drugs as context along with insights from key informant interviews.

Pharmacotherapy is part of a spectrum of potential treatments for obesity, as depicted in the American Diabetes Association guidelines discussed below. Other treatment options include behavioral interventions, which are recommended by the USPSTF for children and adolescents and adults with obesity,[187,188] and bariatric procedures. Oregon's Health Evidence Review Commission (HERC) recently drafted coverage guidance on bariatric procedures.[229] An overview of that evidence can be found on the DERP and MED Clearinghouses.[230]

The USPSTF recommended in 2017 that children and adolescents be screened for obesity and offered or referred for intensive behavioral interventions[187] and then in 2018 recommended that adults with obesity (BMI of 30 or more) be offered intensive behavioral interventions.[188] The USPSTF is developing updated recommendations for weight management for children and adults. For the updated recommendations for both age groups, the task force will review 3 key questions related to whether behavioral, pharmacological, or combined interventions involving primary care (1) improve health outcomes, (2) improve weight or cardiometabolic outcomes, and (3) are associated with any harms.[231,232] For children and adolescents, a fourth key question relates to whether such interventions improve behavioral outcomes.[231] Although research plans have been published, the timeline for the updated recommendations is unclear.[233,234]

Meanwhile, the challenges of keeping guidelines current in a shifting landscape are apparent from the example of the Canadian Task Force on Preventive Health Care (CTFPHC). In 2015, the CTFPHC published recommendations for prevention and treatment of overweight and obesity in children and youth and in adults.[235,236] As of December 2022, however, the CTFPHC placed updates on hold, despite acknowledging that the 2015 recommendations were out-of-date.[235,236] Explaining the decision, the CTFPHC cited changing understandings of obesity, a shift in focus from weight loss to health outcomes valued by patients, changing treatment options (including medications), and planned new national guidelines on obesity.[235,236]

To illustrate the pace of change, the timeline in Figure 99 shows the years since 2012 when the FDA-approved weight management drugs and the years when select guidelines and practice statements were published.

Figure 99. Timeline of FDA Approvals and Guideline Publications

Year	2012	2014	2015	2016	2017	2020	2021	2022	2023
FDA Approvals	Qsymia approved by FDA	Contrave and Saxenda approved by FDA				Imcivree approved by FDA; Saxenda approved for 12- to 17-year-olds	Wegovy approved by FDA	Wegovy and Qysmia approved for 12- to 17-year-olds	
Guidelines Published		AHA/ ACC/ TOS (adults)[237]	Endocrine Society (adults)[238]	American Diabetes Association[239]	Endocrine Society (children)[240]	US Department of Veterans Affairs and US Department of Defense[241]		Obesity Medicine Association,[242] American Gastroenter-ological Association[185]	American Academy of Pediatrics[243]

Abbreviations. ACC: American College of Cardiology; AHA: American Heart Association; FDA: US Food and Drug Administration; TOS: The Obesity Society.

Select Recent Guidelines for Care of Adults with Overweight or Obesity

Highlights from select guidelines are provided for context. This discussion does not reflect a systematic review of guidelines on pharmacotherapy for weight management.

American Gastroenterological Association

The American Gastroenterological Association (AGA) published its clinical practice guideline on pharmacological interventions for adults with obesity in 2022.[185] The AGA strongly recommends using weight management drugs in conjunction with behavioral interventions, rather than behavioral interventions alone, for adults who have either overweight with weight-related comorbidities or obesity and who have not successfully lost weight with behavioral interventions.[185] The AGA notes that weight management medications typically require ongoing use and the choice of medication for a particular patient should take into account not only clinical factors (e.g., comorbidities) but also the patient's preferences and ability to afford the medication.[185] Among the FDA-approved weight management drugs, the AGA suggests prioritizing semaglutide 2.4 mg (Wegovy), which produces stronger results than other drugs.[185] Use of semaglutide is subject to considerations of potential side effects (e.g., nausea and vomiting, which may be decreased by gradually increasing doses) and risks of pancreatitis and gallbladder disease.[185] Depending on a patient's profile, other weight management drugs may be preferred because of their effectiveness in treating comorbidities.[185] For example, patients who have comorbid migraines may prefer phentermine-topiramate (Qsymia) because topiramate also is a migraine treatment.[185] Patients who have comorbid depression or are trying to quit smoking may prefer naltrexone-bupropion (Contrave).[185] The AGA suggests against the use of orlistat (Xenical), but acknowledges that it may reasonably be preferred by some patients who value a small decrease in weight and accept the gastrointestinal side effects.[185] Each medication also has contraindications or risks that require monitoring.[185]

Among evidence gaps, the AGA observes that although behavioral interventions are foundational to obesity treatment, these interventions lack a consistent definition, and the behavioral interventions actually used in clinical practice may range from unstructured, patient-reported efforts to participation in an established treatment program.[185] Although evidence about health disparities is lacking, the AGA notes there is a risk that use of these medications may exacerbate disparities, because of differing rates of access to the medications, coupled with higher obesity prevalence among Black and Hispanic adults compared with White adults.[185]

Obesity Medicine Association

The Obesity Medicine Association (OMA) clinical practice statement on antiobesity medications and investigational agents is derived from a proprietary algorithm.[242] It is geared to help clinicians rather than support policymakers. The statement includes detailed descriptions of numerous weight management drugs, including but not limited to the drugs that are the focus of this report, how they work, and their side effects and contraindications.[242] It also summarizes each drug's FDA approval, side effects, and potential interactions with other drugs.[242] The OMA notes that the drugs vary in the effectiveness for weight loss and metabolic health, and that individuals experience varying responses to the drugs.[242] Accordingly, the OMA recommends a shared decision-making process that includes considerations such as safety and contraindications, efficacy, tolerability, and cost.[242] The OMA compares the development and acceptance of weight management drugs to that of diabetes, hypertension, and hypercholesterolemia drugs that have

become standards of care.[242] Among their takeaway messages about the development of weight management drugs, the OMA guideline authors predict, "Clinical cardiovascular outcome trial support for cardiovascular benefits is likely the binary switch that will transform the current limited use of antiobesity medications into future standards of care for patients with obesity."[242(p19)]

American Diabetes Association

In 2016, the American Diabetes Association (ADA) first included in its annual standards of care publication a section on obesity and weight management for the prevention and treatment of type 2 diabetes.[244] The 2016 ADA guidance describes pharmacotherapy options as typically having side effects, poor rates of adherence, and limited results.[239] Since then, the ADA has continued to regularly update its clinical practice recommendations for weight management to prevent and treat type 2 diabetes.[245]

The ADA's current pharmacotherapy recommendations emphasize weight management drugs' effectiveness for adults with a BMI of 27 or higher and type 2 diabetes, in combination with nutrition, physical activity, and behavioral counseling, and with appropriate attention to potential risks and contraindications.[245] Table 87 provides a snapshot of the ADA's 2023 recommendations for treatment options at different BMIs.

Table 87. American Diabetes Association Treatment Options for Overweight and Obesity in Adults with Type 2 Diabetes

Treatment Option	BMI		
	25.0-26.9 (or 23.0-24.9 for Asian Americans)	27.0-29.0 (or 25.0-27.4 for Asian Americans)	≥ 30 (or ≥ 27.5 for Asian Americans)
Nutrition, physical activity, and behavioral counseling	Treatment may be indicated for motivated individuals	Treatment may be indicated for motivated individuals	Treatment may be indicated for motivated individuals
Pharmacotherapy		Treatment may be indicated for motivated individuals	Treatment may be indicated for motivated individuals
Metabolic surgery			Treatment may be indicated for motivated individuals

Source. Adapted from the American Diabetes Association. ElSayed, NA.[245]

The ADA recommends monthly assessments for the first 3 months an individual is on weight management drugs and at least quarterly assessments on an ongoing basis.[245] For individuals who experience at least 5% weight loss in the first 3 months on these drugs, the ADA recommends continuing on the same drug, unless the patient has problems tolerating or affording it.[245] If an individual does not have that level of early response on a drug, the ADA recommends discontinuing that drug and considering a switch to a different treatment.[245] Among evidence gaps, the ADA observes that clinical trials so far have provided limited data about use of weight management drugs among people with type 1 diabetes.[245]

American Academy of Pediatrics' Guidelines for Care of Children with Overweight or Obesity

The American Academy of Pediatrics (AAP) recently issued a clinical practice guideline on treatment of children with overweight and obesity and plans to issue a policy statement on obesity prevention.[243] The AAP guideline addresses pharmacotherapy as a potential component of treatment, but emphasizes comprehensive obesity treatment, defined to include not only clinical considerations but also consideration of social drivers of health.[243] The AAP also stresses the importance of routinely evaluating pediatric patients and providing early identification of overweight, obesity, and any obesity-related comorbidities, which otherwise may not be recognized.[243] Prompt engagement in intensive health behavior and lifestyle treatment (IHBLT) is foundational, although access to these programs is often limited.[243] Any use of weight management drugs should be accompanied by IHBLT.[243]

The AAP's recommendations for the use of weight management drugs depend on the child's age[243]:

- For children under age 12, AAP rates the evidence as insufficient to recommend the use of weight management drugs for obesity alone.
- For children ages 8 to 11, AAP recommends that medications *may* be offered as a component of obesity treatment, especially if the child has severe comorbidities that present imminent and life-threatening risks.
- For children age 12 or older, medications should be offered as an adjunct to IHBLT and in keeping with the indications and potential harms and benefits.
- For children age 13 or older who have severe obesity, a referral to be evaluated for bariatric surgery should be made.

Box 3. Children's Access to Intensive Health Behavior and Lifestyle Treatment

Although IHBLT is a core component of caring for children and adolescents, the AAP notes limits on access: "These limitations include the relative scarcity and distribution of such treatment programs and pediatricians or other pediatric health care providers with experience and/or training in pediatric obesity treatment, family transportation challenges, loss of school or work time to attend multiple recurring appointments during what are typically working hours, SdoHs [social drivers of health], competing health issues for children or family members, and mismatched expectations between the family (who may expect significant weight loss) and pediatricians or other pediatric health care providers. IHBLT is appropriate for typically developing children and adolescents as well as CYSHCN [children and youth with special health care needs], although will require modification based on the patient's unique health conditions and developmental factors."[243]

The AAP also noted research gaps that need to be addressed, including research on the long-term effects of these drugs on weight and on the development of comorbidities during childhood and into adulthood; how the drugs' effectiveness may vary depending factors such as the severity of obesity, social drivers of health, and comorbidities; and details about specific interventions offered to support lifestyle change and continuation in treatment.[243]

Subject Matter Experts' Views on Treatment Pathways

Care Team

Subject matter experts stressed the importance of multidisciplinary teams to provide comprehensive care for patients with obesity (F.C. Stanford, E. Grunvald, personal communications). One key informant identified a gold standard care team as including obesity

medicine physicians, dieticians to do individual or group sessions, bariatric surgeons, pharmacy techs, and support staff who help with insurance (E. Grunvald, personal communication). Obesity psychologists and exercise physiologists were also identified as essential team members to address patients' needs (F.C. Stanford, personal communication).

Management in primary care, involving some counseling on lifestyle modifications, prescriptions, and periodic follow-up, can work well with obesity treatment, similar to care for other chronic conditions (E. Grunvald, personal communication). This model would work particularly well if primary care providers see the patients with more straightforward needs and specialists see patients with more complex circumstances (e.g., patients who need a combination of medication and bariatric surgery or who need to lose weight to qualify for an organ transplant) (E. Grunvald, personal communication). For that approach to work, however, medical education about obesity must be standardized and widespread (F.C. Stanford, personal communication). Better education could also reduce the stigmatization of people with obesity (F.C. Stanford, personal communication). Too few providers currently are prepared to treat patients with obesity and related comorbid conditions, particularly during a typical 15-minute primary care visit (F.C. Stanford, personal communication). An obesity specialist can feel comfortable prescribing weight management drugs to treat an age spectrum from adolescents to older adults; still, too few physicians have been trained to care for the population with obesity (F.C. Stanford, personal communication).

Pediatric primary care providers are less likely to have experience with weight management drugs, not only because the FDA approvals for adolescents are relatively recent but also because adolescents with diabetes are less likely to be treated with liraglutide or semaglutide than adults are (J. Michel, personal communication). Until pediatric primary care providers have more experience seeing which patients have good outcomes with weight management drugs and understanding the profile of patients who may benefit, they may find it appropriate to refer to providers with some additional experience or training (J. Michel, personal communication). The AAP guidelines are helpful but still new, and the lack of data on the long-term effects (including risks of side effects, eating disorders, and stigma) is particularly troubling when caring for a child or adolescent who is not currently experiencing adverse health effects caused by excess weight (J. Michel, personal communication). Lack of access to obesity specialists, however, can be a concern for children and adolescents with Medicaid coverage, not only because of a lack of capacity among pediatric obesity specialists but also because engagement in intensive treatment is challenging for families to maintain (J. Michel, personal communication).

Identifying Candidates for Pharmacotherapy

The key informants we interviewed agreed that BMI should not be the sole indicator to identify patients who may be candidates for pharmacological or other intensive interventions; rather, an individualized approach is needed (F.C. Stanford, E. Grunvald, J. Michel, personal communication). It is essential to look at health complications, including psychosocial complications, caused by excess weight (E. Grunvald, personal communication). For pediatric patients, BMI should not be the sole factor in referring to a more intensive treatment program, but referrals should be considered for pediatric patients with more comorbidities or risk factors or who are gaining weight at an accelerating pace (J. Michel, personal communication).

An individualized approach includes considering the patient's history, laboratory results, comorbidities, treatment preferences, and insurance coverage (F.C. Stanford, personal communication). Depending on a patient's comorbidities, a weight management drug could be chosen to help address multiple needs; for example, topiramate can help address both weight management and migraines (F.C. Stanford, E. Grunvald, personal communication). In addition, it is essential to understand what has or has not worked for a patient in the past (F.C. Stanford, personal communication).

Obesity is a highly individualized disease involving complex biological and environmental interactions (F.C. Stanford, E. Grunvald, personal communication). Although individual patients react differently to specific medications, the evidence base to tailor pharmacotherapies for individual patients is lacking (F.C. Stanford, E. Grunvald, personal communication). As a result, individuals may need to try multiple options to find a medication that works in their case; the evidence base is not developed to enable obesity specialists to target medications the way, for example, oncologists can target cancer treatments (F.C. Stanford, personal communication).

Bariatric surgery may be a better option for some patients, for example, patients who have type 2 diabetes that was diagnosed in the past 8 to 10 years, because they have the greatest chance of diabetes going into remission (E. Grunvald, personal communication). Also, some patients with very severe obesity may benefit from bariatric surgery in addition to medication, because losing even 15% to 20% of their body weight with medication may not alleviate their health issues, especially biomechanical complications (E. Grunvald, personal communication).

When patients consult an obesity specialist, they typically have tried multiple times to lose weight with lifestyle modifications (F.C. Stanford, E. Grunvald, personal communication). Weight management drugs help patients choose more healthful diets despite being surrounded by an obesogenic environment; although lifestyle modifications are foundational, they do not work as well without the drugs (E. Grunvald, personal communication). Physical activity adds only a little to weight loss (as opposed to weight maintenance and maintenance of muscle mass); still, patients are always counseled to engage in regular physical activity because of its many other health benefits (E. Grunvald, F.C. Stanford, personal communication).

Cost and Access

The FDA-approved indications for these drugs provide clear guidelines; however, they would be better described as chronic obesity management or chronic obesity treatment, because weight loss suggests to the public something that a person would go on and off (E. Grunvald, personal communication). Obesity is a chronic, relapsing and remitting disease, and it is rare that someone who responds to weight management medication can maintain a healthy weight with a smaller or discontinued dosage (E. Grunvald, F.C. Stanford, personal communication).

Our key informants noted concerns with reauthorization policies that require patients to reach a maximum dose (E. Grunvald, F.C. Stanford, personal communication). Typically, when patients start using weight management drugs, their response to the medication becomes clear within the first 3 to 6 months, depending on the agent (E. Grunvald, personal communication). However, some patients do not respond well until they have built up to higher doses of the medication, and they may need time to build tolerance to adverse effects for the maximum dose

(E. Grunvald, personal communication). If a coverage policy assesses a patient's response before the patient has reached the highest dose and then denies reauthorization if the patient has not yet lost enough weight, coverage may end before it is clear whether the patient will respond (E. Grunvald, personal communication). Conversely, some patients respond well to lower doses and moving them to a higher dose is unhelpful (F.C. Stanford, personal communication).

For patients whose insurance covers incretin therapies for diabetes but not for weight management, worsening laboratory results may be viewed as a grim cause for celebration, as adding a diabetes diagnosis opens the door to treatment options that are otherwise financially out of reach (F.C. Stanford, personal communication). In addition, drug shortages cause severe access problems even for patients whose plans cover these drugs (F.C. Stanford, personal communication). The hope is that drug costs may decrease as oral forms of GLP-1s become available, new medications are approved, and older drugs become available in generic forms, but it is unclear when pricing may change (E. Grunvald, F.C. Stanford, personal communication). At this time, cost-effectiveness is an open question (E. Grunvald, personal communication). For more discussion, see the cost effectiveness section above.

Discussion

Summary of Evidence for Effectiveness and Harms

Studies of comparative effectiveness and potential for harms across pharmacological agents for weight management in the published literature are limited. While, overall, the included studies demonstrated that all medications of interest were effective at weight loss compared to placebo, there is bias when comparing effect sizes of different drugs across studies of placebo-controlled data because the magnitude of effects are influenced by study design (e.g., sample size, duration of treatment) and study population (e.g., baseline weight, comorbid conditions), without conducting a network meta-analysis. (Quality network meta-analyses use statistical techniques that reduce bias when comparing outcomes, and allow relative rankings of interventions.[246]) Although recent published network meta-analyses[247-249] do not include all the pharmacologic agents of interest, the findings in this report are generally supported by the otherwise relevant findings in the published network meta-analyses.

Adults

For weight outcomes that can be compared to MCIDs, or clinically meaningful improvements, as reported in the literature, our findings demonstrated semaglutide, tirzepatide, and phentermine-topiramate achieved clinically meaningful improvements in weight loss compared to placebo, of greater than 5%, while liraglutide and naltrexone-bupropion did not. Exenatide demonstrate a meaningful loss of weight compared to glibenclamide, and semaglutide demonstrated a meaningful difference in weight loss compared to liraglutide.

The largest weight loss effect from the included trials was with tirzepatide after 72 weeks of treatment in adults; however, long-term studies are needed to determine whether weight loss will continue after 72 weeks (graph demonstrated downward trajectory at end of trial[81]), and can reach levels of 20% to 30% weight loss associated with bariatric surgery[34]

Only tirzepatide, in 1 study, achieved clinically meaningful improvements in SBP compared to placebo; all other drugs with this outcome (not measured in the study for exenatide) achieved

statistically significant improvements, but did not reach the 5 mmHg threshold. In the STEP 8 study comparing semaglutide and liraglutide, there was no difference in change in SBP.

All pharmacologic agents reviewed in this report, except for naltrexone-bupropion, improved LDL cholesterol compared to placebo, but none appeared to meet levels considered clinically important; there was no difference between semaglutide and liraglutide in the STEP 8 trial.

In people with elevated HbA1c, we found that all agents achieved clinically meaningful improvements compared to placebo; however, it is less clear if there are further improvements in people with levels that are borderline high, or within normal limits. There was no difference in HbA1c levels between the comparative studies of exenatide versus glibenclamide, and semaglutide versus liraglutide.

Because of the heterogeneity of methods and definitions of safety outcomes in the included studies, it is challenging to compare adverse events across studies and drugs; however, the relatively low number of SAEs across all studies could suggest the overall safety profile of these drugs as relatively good. However, it is important to point out that many of these studies did not describe the conditions of these serious events, nor whether the events were attributed to the study drug. Importantly, we found that all drugs in adults contributed to adverse events that resulted in drug discontinuation or study withdrawals, compared to placebo; in the STEP 8 trial, liraglutide was attributed to more AEs that led to withdrawals than semaglutide.

- While our findings clearly show that individuals who take GLP-1 agonists are more likely to experience gastrointestinal issues compared with placebo, it is less clear which drugs cause more gastrointestinal distress.
- We found that the 2 drugs with stimulant properties also impact the central nervous system; paresthesia (tingling or pricking sensation of the peripheral nerves) is experienced in about 20% of people who take phentermine-topiramate, while dizziness and headaches are a common symptom of people who take naltrexone-bupropion.
- We were also concerned with the very large drop-out rates in the studies of naltrexone-bupropion (49% to 63%) and phentermine-topiramate (54% to 62%) that reported mostly vague and broad categories for reasons of withdrawal (e.g., "lost to follow-up," "withdrew consent," "drug non-compliance"). Without a more detailed understanding of why drop-out rates were higher for these drugs, it remains challenging to optimize prescribing guidelines for best practice.

Overall physical functioning QoL was improved in studies of liraglutide, semaglutide, tirzepatide, and naltrexone-bupropion; it was not measured in studies of exenatide and phentermine-topiramate.

Youth

All 4 pharmacologic agents studied in youth demonstrated significant, and clinically meaningful, weight loss compared to placebo. However, these agents were not as effective at improving indirect measures of risks for comorbid conditions as demonstrated in adults. Only liraglutide showed significant improvements in SBP, but not at meaningful levels, and only semaglutide demonstrated significant improvements in LDL cholesterol, but also not at meaningful levels (studies of phentermine-topiramate did not report change in LDL cholesterol). Although

semaglutide and liraglutide had significant improvements in HbA1c, only semaglutide met the threshold for a meaningful difference. It should be noted, however, that the evidence for whether early intervention for childhood dyslipidemia or elevated blood pressure can prevent future cardiovascular disease is weak and remains controversial.[250,251]

For the most part, the patterns of overall AEs and SAEs in the studies of youth were similar to those experienced by adults, except there were no differences in withdrawals due to AEs between intervention and placebo groups across all agents except for liraglutide (the results were mixed for liraglutide where 1 study showed few overall, and the other study had 13 withdrawals due to AEs with liraglutide compared to none in the placebo group).

Quality of life was only measured in studies of liraglutide and exenatide. There was no difference across groups for both drugs; this was in contrast to the positive effects found in adults for liraglutide.

Limitations of Effectiveness and Harms Evidence

Overall, limitations of this body of evidence include lack of:
- Comparative effectiveness trials of at least 1 year
- Trials comparing drugs of interest to other common interventions including bariatric surgery (see below) and intensive diet and exercise behavioral therapy
- Quality and complete reporting of reasons for study withdrawal, SAEs
- Long-term effectiveness and harms outcomes
- Long-term off-treatment primary analyses
- Studies focusing on obesity-related comorbid risk factors
- Measures of QoL
- Studies not funded by industry

Given that bariatric surgery is becoming a more common and effective way to treat more serious cases of obesity, it was somewhat remarkable that we did not identify any studies comparing surgery with pharmacological treatment options. The few trials that looked at bariatric surgery (but were ultimately excluded) studied weight loss medications with the goal of either maintaining weight loss after bariatric surgery, or pretreating individuals with medications to improve surgery outcomes. The single systematic review we identified with this comparison included 6 studies comparing GLP-1 RA with bariatric surgery, but none were eligible for this report (three studies were retrospective cohort studies, and 2 were RCTs that pooled "various" GLP-1 Ras in a single arm).[252] The authors concluded, however, that change in BMI for all surgery types was greater than with weight loss medications.[252]

Coverage and Payer Policies (KQ4)

- Coverage of weight management drugs is inconsistent and is fluctuating as payers assess the costs and benefits of covering these drugs.
- When payers opt to cover weight management drugs, they typically set PA requirements.
  - Consistent with the FDA-approved indications, initial PA criteria for Saxenda (liraglutide), Wegovy (semaglutide), Contrave (bupropion and naltrexone), and Qsymia (phentermine and topiramate) usually relate to having obesity or having overweight (BMI of 27 or

greater) with weight-related comorbidities. The required comorbidities or risk factors vary across payers.

- o Reauthorization typically depends on achieving and maintaining specified weight loss. Sometimes reauthorization criteria also are explicit about the patient's toleration of ongoing maintenance doses of the drug. Reauthorization periods vary depending on the payer and the drug.
- o Most state Medicaid programs we interviewed do not set duration limits on the use of these drugs.
- Payers also are working to limit off-label use of diabetes medications such as tirzepatide (Mounjaro) for weight management, for example, by requiring documentation of a diabetes diagnosis during the PA process.
- State Medicaid programs may receive supplemental rebates if they add weight management drugs to their PDLs, but doing so may limit the PA criteria they can set for those drugs.

Treatment Pathways (KQ5)

- Clinical practice guidelines are rapidly evolving as new drugs have come onto the market.
  - o The USPSTF is working on recommendations for weight management interventions for children and adults, and pharmacotherapy is included in USPSTF's review. Publication dates, however, have not been announced.
- More guidelines are available for treatment of adults than for treatment of children. In addition, children are less likely than adults to have used GLP-1s as part of diabetes treatment, so pediatricians are less likely to have seen patients are on other formulations of these drugs. This may add to pediatric primary care providers' lack of comfort prescribing weight management drugs.
- Intensive behavior and lifestyle interventions are foundational to treatment, but often difficult to access.

State Considerations

Some significant questions remain unanswerable for now, such as whether adverse effects may emerge with long-term use in a larger population, whether the drugs' effect on patients' weight and health will generate savings in treatment over an extended period, and whether drug makers will reduce pricing as additional weight management drugs gain FDA approval and generic versions become available.

State Medicaid programs are likely to face conflicting demands related to coverage of these medications. On the one hand, these drugs are receiving widespread attention and have become part of popular culture. Consumer demand has been high enough to cause shortages in semaglutide, affecting people who have been prescribed formulations for diabetes care.[27] The surge in demand appears to be a response to accounts on social media and elsewhere of people experiencing exceptionally strong results, although stories also are surfacing from people who have experienced severe side effects.[253] Drug makers are busily lobbying Congress to change Medicare coverage policies to allow for coverage of weight management drugs, with some hope that if Medicare coverage changes, other payers would follow suit.[254] On the other hand, the newer drugs currently FDA-approved for weight loss have high prices and many potential users, adding up to substantial costs. In addition, although individuals' expectations about weight loss

may be high because of anecdotal accounts of extraordinary weight loss, the average weight loss is under 5% with liraglutide, 8% to 9% with phentermine-topiramate, and 11% to 12% with semaglutide.

Although state Medicaid programs typically must cover manufacturers' covered outpatient drugs if the manufacturer has agreed to participate in the Medicaid Drug Rebate Program, weight loss drugs are among the exceptions that may be excluded or otherwise restricted.[46,255] As state Medicaid programs navigate decisions about coverage, important considerations arise related to state plan design, utilization management tools, and value-based purchasing approaches.

State Plan Design

Depending on the structure of the state's pharmacy benefit and who bears financial risks of drug coverage, different issues will arise. If pharmacy benefits or specific drug classes are carved out of managed care, then state Medicaid programs will have more covered lives and thus may have a larger lever for negotiating rebates from drug makers. Since 2018, California, New York and Ohio have carved drugs out of managed care and placed them in the FFS benefit.[256] If pharmacy benefits are covered under managed care, managed care organizations (MCOs) may be concerned about the costs they will bear for coverage of these drugs. State Medicaid programs will need to work with their MCOs to address the effect on coverage on capitation rates.

A 2018 survey found that most state Medicaid programs with comprehensive managed care carve pharmacy benefits into managed care, although some made exceptions for high-cost drugs.[257] There has been some movement toward carving pharmacy benefits out of managed care and planning additional carve-outs for high-cost drug classes.[258] Among the states we interviewed for this report, California and Wisconsin Medicaid carve pharmacy benefits out of managed care, while Michigan and Mississippi Medicaid do not.

Utilization Management Tools

State Medicaid programs also can use utilization management tools and may require their MCOs to use the same tools.

Preferred Drug List

Most state Medicaid programs use a PDL for their fee-for-service population, and growing numbers require their managed care organizations to use the same PDL.[258] Programs that opt to cover weight management drugs will want to carefully consider whether to add them to their PDL. Adding them to the PDL offers the advantage of supplemental rebates but could also limit the state's ability to set additional criteria for use of the drugs. Among the state Medicaid programs we interviewed, all but 1 (Wisconsin) had placed some weight management drugs on their PDL.

Prior Authorization

Prior authorization requirements are very common for weight management drugs. Among the state Medicaid programs we interviewed, all but 1 (California) require PA authorization for

weight management drugs. This approach can help limit use to people for whom the drugs are medically indicated.

State Medicaid programs also may use PA and reauthorization to ensure that people using weight management drugs receive appropriate counseling. Ongoing counseling on nutrition and physical activity may need to be tailored for people on weight management drugs, who should be advised about physical activity to mitigate the loss of lean muscle mass that occurs when a person loses weight quickly.[253]

Reauthorization criteria also will need to account for changes in health conditions over time. For example, a person would meet FDA-approved indications based on having a BMI of 27 and a weight-related comorbidity of type 2 diabetes, but after losing weight, those indications may no longer be present. Reauthorization criteria therefore may relate to maintaining weight loss from baseline so people whose health conditions improve do not lose access to coverage of the drugs.

Quantity Limits

Quantity limits may be set to limit the amount of a drug that is dispensed at a time. California Medicaid and Cigna both use quantity limits for weight management drugs. Because people may face difficulty tolerating these medications, state Medicaid programs could consider smaller quantity limits initially and larger quantity limits after tolerance has been established.

Step Therapy

Step therapy requires patients to try a therapeutically equivalent but lower-cost drug before being approved for a higher-cost drug.

Cost Sharing

State Medicaid agencies have the option to set copays, subject to maximum allowable cost-sharing limits (42 CFR 447.42, 42 CFR 447.53). States may choose to set higher copays for nonpreferred drugs (42 CFR 447.42, 42 CFR 447.53). A 2019 survey found that most state Medicaid programs have copays for some pharmacy benefits.[258]

Value-based Purchasing Approaches

State Medicaid agencies may find opportunities to negotiate with drug makers for additional rebates and program savings. A range of opportunities are available:

- Placing select drugs on the PDL, depending on the supplemental rebates available from the manufacturers.
- Collaborating with other agencies for joint procurement (e.g., in partnership with state employee health insurance). States that are interested in this approach may wish to review the State Medicaid Alternative Reimbursement and Purchasing Test for High-cost Drugs (SMART-D) series of briefs, especially the executive summary brief *Multi-agency Purchasing Framework for States*.[259] These briefs provide a framework and examples to inform development.
- Engaging through multistate purchasing pools. Many states have entered into purchasing pools to negotiate supplemental rebates.[258] If other states in the pool also wish to pursue

coverage of weight management drugs, there may be opportunities to use that purchasing power for leverage.

- Pursuing outcomes-based supplemental rebate contracts. CMS defines value-based purchasing arrangements as linking cost to effectiveness or payments to actual performance or expenses. 42 CFR 502. Increasingly, states are pursuing value-based arrangements for pharmacy, though development and negotiation can be time-consuming.[258]

Additional Considerations

As state Medicaid programs consider coverage of weight management drugs, they may want to review related benefits at the same time. Especially for children and adolescents, there may be opportunities to promote obesity prevention through support for nutrition and physical activity. Preventive interventions will require multisector collaboration with public health, education, and housing to reduce obesogenic pressures. For people who already have overweight or obesity, coverage considerations could include improving access to intensive behavioral interventions and considering coverage of and access to bariatric surgery.

If unsafe formulations of "generic" or compounded weight management drugs cause health problems in a state, then state Medicaid programs could consider partnering with their colleagues in pharmacy licensing and public health to help raise public awareness of risks associated with unapproved sales of "generic" or compounded semaglutide. Because the list price for a month's worth of semaglutide or liraglutide exceeds $1300, most people cannot afford these drugs without insurance coverage.[47] Some consumers order "generic" semaglutide from compounding pharmacies or other sources, even though no FDA-approved generic form of semaglutide exists.[260] Compounding pharmacies may sell semaglutide salts rather than the tested and FDA-approved form of semaglutide.[260] The FDA has expressed concern about the use of semaglutide salts and has warned patients that semaglutide salts may be unsafe when compounded into a semaglutide preparation.[261]

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Appendix A. Methods

Clinical Evidence Methods

Search Strategy

Researchers from the Center for Evidence-based Policy (Center) searched Drug Effectiveness Review Project (DERP) and Medicaid Evidence-based Decisions Project (MED) bibliographic databases and gray literature clinical evidence sources to identify randomized controlled trials (RCTs), nonrandomized studies, and systematic reviews (with and without meta-analyses) including the terms *overweight, obesity, excess weight, liraglutide, semaglutide, phentermine-topiramate, tirzepatide, setmelanotide, exenatide, dulaglutide*, and *naltrexone-bupropion*. We limited records retrieved to those studies focused on human subjects and published in the English language. We also used RCT, nonrandomized, and cost-effectiveness filters to limit records retrieved. Systematic reviews were used for reference list searching and not as evidence sources. All searches were conducted on February 3, 2023, with the exception of Lens.org, which was searched on May 5, 2023.

Bibliographic Databases

Database	Platform	Issue/Version	Total Number of Records Retrieved
CENTRAL and CDSR	Wiley	Issue 10 of 12, February 2023	2,979
MEDLINE ALL	Ovid	1946 to February 2023	4,212
EBM Reviews – NHS Economic Evaluation Database	Ovid	First Quarter 2016	18
SCOPUS	Elsevier	N/A	664
Lens.org[a]	N/A	N/A (searched May 5, 2023)	110

Note. [a] For cost-effectiveness studies only.

Abbreviations. CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; EBM: evidence-based medicine; N/A: not applicable; NHS: National Health Service.

Ovid MEDLINE ALL Search Strategy

1	exp Overweight/
2	obesity/ or obesity, abdominal/ or obesity, maternal/ or obesity, metabolically benign/ or obesity, morbid/ or pediatric obesity/
3	(obes* or overweight or "over weight").ti,ab,kf.
4	((excess* or high or unhealthy) adj3 (adipos* or weight or "body weight" or bodyfat or "body fat" or "body mass inde*" or BMI)).ti,ab,kf.
5	Weight Loss/
6	(weightloss or (weight adj3 (manag* or maintain* or loss))).ti,ab,kf.
7	1 or 2 or 3 or 4 or 5 or 6
8	exp Anti-Obesity Agents/
9	Liraglutide/
10	(liraglutide or saxenda* or NN2211 or "NN 2211" or "NN-2211").mp.
11	((phentermine adj3 topiramate) or Qsymia* or qsiva* or topiramate-phentermine or "phentermine-topiramate" or VI0521 or "VI 0521" or "VI-0521").mp.

12	((bupropion adj3 naltrexone) or contrave* or "bupropion-naltrexone" or CID11556075 or "CID 11556075" or "CID-11556075").mp.
13	(semaglutide or wegovy* or NN9535 or "NN 9535" or "NN-9535").mp.
14	(tirzepatide or mounjaro* or LY3298176).mp.
15	8 or 9 or 10 or 11 or 12 or 13 or 14
16	(setmelanotide or imcivree or BIM-22493 or RM-493 or IRC-022493).mp.
17	(random* adj3 assign*).ab. or ("clinical trial" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single* or doubl* or tripl* or treb* or quad*) adj1 (blind* or mask*))).ti,ab,kw. Or ("2 arm" or "two arm" or "3 arm" or "three arm" or "4 arm" or "four arm" or "5 arm" or "five arm").ti,ab,kw. Or quasi*.ti,ab.
18	(phase 3* or phase iii* or phase 4* or phase iv*).ti,ab. Or (placebo* or head-to-head or (compar* adj3 (effectiveness or efficacy))).ti,ab,kw. Or Comparative Effectiveness Research/ or (active adj1 (comparator* or control$1 or treatment*)).ti,ab.
19	17 or 18
20	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
21	19 or 20
22	(7 and 15 and 21) or 16
23	or/9-14,16
24	Economics/ or exp "costs and cost analysis"/ or Economics, Dental/ or exp economics, hospital/ or Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/
25	(economic* or cost$1 or costly or costing or price or prices or pricing or pharmacoeconomic* or health technology assessment* or hta or cost-effective* or cost-utility or cost utility or cost benefit* or cost-benefit* or value for money or value-for-money or budget* or (expenditure* not energy)).ti,ab,kf. or health technology assessment winchester england.jn. or ec.fs.
26	or/24-25
27	(((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. or (letter or editorial or historical article).pt.
28	26 not 27
29	23 and 28
30	22 or 29
31	limit 30 to english language
32	(animals/ not (animals/ and humans/)) or (bovine$1 or canine$1 or cat$1 or chimpanzee$1 or dog$1 or feline$1 or hen$1 or mice or monkey$1 or mouse or murine or pig$1 or porcine or rabbit$1 or rat or rats or rattus or rhesus or rodent$1 or zebrafish).ti.
33	31 not 32

CDSR and CENTRAL via the Cochrane Library Search Strategy

1	MeSH descriptor: [Overweight] explode all trees
2	MeSH descriptor: [Obesity] this term only
3	MeSH descriptor: [Obesity, Maternal] this term only
4	MeSH descriptor: [Pediatric Obesity] this term only
5	MeSH descriptor: [Obesity, Morbid] this term only
6	obese* OR overweight OR over weight
7	(excess* near/3 adipos*) OR (excess* near/3 weight) OR (excess* near/3 body weight) OR (excess* near/3 bodyweight) OR (excess* near/3 BMI) OR (excess* near/3 body mass inde*)
8	(high near/3 adipos*) OR (high near/3 weight) OR (high near/3 body weight) OR (high near/3 bodyweight) OR (high near/3 body fat) OR (high near/3 BMI) OR (high near/3 body mass inde*)
9	(unhealthy near/3 weight) OR (unhealthy near/3 body) OR (unhealthy near/3 body fat) OR (unhealthy near/3 BMI) OR (unhealthy near/3 body mass inde*)
10	MeSH descriptor: [Weight Loss] this term only
11	weightloss OR (weight near/3 manag*) OR (weight near/3 maintain*) OR (weight near/3 loss)
12	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13	MeSH descriptor: [Liraglutide] this term only
14	liraglutide OR Saxenda OR NN2211 OR NN 211 OR NN-2211
15	(phentermine near/3 topiramate) OR Qsymia OR qsiva OR topiramate-phentermine OR phentermine-topiramate OR VI0521 OR VI 0521 OR VI-0521
16	(buproprion near/3 naltrexone) OR contrave OR naltrexone-buproprion
17	semaglutide OR wegovy OR NN 9353
18	tirzepatide OR LY3298176
19	setmelanotide OR imcivree OR RM-493
20	13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21	12 AND 20
22	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
23	(glucacon-like peptide 1 near/3 agonist*) OR (glucagon-like peptide-1 near/3 agonist*) OR (glucagon-like peptide-1 near/3 analog*) OR (glucagon like peptide 1 near/3 agonist*) OR (glucagon like peptide 1 near/3 analog*)
24	(GLP1* near/3 agonist*) OR (GLP1* near/3 analog*) OR (GLP-1 near/3 agonist*) OR (GLP-1 near/3 analog*) OR (GLP 1 near/3 agonist*) OR (GLP 1 near/3 analog*)
25	Victoza
26	ozempic OR rybelsus
27	albiglutide OR tanzeum
28	dulaglutide OR LY05008 OR trulicity
29	MeSH descriptor: [Exenatide] this term only
30	exenatide OR TCA 650 OR ORMD-0901 OR byetta* OR bydureon bcise
31	lixisenatide or adlyxin
32	23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31
33	22 AND 32
34	33 NOT 21

EBM Reviews – NHS Economic Evaluation Database

For cost-effectiveness studies only.

1	Glucagon-Like Peptide 1/
2	(liraglutide or saxenda* or NN2211 or "NN 2211" or "NN-2211").mp.
3	((phentermine adj3 topiramate) or Qsymia* or qsiva* or topiramate-phentermine or "phentermine-topiramate" or VI0521 or "VI 0521" or "VI-0521").mp.
4	((bupropion adj3 naltrexone) or contrave* or "bupropion-naltrexone" or CID11556075 or "CID 11556075" or "CID-11556075").mp.
5	(semaglutide or wegovy* or NN9535 or "NN 9535" or "NN-9535").mp.
6	(tirzepatide or mounjaro* or LY3298176).mp.
7	(setmelanotide or imcivree or BIM-22493 or RM-493 or IRC-022493).mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7

Scopus

For cost-effectiveness studies only.

1. Article title, Abstract, Keyword: obes* OR overweight OR "over weight"
2. Article title, Abstract, Keyword: excess* W/3 adipos* OR weight OR "body weight" OR bodyweight OR bmi OR "body mass inde*" OR bmi OR "body fat"
3. Article title, Abstract, Keyword: high W/3 adipos* OR weight OR "body weight" OR bodyweight OR bmi OR "body mass inde*" OR bmi OR "body fat"
4. Article title, Abstract, Keyword: weight W/3 manag* OR maintain* OR loss
5. 1 OR 2 OR 3 OR 4
6. Article title, Abstract, Keyword: liraglutide OR saxenda OR nn2211 OR "NN 211"
7. Article title, Abstract, Keyword: phentermine W/3 topiramate
8. Article title, Abstract, Keyword: qsymia OR qsiva OR topiramate-phentermine OR phentermine-topiramate OR vi0521 OR "VI 0521" OR vi-0521
9. Article title, Abstract, Keyword: buproprion W/3 naltrexone
10. Article title, Abstract, Keyword: contrave OR naltrexone-buproprion
11. Article title, Abstract, Keyword: semaglutide OR wegovy OR "NN 9353"
12. Article title, Abstract, Keyword: tirzepatide OR ly3298176
13. Article title, Abstract, Keyword: setmelanotide OR imcivree OR rm-493
14. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. Article title, Abstract, Keyword: economic* OR cost$ OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "health technology assessment*" OR hta OR cost-effective* OR cost-utility OR "cost utility" OR "cost benefit*" OR cost-benefit* OR "value for money" OR value-for-money OR budget*
16. Article title, Abstract, Keyword: expenditure* AND NOT energy
17. 14 OR 15
18. 5 AND 14 AND 17

Lens.org

For cost-effectiveness studies only.

Search 1: (liraglutide OR saxenda* OR NN2211 OR "NN 2211" OR "NN-2211" OR Qsymia* OR qsiva* OR topiramate-phentermine OR "phentermine-topiramate" OR VI0521 OR "VI 0521" OR "VI-0521" OR naltrexone-bupropion OR contrave* OR "bupropion-naltrexone" OR CID11556075 OR "CID 11556075" OR "CID-11556075" OR semaglutide OR wegovy* OR NN9535 OR "NN 9535" OR "NN-9535" OR tirzepatide OR mounjaro* OR LY3298176) AND (obesity OR obese OR overweight OR "weight management") AND title:(costs OR cost OR cost-effectiveness OR pharmacoeconomic* OR QALY OR budget* OR economic* OR pricing OR "cost benefit" OR cost-benefit OR "health technology assessment" OR cost-utility OR "cost utility" OR QALY)

Search 2: (liraglutide OR saxenda* OR NN2211 OR "NN 2211" OR "NN-2211" OR Qsymia* OR qsiva* OR topiramate-phentermine OR "phentermine-topiramate" OR VI0521 OR "VI 0521" OR "VI-0521" OR naltrexone-bupropion OR contrave* OR "bupropion-naltrexone" OR CID11556075 OR "CID 11556075" OR "CID-11556075" OR semaglutide OR wegovy* OR NN9535 OR "NN 9535" OR "NN-9535" OR tirzepatide OR mounjaro* OR LY3298176) AND (obesity OR obese OR overweight OR "weight management") AND abstract:(costs OR cost OR cost-effectiveness OR pharmacoeconomic* OR QALY OR budget* OR economic* OR pricing OR "cost benefit" OR cost-benefit OR "health technology assessment" OR cost-utility OR "cost utility" OR QALY)

Gray Literature Sources

- Agency for Healthcare Research and Quality (AHRQ)
  - Effective Health Care (EHC) Program
  - Evidence-based Practice Centers (EPC) Reports
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Health Evidence Review Commission (HERC)
- Institute for Clinical and Economic Review/California Technology Assessment Forum (CTAF)
- IPD Analytics
- Veterans Administration Evidence-based Synthesis Program (VA-ESP)
- Washington Health Technology Assessment (WA HTA)

We used Google (DuckDuckGo) and Google Scholar for background and gray literature searches. We also searched AHRQ, CADTH, HERC, Institute for Clinical and Economic Review/CTAF, International HTA database, IPD Analytics, VA-ESP, and WA HTA to identify systematic reviews and gray literature using the search terms below.

Gray Literature Search Terms

antiobesity drugs
Bydureon BCise
Byetta
chronic weight management drugs
Contrave
dulaglutide
exenatide
GLP-1 agonists
Imcivree
liraglutide

lixisenatide
Mounjaro
naltrexone-bupropion
obesity drugs
Ozempic
phentermine-topiramate
Qsymia
Rybelsus
Saxenda
semaglutide
setmelanotide
tirzepatide
Trulicity
Victoza
Wegovy
weight loss drugs

Ongoing Studies

We searched the following DERP sources for ongoing studies using the search terms *overweight, obesity, dulaglutide, exenatide, liraglutide, naltrexone-bupropion, phentermine-topiramate, semaglutide, setmelanotide,* and *tirzepatide:*

- ClinicalTrials.gov
- International Clinical Trials Registry Platform (WHO)
- US Food and Drug Administration (FDA)
- Novo Nordisk (manufacturer of Ozempic, Saxenda, Victoza, and Wegovy)
- Orexigen Therapeutics (manufacturer of Contrave)
- Vivus (manufacturer of Qsymia)
- Rhythm Pharmaceuticals (manufacturer of Imcivree)
- Eli Lilly (manufacturer of Mounjaro and Trulicity)
- Astra Zeneca (manufacturer of Byetta and Bydureon BCise)
- Sanofi (manufacturer of Adlyxin)

Inclusion and Exclusion Criteria for Evidence Review

Study Component	Inclusion	Exclusion
Populations	• Adults who are overweight or obese (BMI ≥ 25 kg/m^2, or lower BMIs in specific groups [e.g., Japanese populations]) • Children who are overweight or obese (e.g., BMI > 85th percentile for sex and height) Additional criteria for setmelanotide only: • Individuals who are overweight or obese due to particular genetic variants resulting in proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) deficiency, Bardet-Biedl syndrome (BBS), or Alström syndrome	• Studies that included persons not classified as overweight or obese (i.e., weight classification not part of study eligibility criteria) • Pregnant and breastfeeding individuals • Secondary overweight or obesity due to other pharmacotherapy (e.g., clozapine for schizophrenia) or condition (e.g., hypothalamic tumors, brain injury)

Study Component	Inclusion	Exclusion
Interventions	FDA-approved pharmacological interventions for chronic weight management alone, in combination with another listed intervention, or in combination with other weight management interventions including diet and exercise, other lifestyle interventions, and metformin • Liraglutide (Saxenda) • Semaglutide (Wegovy) • Naltrexone and buproprion (Contrave) • Phentermine and topiramate (Qsymia) • Tirzepatide (Mounjaro/LY3298176) • Setmelanotide (Imcivree) Other GLP-1 agonists (or doses of the drug) that are FDA-approved for conditions other than obesity (i.e., diabetes) that are sometimes used off label for weight management • Liraglutide (Victoza) • Semaglutide (Ozempic, Rybelsus) • Dulaglutide (Trulicity) • Exenatide (Byetta, Bydureon BCise) • Lixisenatide (Adlyxin)	• Other FDA-approved or off-label use drugs or devices for weight loss (e.g., orlistat, SGLT2 inhibitors, superabsorbent hydrogel) • Included drugs as fixed-ratio combinations with other drugs (e.g., IdegLira, LexiLan)
Comparators	• Another listed intervention (head-to-head) • Standard of care, including other medical management approaches (e.g., orlistat, metformin) • Lifestyle interventions (e.g., diet, physical activity, counseling, education) • Surgery and other interventional procedures or devices (e.g., bariatric surgery, superabsorbent hydrogel) • Placebo	• Studies without a comparator intervention • Studies with indirect comparisons (e.g., historical controls) • Other GLP-1 agonists not approved for diabetes or chronic obesity
	Additional criteria for setmelanotide only: • No treatment	No additional information

Outcomes	Efficacy
	• Body weight
	• Percent change in weight
	• Proportion with at least 5%, 10% weight loss
	• Change in BMI
	• Duration (e.g., months, years) of weight or BMI change
	• Change in weight-related comorbidities:
	  o Type 2 DM: HbA1c
	  o Risk factors for CVD: LDL, blood pressure
	  o Change in medication use for weight-related comorbidities (e.g., insulin, antihypertensives)
	• Health-related QoL (e.g., validated instruments
	Safety
	• AEs
		• Other weight-related comorbidities not listed, including those for cancer, chronic kidney disease
		• Change in adiposity using research instruments or methods (e.g., DEXA scan, bioelectrical impedance measures)
		• Unvalidated questionnaires to measure QoL

Study Component	Inclusion	Exclusion
	• SAEs • Discontinuation of treatment due to AEs Costs and cost-effectiveness • Health care utilization and cost • Frequency of hospitalization • Hospital LOS • Frequency of primary care visits • Total costs of care • Other cost-effectiveness outcomes (ICERS, QALYs)	
Setting	• Any clinical setting in countries categorized as very high on the United Nations Human Development Index • US setting only for cost data and analysis studies	• Nonclinical settings (e.g., studies in healthy volunteers, animal models of disease) • Countries categorized other than very high on the United Nations Human Development Index • Non-US settings for cost data and analysis studies

Study design	• RCTs with a duration of at least 12 months with these exceptions:
	  o At least 6 months for studies in pediatric participants or persons with type 1 DM
	  o Phase 3 or higher unless none are identified for drug of interest
	• Prospective NRSs with a duration of at least 24 months and a minimum sample size of 100 participants
	• Cost-effectiveness studies and other formal comparative economic evaluations with US perspective or setting
	Additional criteria for setmelanotide only:
	• NRSs for the effectiveness and harms with no size or duration limit
	• Single-arm studies
		• Abstracts, conference proceedings, posters, editorials, letters
		• Qualitative studies
		• Phase 1 and phase 2 studies unless phase 3 and higher are not identified for the particular intervention
		• Cost-effectiveness studies from non-US countries or older than in past 5 years

Publication	• Studies in peer-reviewed journals, technology assessments, or publicly available reports • Published in English • Cost-effectiveness studies published within the past 5 years	• Studies not peer-reviewed • Studies that cannot be located • Studies in languages other than English • Studies in non-human animals

Abbreviations. AE: adverse event; BMI: body mass index; CVD: cardiovascular disease; DEXA: dual x-ray absorptiometry; DM: diabetes mellitus; FDA: US Food and Drug Administration; GLP-1: glucagon-like peptide; HbA1c: hemoglobin A1C; ICER: incremental cost-effectiveness ratio; LDL: low-density lipoprotein cholesterol; LOS: length of stay; NRS: nonrandomized study; QALY: quality-adjusted life year; QoL: quality of life; RCT: randomized controlled trial; SAE: serious adverse event; SGLT2: sodium-glucose cotransporter-2.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which there was disagreement about eligibility, a third experienced

researcher resolved the disagreement. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way using DistillerSR.[262] A second experienced researcher reviewed all the data entered. We attempted to resolve discrepancies through discussion. When discussion did not resolve the issue, a third experienced researcher settled disagreements.

Participant Characteristics and Association with Outcomes

When discussing risk and protective factors or variables in statistical models in DERP research products, in almost all cases, we are referring to associations of participant characteristics with outcomes, and not causation of outcomes. This is important because participant characteristics, such as race and ethnicity, serve as proxy or surrogate measures for underlying etiological factors not measured or evaluated in analyses. Etiological factors that might cause differences in outcomes for subgroups of participants could include systemic racism or other forms of systemic discrimination, stress, poverty, housing instability, or epigenetics. For example, by describing any differences in outcomes by race and ethnic groups, we are noting observed associations; these associations are not caused by biological determinants of being Black, White, or Hispanic.

Risk-of-Bias Assessment

We assessed the risk of bias (RoB) of the included RCTs and nonrandomized studies using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for.[263-266] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the RoB of a study, a third rater resolved the disagreement.

Randomized Controlled Trials

Low-RoB RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low drop-out rates; and intention-to-treat analyses. Low-RoB RCTs also have low potential for bias from conflicts of interest and funding source(s). Moderate-RoB RCTs have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-RoB RCTs have clear flaws that could introduce significant bias.

Quasi-experimental Studies

Low-RoB quasi-experimental studies have a control group that is unexposed to the intervention being studied; methods are in place to prevent contamination bias; pre- and post-measures are done concurrently; and participant characteristics are balanced between groups or controlled for by propensity scores, by statistical adjustment, or both. Moderate-RoB quasi-experimental studies have incomplete information about methods that might mask important limitations, a meaningful conflict of interest, or are at risk for contamination bias. High-RoB quasi-experimental studies do not have a control group (i.e., before and after studies or interrupted time series) or have other clear flaws that could introduce significant bias.

Cost-Effectiveness Studies

Low-RoB cost-effectiveness studies include a clear description of the target population, analytic perspective, and justifiable time horizon; comparators and modeling methods are described, appropriate, and tested for uncertainty, with sound effectiveness, cost and health utility input data. Low-RoB cost-effectiveness studies also have relevant and sound outcomes and low potential for bias from conflicts of interest and funding source(s). Moderate-RoB cost-effectiveness studies might include model input data that could bias results, time horizons that burden general assumptions, and incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-RoB cost-effectiveness studies have a clear, high RoB that would affect findings.

Certainty-of-Evidence Assessment

We assigned each outcome a summary judgment for the overall certainty of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[267,268] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall certainty of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Meta-analyses

Meta-analyses were performed using RevMan 5.4[51] for major outcomes with sufficient published data from studies that were assessed for RoB and that evaluated the effectiveness and harms of pharmacologic agents for weight management.

Cost-effectiveness Study Definitions and Assessment

Cost-effectiveness studies evaluate the balance between the costs and benefits of a health care intervention. They answer the question, "How much health benefit do we get for our money?"[269] Definitions of measures commonly used in cost-effectiveness analyses include:

- **Cost-effectiveness ratio (CER):** The ratio of dollars spent on an intervention compared to the health or societal benefit obtained.
- **Quality-adjusted years of life (QALY):** Life years gained from an intervention with judgments about the quality of life years gained, used to measure the value of health outcomes.[270] One QALY is 1 year of life multiplied by the utility associated with that life. The utility of a health state is expressed on a scale ranging from 0 to 1, where 0 represents the utility of the state "dead," and 1 represents the utility of the state "perfect health."[271] For example, a year with cirrhosis is a less desirable state and has a QALY of 0.76 compared to living without hepatitis C virus, which has a QALY of 1.0.[272]
- **Incremental cost-effectiveness ratio (ICER):** The ratio of the change in costs to the change in health benefits between two alternative treatments.[273] This results in a single metric of cost per life year gained when using one intervention over another.
- **Willingness-to-pay threshold:** A maximum financial investment an entity (society, country or region, organization) is willing to invest to give a patient an additional QALY.[274]

Since the 1990s, many researchers and policymakers have used the benchmark of $50,000 per QALY gained as a subjective threshold for defining cost-effective care or care that is a good value.[269] Because of increases in health care expenditures and per capita annual incomes in more recent times, many economists argue $50,000 per QALY is too low, and cost-effectiveness studies are now reporting willingness-to-pay thresholds of $100,000 per QALY or higher.[275] Neumann et al., suggested organizations consider multiple thresholds, including $50,000, $100,000, and $200,000 per QALY instead of relying on a single benchmark, and balance the decision based on other factors including the budget available for other needs and demands of the population it serves.[275] For this report, Center researchers summarized cost-effectiveness designations across multiple willingness-to-pay thresholds and described the raw cost per QALY findings when possible to allow Medicaid administrators make their own judgments about the preferred willingness-to-pay threshold that reflects their constraints.

Policy Methods

Search Strategy

We conducted a search of MED and DERP policy sources to identify relevant policy briefs, national policy summaries, laws, regulations, and guidance using the terms M*edicaid "weight loss" drug*; drug names (*wegovy, saxenda, liraglutide, semaglutide, contrave, bupropion and naltrexone, qsymia, phentermine, setmelanotide, imcivree, tirzepatide, mounjaro*) alone and in combination with *Medicaid*; *Medicaid "weight management"*; *obesity*; *weight loss*; *antiobesity medication*; *antiobesity*; *anti-obesity*; and *antiobesity drug.* Additionally, we conducted DuckDuckGo searches using the terms *Medicaid coverage "weight management" drugs*; *obesity "treatment pathway"*; *clinical guidelines for obesity treatment*, and *obesity medicine professional society guidelines*, and we reviewed key sources from reference lists. For state-specific coverage policies, we searched state websites and provider manuals for California, Louisiana, Michigan, Mississippi, Oregon, Texas, Washington, Wisconsin, and Virginia.

We also interviewed Medicaid officials in 5 states and 3 subject matter experts.

We searched for major private payer policies using the following sources: private payer websites including Aetna, Cigna, and Anthem. Search terms used include *liraglutide, semaglutide, contrave, qsymia, imcivree, tirzepatide, bupropion and naltrexone, phentermine and topiramate,* and *setmelanotide.* We searched the US Office of Personnel Management website and carrier letters for *anti-obesity*.

Policy Sources Searched

- AcademyHealth
- Alliance for Health Policy
- American Public Human Services Association
- Arnold Ventures
- Association of State and Territorial Health Officials
- Bipartisan Policy Center
- Center for Budget and Policy Priorities
- Center for Health Care Strategies, Inc.
- Center for Public Health Law Research
- Centers for Disease Control and Prevention (CDC)
- Centers for Medicare & Medicaid Services (CMS)
- Center for Medicare & Medicaid Innovation (CMS Innovation Center)
- Commonwealth Fund
- Congress.gov
- Drugs.com
- Federal Register
- Guidelines International Network
- Health Affairs Blog
- Health Resources and Services Administration (HRSA)
- Health Systems Evidence (McMaster University)

- Henry J. Kaiser Family Foundation
- Institute for Medicaid Innovation
- IPD Analytics
- Manhattan Institute
- Mathematica Policy Research
- Medicaid and CHIP Payment and Access Commission (MACPAC)
- Medicare Payment Advisory Commission (MedPAC)
- Milbank Memorial Fund
- National Academy for State Health Policy
- National Academies of Sciences, Engineering, and Medicine
- National Academy of Insurance Commissioners
- National Association of State Budget Officers
- National Association of State Medicaid Directors
- National Conference of State Legislatures
- National Governors Association
- National Health Law Program
- Pew Charitable Trusts
- RAND Corporation
- Robert Wood Johnson Foundation
- State Health & Value Strategies
- Urban Institute
- US Code
- US Code of Federal Regulations (CFR)
- US Department of Health and Human Services, Appeals Board Drug Coverage Determination Decisions
- US Department of Health and Human Services, Office of Inspector General
- US Department of Health and Human Services, Office of Minority Health
- US Federal Register
- US Food and Drug Administration (FDA)
- US Government Accountability Office (GAO)
- US Preventive Services Task Force (USPSTF)

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Appendix B. Characteristics of Included Studies for Effectiveness and Harms

Table B1. Study Characteristics of Included Trials

Name; Author, Yr Number; Design N Randomized Location	Interventions (n) Titration Schedule Duration + Follow-up	Key Participant Inclusion/Exclusion Criteria	Run-In	Background Treatment(s)
Semaglutide vs. liraglutide				
STEP 8[55] Rubino et al., 2022 NCT04074161 RCT – open-label for active treatments; blinded to placebo N = 338 US	• SC semaglutide 2.4 mg weekly (126) • SC liraglutide 3.0 mg daily (127) • Placebo (85) Semaglutide: • Initiated at 0.25 mg and escalated in fixed-dose regimen every 4 weeks until target dose reached Liraglutide: • Initiated at 0.6 mg and escalated by 0.6 mg weekly until target dose reached ○ 68 weeks + 7 weeks (AEs and pulse only summarized at 75 weeks as descriptive stats only)	Inclusion • Age ≥ 18 years • BMI ≥ 30.0 kg/m² or ≥ 27.0 kg/m² with the presence of at least 1 of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, OSA, or CVD. • History of at least 1 self-reported unsuccessful dietary effort to lose body weight Exclusion • HbA1c ≥ 6.5% (48 mmol/mol) • History of T1DM or T2DM • Treatment with glucose-lowering agent(s) within 90 days before screening • A self-reported change in body weight > 5 kg (11 lb) within 90 days before screening • Treatment with any medication for the indication of obesity within the past 90 days before screening • Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening; (2) lap banding, if the band has been removed > 1 year before screening; (3) intragastric balloon, if the balloon has been removed > 1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year before screening. • Uncontrolled thyroid disease	None	Diet and exercise • Counseling on diet (500 kcal daily deficit) and physical activity (minimum 150 minutes per week)

Liraglutide				
Elkind-Hirsch et al., 2020[66] NCT01234649 RCT N = 153 US	• SC liraglutide 1.8 mg daily (78) • Placebo (75) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 80 to 84 weeks randomized	Inclusion • Postpartum nonpregnant, nondiabetic overweight (BMI ≥ 25) female participants • Aged 18 years to 45 years of age • Experienced GDM during index (within 12 months) pregnancy • Willing to use effective contraception • Not breastfeeding for at least 3 months • Presented with metabolic abnormalities on their postpartum OGTT (inclusive of insulin resistance, impaired beta cell response and glucose intolerance) Exclusion: • Persons with diabetes • Current history of smoking • Taking drugs that affect gastrointestinal motility, carbohydrate metabolism, and lipid-lowering and/or antiobesity drugs within 3 months of the study	None	Diet and exercise • Standardized dietary advice and appropriate written information on a balanced weight-reducing diet and daily exercise (such as walking, using stairs) Metformin • Metformin 2,000 mg per day • Metformin extended-release was initiated at dose 500 mg daily (with dinner) for 2 weeks and increased to 500 mg twice daily (breakfast and dinner) for 2 weeks. The dose was increased to 500mg am, 1000mg pm (with breakfast and dinner) for 2 weeks and then increased to the final dose of 2,000 mg
Ellipse[71] Tamborlane et al., 2019 NCT01541215 RCT N = 135 US, Canada + 33 countries in Europe, Central America, South America, Asia, Africa, and Australia	• SC (up to) liraglutide 1.8 mg daily (66) • Placebo (69) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached as tolerated 26 weeks randomized + 26 open-label (those on placebo discontinued injection but stayed on metformin)	Inclusion • Children and adolescents between the ages of 10 to 17 years • Diagnosis of T2DM and treated for at least 90 days with diet and exercise alone, or diet and exercise in combination with metformin monotherapy • The metformin and/or basal insulin) dose must be stable for at least 30 or 60 days (respectively) prior to screening • HbA1c ≥ 7.0% and ≤ 11% if diet and exercise treated, or ≥ 6.5% and ≤ 11% if treated with metformin • BMI > 85th percentile of the general age and gender matched population *To be randomized, participants had to achieve fasting plasma glucose level between 126 mg and 220 mg per deciliter (7.0 mmol and 12.2 mmol per liter) and with a stable metformin*	Duration 11 to 12 weeks Description 3 to 4 weeks titration of metformin to maximum dose tolerated (between 1,000 and 2,000 mg per day), followed by 8 weeks of	Diet and exercise • Counseling according to local standards Metformin • Maintenance dose after run-in, with or without basal insulin Other • Those who were treated with basal insulin reduced their doses by 20% at the time of randomization; after completion of intervention dose-

		dose (in most patients, 1,000 mg to 2,000 mg per day) for at least 8 weeks Exclusion • T1DM • Maturity-onset diabetes of the young • A fasting C-peptide level of less than 0.6 ng per milliliter, or antibodies against insulinoma-associated 2 or glutamic acid decarboxylase • The use of any antidiabetic agent other than metformin or basal insulin within 90 days before screening • A history of pancreatitis • Serum calcitonin levels of 50 ng or more per liter • A personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 • An alanine aminotransferase level 2.5 times the upper limit of the normal range or higher • Serum creatinine levels greater than the upper limit of the normal range for age • A recent history of heart disease, proliferative retinopathy or maculopathy; and recurrent severe hypoglycemia or hypoglycemic unawareness	metformin maintenance	escalation basal insulin could be increased to no more than baseline level
Ghanim et al., 2020[67] NCT01753362 RCT N = 84 US	• SC liraglutide 1.8 mg daily (42) • Placebo (42) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 26 weeks randomized	Inclusion: • T1DM on continuous subcutaneous insulin infusion (i.e., insulin pump) or multiple (four or more) injections of insulin per day • Using CGM device or regularly measuring their blood sugars four times daily • HbA1c of less than 8.5% • Age 18-75 years • BMI≥ 25kg/m^2 • Age at diagnosis of T1DM should be < 30 years Exclusion: • T1DM for less than 6 months • Coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery or coronary angioplasty) in the previous four weeks • Hepatic disease (transaminase > 3 times normal) or cirrhosis • Renal impairment (serum eGFR < 30ml/min/1.73 m^2) • HIV or Hepatitis B or C positive status, history of pancreatitis, gastroparesis, or thyroid carcinoma	Duration 2 weeks Description Baseline testing and monitoring	All participants on basal insulin • Insulin titrations were carried out every 2 to 4 weeks throughout the study and in all patients to target blood sugars between 70 and 180 mg/dL

		• Use of any agent other than insulin for treatment of diabetes (metformin, pramlintide or thiazolidinediones) • Pregnancy or breastfeeding		
Kelly et al., 2020[60] NCT02918279 RCT N = 251 US, Belgium, Mexico, Russia, Sweden	• SC liraglutide 3.0 mg daily (125) • Placebo (126) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks randomized + 26 weeks off treatment	Inclusion: • Pubertal adolescents (12 to < 18 years of age) • Obesity (BMI ≥ 30 kg/m² and ≥ 95th percentile for age and sex) • Stable body weight > 90 days before screening • Poor response to lifestyle therapy alone • Adolescents with T2DM were eligible Exclusion: • Pre-pubertal individuals • T1DM • Body weight ≤ 60 kg • Calcitonin ≥ 50 ng/L • Secondary causes of obesity • Treatment with medications within 90 days before treatment that may cause significant weight change • Antidiabetic treatment other than metformin • Previous surgical treatment or other diet attempt treatments (herbal, OTC medications, organized weight reduction programs)	Duration 12 weeks Description Lifestyle counseling for healthy nutrition and physical activity for weight loss	Diet and exercise • Individualized counseling in healthy nutrition that was performed by a certified dietician • Participants were encouraged to engage in 60 minutes of moderate- to high-intensity physical activity daily
LIDO[72] Dubé, 2017 NCT01787916 RCT crossover N = 15 Canada	• SC liraglutide 1.8 mg daily (15) • Placebo (15) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg after 7 to 10 days (upon tolerance) until target dose reached 24 weeks randomized	Inclusion • Adults with T1D duration who had been treated for more than 5 years with insulin (multiple daily injections or continuous subcutaneous insulin infusion) • Non-smoking • Aged between 18 and 50 years • Without major diabetes-related complications • BMI ≥ 25 kg/m² Exclusion • HbA1c > 8.5% • Personal or familial history of medullary thyroid cancer, pancreatitis, CVD, and gastroparesis.	None	All participants were on insulin • Insulin doses were reduced by 10% to 15% at randomization and then adjusted in accordance with self-measured blood glucose
LIRA-1 Dejgaard et al., 2016[69] NCT01612468 RCT	• SC liraglutide 1.8 mg daily (50) • Placebo (50) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg	Inclusion • Diagnosed with T1DM in accordance with WHO criteria for more than 1 year • Aged 18 years or older • With a BMI more than 25 kg/m² and HbA1c more than 8% (64 mmol/mol).	None	All participants were on insulin (no required type and frequency of insulin use) Insulin type was not allowed to change after randomization

N = 100 Denmark	weekly until target dose reached 24 weeks randomized	Exclusion • Insulin pump treatment • Hypoglycemia unawareness • Gastroparesis • Impaired kidney function • Liver disease with raised alanine aminotransferase more than three times the upper normal range • History of pancreatitis • Pregnancy or lactation		
LOSEIT[64] Gudbergsen et al., 2021 NCT02905864 RCT N = 156 Denmark	• SC liraglutide 3.0 mg daily (80) • Placebo (76) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 52 weeks randomized	Inclusion: • Clinical diagnosis of knee OA • Age ≥ 18 years and < 75 years • BMI ≥ 27 kg/m^2 • Stable body weight during the previous 3 months • Motivated for weight loss *To be randomized, participants had to achieve ≥ 5% weight loss after run-in period* Exclusion: • Ongoing participation, or participation within the last 3 months, in an organized weight loss program • Current or history of treatment with medications that may cause significant weight gain for at least 3 months before this trial • Current use or use within three months before this trial of GLP-1 receptor agonist, pramlintide, sibutramine, orlistat, zonisamide, topiramate, or phentermine • T1DM • T2DM treated with glucose-lowering drugs other than metformin • Alloplasty in target knee joint • End stage disease in target knee joint • Pregnancy, breastfeeding	Duration 8 weeks Description Intensive supervised weight loss program with counseling and low-calorie formula diet from Cambridge Weight Plan (800 to 1,000 kcal per day)	Intensive diet therapy • Those successful with ≥ 5% weight loss during 8-week run-in period continued a tapering dietary intervention for 8 weeks (week 0 to 8) and were randomized to liraglutide or placebo for 52 weeks • The initial 8 weeks after randomization included a dietician-led partial reintroduction of regular meals in combination with formula diet products; all participants (irrespective of random assignment) were scheduled for group sessions every second week • No dietary consultancies were offered after week 8, but patients were instructed to aim for 1,200 kcal/d from week 0 to 8 and for an intake of 1,500 kcal/d from week 8 to 52 • Patients were offered 1 to 2 daily meal replacements with a formula diet from week 8 to 52
SCALE Diabetes[57]	• SC liraglutide 3.0 mg daily (423)	Inclusion • Diagnosed with T2DM (HbA1c level 7.0%-10.0%)	None	Diet and exercise

Davies et al., 2015 NCT01272232 RCT N = 846 US, France, Germany, Israel, South Africa, Spain, Sweden, Turkey, United Kingdom	• SC liraglutide 1.8 mg daily (211) • Placebo (212) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks + 12 weeks observational off-drug period	• Overweight or obese (BMI ≥ 27.0) adults (age ≥ 18 years) • With stable body weight (< 5 kg change in the last 3 months) • Treated with diet and exercise alone, or in combination with 1 to 3 oral hypoglycemic agents (metformin, thiazolidinedione, sulfonylurea) Exclusion • Treatment with GLP-1 receptor agonists (including liraglutide or exenatide), dipeptidyl peptidase-4 (DPP-4) inhibitors, or insulin, within the last 3 months prior to screening • Recurrent major hypoglycemia or hypoglycemic unawareness • Use of any drug (except for metformin, sulfonylurea or glitazone), including investigational drugs, which in the investigator's opinion		• Monthly counseling to increase their physical activity to at least 150 minutes of brisk walking per week and to reduce their daily energy intake to 500 kcal below their individualized daily total energy requirements, with food diary
SCALE IBT[63] Wadden et al., 2020 NCT02963935 RCT N = 282 US	• SC liraglutide 3.0 mg daily (142) • Placebo (144) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks	Inclusion • Eligible participants were aged ≥ 18 years, with stable body weight (maximum 5-kg self-reported weight change within 90 days before screening) and BMI ≥ 30 kg/m^2 Exclusion • Glycated hemoglobin (HbA1c) ≥ 6.5% • T1DM or T2DM • Use of medications (in the past 90 days) known to induce significant weight loss or gain • Inadequately treated hypertension • Pregnancy or breastfeeding • History of CVD, severe congestive heart failure, second-degree or greater heart block, medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pancreatitis, major depressive disorder within the past 2 years • History of suicide attempt, or malignancy within the past 5 years	None	Intensive behavioral therapy • IBT program followed an abbreviated lifestyle counseling protocol adapted from the Diabetes Prevention Program • Participants who weighed < 91 kg (< 200 lb) at randomization were prescribed 1,200 calories daily; for those who weighed 91 to 136 kg (200 to 300 lb) daily calories calculated by body weight (lb) × 6 (kcal/lb), and participants who weighed > 136 kg (> 300 lb) were prescribed 1,800 calories daily • All participants were initially prescribed 100 minutes per week of moderate-intensity physical activity (e.g., brisk walking); physical activity

				was increased by 25 minutes every 4 weeks, with an ultimate goal of 250 minutes per week
SCALE Insulin[59] Garvey et al., 2020 NCT02963922 RCT N = 396 US, Canada, Germany, Israel, Italy, Mexico, Turkey	• SC liraglutide 3.0 mg daily (198) • Placebo (198) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks randomized	Inclusion • Diagnosed with T2DM with an HbA1c ≥ 6.0 to ≤ 10% (42 to 86 mmol/mol) at screening • Receiving stable treatment with any basal insulin (≥ 90 days; no requirement for minimum or maximum dose) and ≤ 2 oral antidiabetic agents • Aged ≥ 18 years with a BMI of ≥ 27 kg/m^2, stable body weight (maximum 5 kg self-reported weight change within 90 days before screening) Exclusion • T1DM • Recurrent severe hypoglycemic episodes within the last year • Use of dipeptidyl peptidase 4 inhibitors, GLP-1 receptor agonists, bolus insulin, or medications known to induce significant weight change in the previous 90 days • Recent history of cardiovascular event or medullary thyroid carcinoma or multiple • Endocrine neoplasia type 2 • Pregnancy, breastfeeding, or intention to become pregnant • History of pancreatitis	None	Intensive behavioral therapy • Physical activity, reduced energy intake and behavioral counseling, and was based on an abbreviated version of the Diabetes Prevention Program counseling • Behavioral counseling of 23 individual or group sessions over 56 weeks; increased physical activity was of moderate intensity, starting at 100 min/week, and increasing by 25 minutes every 4 weeks to a recommended 250 min/week; energy intake was reduced to 1,200 kcal in individuals < 200 lb, to the sum of body weight (lb) x 6 (kcal/lb) in individuals 200 to 300 lb in weight, or to 1,800 kcal for those > 300 lb All participants on basal insulin • Not to exceed the entry dose within the first 5 weeks • Recommended to reduce basal insulin dose by 15% to 20% • Insulin dose adjusted based on self-measured blood glucose values
SCALE Maintenance[62] Wadden et al., 2013	• SC liraglutide 3.0 mg daily (212)	Inclusion • BMI ≥ 30 kgm-2, or BMI ≥ 27 kgm-2 with presence of comorbidities of treated or untreated dyslipidemia	Duration 4 to 12 weeks	Diet and exercise • At randomization, participants were

NCT00781937 RCT N = 422 US, Canada	• Placebo (210) 56 weeks randomized + 12 weeks off treatment	and/or hypertension. Untreated dyslipidemia was defined as LDL cholesterol ≥ 160 mgdl-1, or triglycerides ≥ 150 mgdl-1, or high-density lipoprotein (HDL) < 40 mgdl-1 for men and < 50 mgdl-1 for women. Untreated hypertension was defined as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg. • Stable body weight during the previous 3 months (< 5 kg self-reported weight change) • Age ≥ 18 years • Previously undergone dietary weight loss and not able to maintain reduced weight *To be randomized, participants had to achieve ≥ 5% weight loss after run-in period* Exclusion • Diagnosis of T1DM or T2DM • Fasting plasma glucose ≥ 7 mmol/L at run-in (week 12) • Treatment with GLP-1 receptor agonists or medications causing significant weight gain/loss • Bariatric surgery • History of idiopathic acute or chronic pancreatitis, major depressive disorder or other severe psychiatric disorders; or clinically significant active CVD	Description Low-calorie diet (1,200 to 1,400 calories per day) with up to 3 liquid meal replacements per day, in-person and telephone lifestyle counseling including exercise	prescribed a 500 kcal per day deficit diet, based on estimated 24-hour energy expenditure (liquid meal replacements not recommended) • Participants were instructed to continue the recommended physical activity • Face-to-face lifestyle counseling visits (15 to 20 minutes) were provided for a total of 17 visits over 56 weeks
SCALE Obesity and Prediabetes Pi-Sunyer et al., 2015[56] Kolotkin et al., 2016[61] le Roux et al., 2017[58] Kolotkin et al., 2018[68] NCT01272219 RCT N = 3,731 US, Canada + 25 countries in Europe, Central America, South America, Asia, Africa, and Australia	• SC liraglutide 3.0 mg daily (2,487) • Placebo (1,244) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks randomized + 104 weeks for those with prediabetes at baseline (n = 2254) At week 56, participants assigned to liraglutide and were without prediabetes at baseline were randomized to	Inclusion: • Aged ≥ 18 years • Stable body weight, preceding failed dietary effort • BMI ≥ 30, or ≥ 27 if the patient had treated or untreated dyslipidemia or hypertension Exclusion: • T1DM or T2DM • Medications that cause clinically significant weight gain or loss • Previous bariatric surgery • History of pancreatitis, major depressive or other severe psychiatric disorders • HbA1c ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dl • Family or personal history of multiple endocrine neoplasia syndrome type 2 or familial medullary thyroid carcinoma	None	Diet and exercise • Counseling on diet (500 kcal daily deficit) and physical activity (minimum 150 minutes per week), with 3-day lifestyle diary every other month.

	remain on liraglutide or to PBO and followed for an additional 12-weeks			
S-LiTE[65] Lundgren et al., 2021 NCT04122716 RCT N = 195 Denmark	• Exercise + SC liraglutide 3.0 mg daily (49) • SC liraglutide 3.0 mg daily (49) • Placebo (49) • Exercise (48) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 52 weeks randomized	Inclusion: • BMI 32 to 43 (kg/m^2) • Age > 18 and < 65 years • Safe contraceptive method *To be randomized, participants had to achieve ≥ 5% weight loss after run-in period* Exclusion: • Diagnosed with known serious chronic illness including T1DM or T2DM (or a randomly measured fasting plasma glucose > 7 mmol/l), angina pectoris, coronary heart disease, congestive heart disease, severe renal or hepatic impairment, IBD, among other conditions • Pregnancy, expecting pregnancy or breastfeeding	Duration 8 weeks Description Meal replacement therapy diet plan (800 calories per day)	Diet therapy • All participants attended 12 one-on-one consultations with measurement of body weight and dietetic support complying with Danish authorities' dietetic recommendations of sustained weight loss
Semaglutide				
STEP 1 Wilding et al., 2021[80] Wilding et al., 2022[77] NCT03548935 RCT N = 1,961 US, Canada + 14 countries in Asia, Europe, and South America	• SC semaglutide 2.4 mg weekly (1,306) • Placebo (655) Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 68 weeks + 7 weeks off treatment 52-week extension trial off treatment for subgroup who completed treatment throughout primary study	Inclusion • Age ≥ 18 years • BMI ≥ 30.0 or ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, OSA, or CVD • History of at least one self-reported unsuccessful dietary effort to lose body weight Exclusion • Diabetes • Glycated hemoglobin level of 48 mmol per mole (6.5%) or greater History of chronic pancreatitis, acute pancreatitis within 180 days before enrollment, previous surgical obesity treatment, and use of antiobesity medication within 90 days before enrollment method	None	Diet and exercise • Participants received individual counseling sessions every 4 weeks on reduced-calorie diet (500 kcal deficit per day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (with 150 minutes per week of physical activity, such as walking, encouraged) Food and activity diary was reviewed during counseling sessions
STEP 2 Davies et al., 2021[75] NCT03552757 RCT N = 1,210	• SC semaglutide 2.4 mg weekly (404) • SC semaglutide 1.0 mg weekly (403) • Placebo (403)	Inclusion • Diagnosed with T2DM • Age ≥ 18 years • BMI ≥ 27 kg/m^2 • History of at least one self-reported unsuccessful dietary effort to lose body weight • Diagnosed with T2DM ≥ 180 days prior to screening	None	Diet and exercise • Counseling for diet (500 kcal daily calorie reduction) and physical activity (150 minutes per week) with lifestyle change diary

US, Argentina, Canada, Germany, Greece, India, Japan, Russia, South Africa, Spain, United Arab Emirates, United Kingdom	Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 68 weeks	• HbA1c of 7% to 10% (53 to 86 mmol/mol) • Managed with diet and exercise alone, or treated with a stable dose of up to three oral glucose-lowering agents (metformin, sulfonylureas, SGLT2 inhibitors, or thiazolidinediones) for at least 90 days before screening Exclusion • Self-reported change in body weight > 5 kg within 90 days before screening • Previous or planned (during the trial period) obesity treatment with surgery or a weight-loss device • Pregnant, breastfeeding individuals or those who intending to become pregnant, or is of childbearing potential and not using a highly effective contraceptive method		
STEP 3 Wadden et al., 2021[73] NCT03611582 RCT N = 611 US	• SC semaglutide 2.4 mg weekly (407) • Placebo (204) Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 68 weeks + 7 weeks off treatment	Inclusion • 18 years or older • 1 or more unsuccessful dietary efforts to lose weight • BMI of 27 or higher with at least 1 weight-related comorbidity (CVD, dyslipidemia, hypertension, or OSA) or BMI of 30 or higher Exclusion • With diabetes, glycated hemoglobin levels of 6.5% or more (≥ 48 mmol/mol), self-reported bodyweight change greater than 5 kg within 90 days before screening, or prior or planned obesity treatment with surgery or a weight loss device • Treatment with glucose-lowering agent(s) or any medication for the indication of obesity within 90 days before screening Uncontrolled thyroid disease	None	Intensive behavioral therapy • For the first 8 weeks after randomization, participants received a low-calorie diet (1,000 to 1,200 kcal/d) provided as meal replacements (e.g., liquid shakes, meal bars, portion-controlled meals [provided by Nutrisystem, supplied by the sponsor]) • Participants subsequently transitioned to a hypocaloric diet (1,200 to 1,800 kcal/d) of conventional food for the remainder of the 68 weeks, with prescribed calorie intake based on randomization body weight At randomization, participants were prescribed 100 minutes of physical activity per week (spread across 4 to 5 days), which increased by 25 minutes every 4 weeks, to reach 200

				min/wk participants were provided with 30 individual intensive behavioral therapy visits with a registered dietitian, who instructed them in diet, physical activity, and behavioral strategies
STEP 4[74] Rubino et al., 2021 NCT03548987 RCT N = 803 US, Denmark, Israel, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, Ukraine	• SC semaglutide 2.4 mg weekly (535) • Placebo (268) Prior to randomization, all participants started on 0.25 mg semaglutide and increased every 4 weeks to reach 2.4 mg by week 16 and continued on 2.4 mg to week 20 before being randomized to active treatment or placebo 68 weeks + 7 weeks	Inclusion • At least 1 self-reported unsuccessful dietary effort to lose weight • BMI > 30, or a BMI of ≥ 27 with ≥ 1 treated or untreated weight-related comorbidity (hypertension, dyslipidemia, OSA, CVD) Exclusion • T2DM • HbA1c ≥ 6.5% (48 mmol/mol) Self-reported change in body weight of > 5 kg within 90 days of screening	Duration 20 weeks Description All initiated on 0.25 mg semaglutide and titrated up to 2.4 mg by week 16; continued to week 20 before being randomized to active treatment or placebo	Diet and exercise • From trial entry (i.e., week 0) all participants received monthly counseling by qualified health care professionals, prescribed a reduced-calorie diet (500 kcal/d deficit relative to estimated energy expenditure calculated at week 0) and increased physical activity (150 min/wk) Daily records kept by participants (using paper diaries, apps, or other tools) and reviewed during counseling visits.
STEP 5[79] Garvey et al., 2022 NCT03693430 RCT N = 304 US, Canada, Italy, Hungary, Spain	• SC semaglutide 2.4 mg weekly (152) • Placebo (152) Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 104 weeks + 7 weeks off treatment	Inclusion • Aged ≥ 18 years • BMI ≥ 30.0 kg/m^2 or ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, OSA, or CVD • History of at least one self-reported unsuccessful dietary effort to lose body weight Exclusion • HbA1c ≥ 48 mmol/mol (6.5%) • History of T1DM or T2DM • Treatment with glucose-lowering agent(s) within 90 days before screening • A self-reported change in body weight > 5 kg (11 lb) within 90 days before screening • Treatment with any medication for the indication of obesity within the past 90 days before screening	None	Diet and exercise • Behavioral intervention consisted of counseling by a dietitian or similarly qualified healthcare professional every 4 weeks via in-person visits or telephone on adherence to a reduced-calorie diet (500 kcal deficit a day relative to the energy expenditure estimated at randomization) and increased physical activity (150 minutes a week encouraged, for example, walking), both recorded

		• Previous or planned obesity treatment with surgery or weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening; (2) lap banding, if the band had been removed > 1 year before screening; (3) intragastric balloon, if the balloon had been removed > 1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve had been removed > 1 year before screening • Uncontrolled thyroid disease		daily (via a diary, app or other tools, which were reviewed during counseling sessions)

STEP 6[76]
Kadowaki et al., 2022
NCT03811574
RCT
N = 401
Japan, South Korea
	• SC semaglutide 2.4 mg weekly (199)
	• SC semaglutide 1.7 mg weekly (101)
	• Placebo (101)
	Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached
	68 weeks + 7 weeks off treatment
		Inclusion
		• Age ≥ 18
		• BMI ≥ 27·0 kg/m^2 with ≥ 2 weight-related comorbidities (treated or untreated) or BMI ≥ 35·0 kg/m^2 with ≥ 1 weight-related comorbidity (treated or untreated); at least one comorbidity should be hypertension or dyslipidemia (Japan only: or T2DM)
		• History of at least one self-reported unsuccessful dietary effort to lose body weight
		• Japanese participants with T2DM at screening, diagnosed ≥ 180 days prior to the day of screening, treated with either diet and exercise alone or stable treatment with up to three oral antidiabetic drugs (metformin, sulphonylurea, SGLT2i, or glitazone), HbA1c 7.0 to 10.0% (53 to 86 mmol/mol)
		Exclusion
		• Glycaemia related for participants without T2DM:
		  o HbA1c ≥ 48 mmol/mol (6·5%) as measured by the central laboratory at screening
		  o History of T1DM or T2DM
		  o Treatment with glucose-lowering agent(s) within 90 days before screening
		  o Treatment with a glucagon-like peptide-1 receptor agonist within 180 days before screening
		• Diabetes-related for participants with T2DM (Japan)
		  o Treatment with any medication for the indication of diabetes other than stated in the inclusion criteria within the past 90 days prior day of screening only)
		  o Receipt of any other antidiabetic investigational drug within 90 days prior to screening for this trial, or receipt of any investigational drugs not
			None	Diet and exercise
				• Participants were counseled every fourth week via visits or telephone contact by a dietician or similar qualified health care professional with regard to diet and exercise
				• The dietary intervention included a 500kcal deficit per day relative to the estimated total daily energy expenditure
				• Advised to do 150 minutes of physical activity per week (e.g., walking or climbing the stairs)

		affecting diabetes within 30 days prior to screening for this trial ○ Treatment with a GLP-1 receptor agonist within 180 days prior to screening • Serious renal impairment • A self-reported change in body weight > 5 kg (11 lb) within 90 days before screening • Treatment with any medication for the indication of obesity within the past 90 days before screening • Previous or planned obesity treatment with surgery or a weight loss device • Uncontrolled thyroid disease		

STEP TEENS[78]
 	
Weghuber et al., 2022
 	
NCT04102189
 	
RCT
 	
N = 201
 	
US, Austria, Belgium, Croatia, Ireland, Mexico, Russian Federation, United Kingdom
	• SC semaglutide 2.4 mg weekly (134)
	• Placebo (67)
	
	Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached, or as tolerate
	
	68 weeks + 7 weeks off treatment
		Inclusion
		• Aged 12 to < 18 years at the time of signing
		• Body mass index (BMI) ≥ 95th percentile OR ≥ 85th percentile (on sex- and age-specific growth charts) with ≥ 1 weight-related comorbidity (treated or untreated): hypertension, dyslipidemia, OSA, or T2DM
		• History of at least one self-reported unsuccessful dietary effort to lose weight
		• For participants with T2DM at screening the following inclusion criteria applied:
		   ○ Participant was treated with either diet and exercise alone or stable treatment for at least 90 days prior to screening with metformin
		   ○ Glycated hemoglobin ≤ 10.0% (86 mmol/mol) as measured by central laboratory at screening
		Exclusion
		• A self-reported (or by parent[s] where applicable) change in body weight > 5 kg (11 lb) within 90 days before screening, irrespective of medical records
		• Treatment with any medication for the indication of obesity within the past 90 days
		• before screening
		• Previous surgical treatment for obesity (excluding liposuction if performed > 1 year
		• before screening)
		• Uncontrolled thyroid disease at screening, in the opinion of the investigator
		• Participants with secondary causes of obesity (i.e., hypothalamic, monogenic, or endocrine causes)
		• T1DM
		• Prepubertal participants (Tanner stage 1)
			Duration
			12 weeks
			
			Description
			Lifestyle intervention run-in phase according to regulatory guidelines; parents or guardians included
				Diet and exercise
				• Counseling about healthy nutrition and physical activity for weight loss beginning at run-in (week 12) and continuing through the entire trial.
				• Counseling must be done by a certified dietician or a similarly qualified health care professional according to local standards
				• Focus of the counseling in healthy nutrition must be to educate on healthier food choices focus of the counseling in physical activity is to encourage and reinforce a goal of 60 minutes of moderate to high-intensity physical activity per day
				• Activity trackers offered but optional

		• History of major depressive disorder or other severe or serious mental health condition		
Tirzepatide				
SURMOUNT-1[81] Jastreboff et al., 2022 NCT04184622 RCT N = 2,539 US	• SC tirzepatide 15 mg weekly (630) • SC tirzepatide 10 mg weekly (636) • SC tirzepatide 5 mg weekly (630) • Placebo (643) Initiated tirzepatide at 2.5 mg weekly and increased by 2.5 mg every 4 weeks up to target dose 72 weeks + 4 weeks safety period	Inclusion • Have a BMI ≥ 30 or ≥ 27 kg/m^2 and previously diagnosed with at least one of the following weight-related comorbidities: hypertension, dyslipidemia, OSA, CVD • Have a history of at least one self-reported unsuccessful dietary effort to lose body weight • Males willing to use reliable contractive • Females not of childbearing potential Exclusion • T1DM, T2DM • Self-reported change in body weight > 5 kg within 3 months prior to screening • Prior or planned surgical treatment for obesity • Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months • Serious renal impairment • Clinically significant gastric emptying abnormality • History of chronic or acute pancreatitis • Thyroid disease, or secondary obesity	None	Diet and exercise • Lifestyle intervention included regular lifestyle counseling sessions, delivered by a dietitian or a qualified health care professional, to help the participants adhere to healthful, balanced meals, with a deficit of 500 calories per day, and at least 150 minutes of physical activity per week
Exenatide				
Combat-JUDO[83] Weghuber et al., 2020 EudraCT 2015-001628-45 RCT N = 44 Austria, Sweden	• SC exenatide 2.0 mg weekly (33) • Placebo (33) Titration schedule NR 24 weeks + 2 weeks safety follow-up only	Inclusion • Aged age 10 to 18 years • At least 5 months with obesity • Sexually inactive or usage of adequate anticonception, negative pregnancy tests in females, and ability to understand and comply with the requirements of the study • BMI SD score > 2.0 or age-adapted BMI > 30 kg/m^2. Exclusion • Syndromal obesity • Pregnancy or lactation • Gastrointestinal disease, total or partial gastric or small intestine resection • Diabetes mellitus	None	Diet and exercise • 4 sessions each of nutritional, psychological, and physical treatment • Advised participants to follow a traffic light system for diet Psychological sessions aimed to optimize issues related to disturbed eating behavior, sleep pattern, media consumption, and sedentary behavior, exercise at home and at school

		• Kidney disease, hypo-/hyperthyroidism (unless under stable treatment), severe vitamin D insufficiency, or severe sleep apnea • Metformin treatment within 3 months prior to screening or concomitant medication influencing blood glucose or other parameters of the metabolic syndrome • Steroid treatment Concomitant medication addressing attention disorders, antidepressants that can lead to weight gain		
Derosa et al., 2010[84] RCT N = 128 Italy	• SC exenatide 20 µg daily (63) • Oral glibenclamide 15 mg daily (65) Exenatide: 5 µg twice a day for 1 month then increased to 10 µg twice a day for remainder of study Glibenclamide: 2.5mg three times a day for 1 month then glibenclamide 5mg three times a day 52 weeks	Inclusion • With T2DM • Poor glycemic control (i.e., HbA1c level > 8.0%) • Overweight BMI ≥ 25 and < 30 kg/m^2 receiving therapy with metformin at the mean dosage of 1,500 mg/day (SD, 500) • Intolerant to maximum dose metformin at 3,000 mg per day Exclusion • History of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, impaired hepatic function, impaired renal function, or severe anemia • Serious CVD or cerebrovascular conditions within 6 months before study enrollment • Pregnant or breastfeeding individuals	None	Diet and exercise • Controlled-energy diet (near 600 kcal daily deficit) • Standard diet advice was given by a dietitian or specialist doctor, including feedback on food diaries • Encouraged to increase physical activity by walking briskly or cycling for 20 to 30 minutes, 3 to 5 times per week Metformin • Continued on current dose
Fox et al., 2022[82] NCT02496611 RCT N = 66 US	• SC exenatide 2.0 mg weekly (33) • Placebo (33) Initiated and maintained at 2.0 mg weekly 52 weeks	Inclusion • Ages 12 to 18 years • BMI ≥ 1.2 × 95th percentile for age and sex norms or ≥ 35 kg/m^2, whichever was lower • Those who achieved reduction ≥ 5% BMI with meal replacement run-in were randomized Exclusion • Less than Tanner stage 2 • T1DM and T2DM • Previous (within 6 months) or current use of medications used primarily for weight loss • History of bariatric surgery • Dose changes in medications for dyslipidemia, prediabetes, or hypertension within the prior 6 months.	Duration 4 to 8 weeks Description • MRT; products included liquid shakes, prepackaged frozen entrée meals, fresh fruit and vegetables	Diet and exercise • Lifestyle therapy delivered monthly by trained coordinators at each in-person study visit and by telephone for the months during which there was no in-person visit • Adapted from the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored TODAY Study lifestyle therapy materials

				of 1,400 kcal/d	
Naltrexone-bupropion					
COR-1[85] Greenway et al., 2010 NCT00532779 RCT N = 1,742 US	• Oral NalBup 32/360 mg daily (583) • Oral NalBup 16/360 mg daily (578) • Placebo (581) High dose: Initiated at 8 mg/90 mg and escalated in fixed dose weekly to reach final dose at week 4 Low dose: Initiated at 4 mg/90 mg and escalated in fixed dose weekly to reach final dose at week 56 weeks	Inclusion • Aged 18 to 65 years • BMI 30 to 45 kg/m² and uncomplicated obesity, or BMI 27 to 45 kg/m² and controlled hypertension or dyslipidemia Exclusion • Obesity of known endocrine origin • T1DM or T2DM • Cerebrovascular, cardiovascular, hepatic, or renal disease • Previous surgical or device intervention for obesity; or loss or gain of more than 4 kg within3 months before randomization • History of seizures or serious psychiatric illness • Treatment with bupropion or naltrexone in the previous 12 months • History of drug or alcohol misuse in the previous 12 months Pregnant or breastfeeding women	None	Diet and exercise Regular instruction to follow hypocaloric diet (500 kcal per day deficit based on the WHO algorithm for calculating resting metabolic rate) and advice on lifestyle modification (including instructions to increase physical activity)
COR-II[86] Apovian et al., 2013 NCT00567255 RCT N = 1,496 US	• Oral NalBup 32/360 mg daily (1,001) • Placebo (495) Initiated at 8 gm/90 mg daily and increased weekly in fixed dose to target dose by week 5 56 weeks	Inclusion • 18 to 65 years of age • BMI ≥ 30 and ≤ 45kg/m² for subjects with uncomplicated obesity, and BMI of ≥ 27 and ≤ 45kg/m² for subjects with obesity and controlled hypertension and/or dyslipidemia • Normotensive (systolic ≤ 140 mmHg; diastolic ≤ 90 mmHg). Antihypertensive medications allowed with the exception of alpha-adrenergic blockers, and clonidine. • Medical regimen must be stable for at least 6 weeks prior to randomization • Medications for treatment of dyslipidemia are allowed as long as medical regimen has been stable for at least 6 weeks prior to randomization Exclusion • Obesity of known endocrine origin (e.g., untreated hypothyroidism, Cushing's syndrome)	None	Diet and exercise • At baseline, 12, 24, 36, and 48 weeks, participants received instructions to follow a hypocaloric diet (500 kcal/day deficit) and increase physical activity, and behavioral modification advice

		• Serious medical condition (including but not limited to renal or hepatic insufficiency; CHF, history of angina pectoris, myocardial infarction, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke) • T1DM or T2DM • History of surgical or device (e.g., gastric banding) intervention for obesity • History of treatment with bupropion, or naltrexone within the preceding 12 months • Use of drugs, herbs, or dietary supplements believed to significantly affect body weight or participation in a weight loss management program within one month prior to randomization • Loss or gain of more than 4.0 kg within 3 months prior to randomization • Pregnant or breastfeeding women		
COR-BMOD[89] Wadden et al., 2011 NCT00456521 RCT N = 793 US	• Oral NalBup 32/36 mg daily (591) • Placebo (202) Initiated at 8mg/90 mg per day and increased weekly in a fixed-dose regimen until target dose at week 4 56 weeks	Inclusion • Aged 18 to 65 years • BMI of 30 to 45 kg/m², or BMI of 27 to 45 kg/m² in the presence of controlled hypertension and/or dyslipidemia Exclusion • T1DM and T2DM • Significant cerebrovascular, cardiovascular, hepatic, or renal disease • Obesity of known endocrine origin • Previous surgical (or device) intervention for obesity • Loss or gain of > 4 kg within the previous 3 months • Use of medications known to affect body weight • History of seizures • Treatment with bupropion or naltrexone within the previous 12 months • History of drug or alcohol abuse within the previous 12 months • Current smokers and those who had used tobacco or other nicotine products within 6 months before screening Serious psychiatric illness (e.g., bipolar disorder, schizophrenia, bulimia, or conditions requiring psychotropic medications other than low doses of sedative hypnotics).	None	Intensive behavioral modification (BMOD) • Delivered to groups of 10 to 20 persons by registered dietitians, behavioral psychologists, or exercise specialists • Group meetings lasted 90 minutes and were held weekly for the first 16 weeks, every other week for the next 12 weeks, and monthly thereafter (yielding a total of 28 sessions) • All participants were instructed to consume a balanced deficit diet • Participants who weighed ≤ 249 lb were prescribed 1,200 kcal/day, whereas those 250 to 299 lb were prescribed 1,500 kcal/day, with higher allotments for heavier individuals

				Participants were instructed to keep daily records of their activity and aim for up to 360 minutes of activity per week.
COR-Diabetes[88] Hollander et al., 2013 NCT00474630 RCT N = 505 US	• Oral NalBup 32/36 mg daily (335) • Placebo (170) Initiated at 8 mg/90 mg per day and increased weekly in fixed-dose regimen until target dose reached at week 4 56 weeks	Inclusion • 18 to 70 years of age • BMI ≥ 27 and ≤ 45kg/m^2 • WithT2DM and on no injectable hypoglycemic medication or inhaled insulin for more than 3 months • On oral single or combination hypoglycemic medications (biguanides, thiazolidinediones, meglitinides, α-glucosidase inhibitors, sulfonylureas, DPP4 inhibitors) or no medications for the treatment of T2DM; oral hypoglycemic medication must be stable for at least 3 months prior to randomization • Systolic blood pressure < 145 mmHg; diastolic blood pressure < 95 mmHg. Antihypertensive medications are allowed with the exception of alpha-adrenergic blockers, and clonidine • Medications for treatment of dyslipidemia are allowed with the exception of cholestyramine and cholestypol as long as medical regimen has been stable for at least 4 weeks prior to randomization • HbA1c between 7 and 10%, fasting blood glucose < 270 mg/ml, fasting triglycerides < 400 mg/dL. Exclusion • T1DM	None	Diet and exercise • All participants were instructed to follow a hypocaloric diet (500 kcal deficit/day) • Participants received dietary counseling and the "Exchange Lists for Weight Management" booklets in accordance with the ADA guidelines • Participants received advice on behavioral modification, including written instructions, to increase physical activity (to walking for at least 30 minutes most days of the week)

		• Subjects with "brittle-diabetes" or any hospitalization or emergency room visit due to poor diabetic control within the past 6 months, previous history of diabetes-related dehydration leading to hospitalization, history or evidence of ketoacidosis • Obesity of known endocrine origin other than diabetes mellitus (e.g., untreated hypothyroidism, Cushing's syndrome, established PCOS) • Diabetes mellitus secondary to pancreatitis or pancreatectomy • Serious medical conditions (including but not limited to ongoing renal or hepatic insufficiency, heart failure, history of myocardial infarction, angina pectoris, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke • Loss or gain of more than 5.0 kg within previous 3 months • Severe microvascular or macrovascular complications of diabetes • History of surgical or device (e.g., gastric banding) intervention for obesity		
Halseth et al., 2017[90] Halseth et al., 2018[87] NCT01764386 RCT, open-label N = 242 US	• Oral NalBup 32/36 mg daily + CLI (153) • Usual care (89) Initiated at 8 mg/90 mg and increased to final dose over first 3 weeks of study 26 weeks controlled + 52 weeks uncontrolled	Inclusion • Adult male and female subjects, aged 18 to 60 years, had either obesity (BMI 30 to 45 kg/m^2) or overweight (BMI 27 to 45 kg/m^2) with dyslipidemia and/or controlled hypertension. Exclusion • T1DM or T2DM • Myocardial infarction within 6 months before screening; angina pectoris grade III/IV; clinical history of large vessel cortical strokes, including ischemic or hemorrhagic strokes • History of seizures, cranial trauma, bulimia, anorexia nervosa, or other conditions that predispose subjects to seizures • Chronic use or positive screen for opioids • Psychiatric conditions including mania, psychosis, acute depressive illness, or suicide risk • Regular use of tobacco products	None	Diet and exercise • During first 26 weeks NB group received a commercially available comprehensive lifestyle intervention (CLI); usual care received only general advice and recommendations on diet and exercise from their PCP • After 26 weeks all remaining participants received the same NalBup +CLI treatment
Phentermine-topiramate				

CONQUER/SEQUEL	• Oral PhenTop 15/92 mg daily (995)	Inclusion	None	Diet and exercise
Gadde et al., 2011[93] Garvey et al., 2012[95] Davidson et al., 2013[92] Garvey et al., 2014[94] NCT00553787/ NCT00796367 RCT N = 2,487 US	• Oral PhenTop 7.5/46 mg daily (498) • Placebo (994) Initiated at 3·75/23 mg and increased by 3.75/23 mg weekly until target dose reached 56 weeks (CONQUER) + 52 weeks (SEQUEL)	• Adults 18 to 70 years • Overweight or obese with a BMI of 27 to 45 kg/m² (no lower BMI limit for patients diagnosed with diabetes at baseline) • Two or more of the following comorbidities at baseline: o Systolic blood pressure 140 to 160 mmHg o (130 to 160 mmHg in patients with diabetes) o Diastolic blood pressure 90 to 100 mmHg (85 to 100 mmHg in patients with diabetes) o Taking at least two antihypertensive drugs; concentration of triglycerides 2.26 to 4.52 mmol/L o Using at least two lipid-lowering drugs o Fasting blood glucose greater than 5·55 mmol/L o Blood glucose greater than 7.77 mmol/L at 2 hours after oral glucose load during OGTT o Diagnosed with T2DM managed with lifestyle changes or metformin monotherapy o Waist circumference of at least 102 cm for men or at least 88 cm for women For extension study (SEQUEL): • Having completed CONQUER study • Female participants continue with contraception requirements Exclusion • Blood pressure > 160/100 mmHg • Fasting blood glucose > 13·32 mmol/L or triglycerides > 4.52 mmol/L at randomization • T1DM • Use of antidiabetic drugs other than metformin History of nephrolithiasis, recurrent major depression, presence or history of suicidal behavior or ideation with intent to act, and current substantial depressive symptoms For extension study (SEQUEL): • BMI < 22 at the completion of the CONQUER study • Continuously not taking the study drug for .4 week at the completion of the CONQUER study • Developing a condition during the		• Standardized diet and lifestyle modification counseling based on the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) program. At baseline, each patient was provided with written materials and advised to implement lifestyle changes as appropriate, and given instructions to reduce their caloric intake by 500 kcal/day

		• CONQUER study that would interfere with compliance or attainment of study measures Participating in another formal weight-loss program		
EQUIP[91] Allison et al., 2011 RCT N = 1,267 US	• Oral PhenTop 15/92 mg daily (512) • Oral PhenTop 3.75/23 mg daily (241) • Placebo (514) 4-week blinded titration period initiated at 3.75/23 and thereafter increased weekly by 3.75/23 mg increments to the assigned dose 56 weeks	Inclusion • Age 18 to 70 years • BMI ≥ 35 kg/m^2 (no upper limit) • Triglycerides ≤ 200 mg/dl with treatment of 0 to 1 lipid-lowering medication • BP ≤ 140/90 mmHg with treatment of 0 to 2 antihypertensive medications • Fasting serum glucose level ≤ 110 mg/dl. Exclusion • Weight gain or loss > 5 kg within past 3 months • History of eating disorders • Previous bariatric surgery, glaucoma, and nephrolithiasis • Thyroid dysfunction • Chronic systemic glucocorticoid therapy • Bipolar disorder or psychosis history, > 1 lifetime episode of major depression, current depression of moderate or greater severity, presence or history of suicidal behavior or ideation with some intent to act, or antidepressant use that had not been stable for at least 3 months • Stroke, myocardial infarction, life-threatening arrhythmia, or coronary revascularization within past 6 months • Unstable angina, CHF, or known or suspected clinically significant cardiac valvulopathy • Cholelithiasis within past 6 months • Use of any investigational medication or device within the last month	None	Diet and exercise • All patients were provided with standardized lifestyle counseling, based on the LEARN Manual and advised to follow a 500 kcal daily reduction in dietary intake, increased water consumption, and increased physical activity
OB-403[96] Kelly et al., 2022 NCT03922945 RCT N = 223 US	• Oral PhenTop 15/92 mg daily (113) • Oral PhenTop 7.5/46 mg daily (54) • Placebo (56) High dose: • Weeks 1 and 2: 3.75/23 mg daily • Weeks 3 through 12: 7.5/46 mg daily	Inclusion • 12 to less than 17 years of age • BMI in the 95th percentile or greater for age and sex • Tanner stage greater than 1 • Stable body weight • Documented history of insufficient weight loss with lifestyle modification. Exclusion • Treatment with antiobesity medications • History of bariatric surgery or eating disorders	None	Diet and exercise • All participants were instructed to follow a mild hypocaloric diet modification program representing a 500 kcal/day deficit and to implement a family-based lifestyle modification program for adolescents,

	• Weeks 13 and 14: 11.25/69 mg daily • Weeks 15 to end of study: 15/92 mg daily <u>Low dose:</u> • Weeks 1 and 2: phe-top 3.75/23 mg daily • Weeks 3 through end of study: 7.5/46 mg daily 56 weeks	• Stimulant use for treatment of attention-deficit/hyperactivity disorder within 3 months of screening • T1DM • Medical treatment with insulin, sulfonylureas, GLP-1 agonists, SGLT-1 inhibitors, and SGLT-2 inhibitors • Congenital heart disease • Obesity of a known genetic or endocrine origin • Elevated blood pressure • History of bipolar disorder or psychosis, major depressive disorder, current depression of moderate or greater severity, or presence or history of suicidal behavior or ideation with intent to act		• as tolerated, throughout the study period • Lifestyle program included physical activity, behavior change, and family support
Setmelanotide				
Clement et al., 2020[100] Kuhnen et al., 2022[99] NCT02896192 NCT03287960 Single-arm N = 22 US, Belgium, France, Germany, the Netherlands, the United Kingdom	SC setmelanotide 3.0 mg daily (22) Initiated at 0.5 mg daily for individuals ≤ 18 and 1.0 mg daily for individuals > 18 years, and increased every 2 weeks by 0.5 mg until target dose 12 weeks at therapeutic dose + 40 weeks of phases (including 4 weeks on PBO in persons with successful weight loss)	<u>Inclusion</u> • Homozygous or compound heterozygous variants in POMC, PCSK1, or LEPR • Age 6 years and above • Obesity with BMI ≥ 30 kg/m^2 (age ≥ 18 years); obesity with BMI ≥ 95th percentile for age on growth chart assessment (age < 18 years) <u>Exclusion</u> • A recent diet or exercise regimen, or both, resulting in weight loss or stabilization and previous gastric bypass surgery resulting in more than 10% weight loss with no evidence of weight regain • Current or history of severe lung, liver, or kidney disease	None	None/NR
Haqq et al., 2022[97] Forsythe et al., 2023[98] NCT03746522 RCT + open-label N = 38 US, Canada, France, Spain, the United Kingdom	SC setmelanotide 3.0 mg daily (19) Placebo (19) Patients < 16 years initiated at 1.0 mg and ≥ 16 years at 2.0 mg and increased by 1.0 mg per week to target dose; dose escalation repeated	<u>Inclusion</u> • BBS clinical diagnosis as per Beales criteria or Alström syndrome diagnosis as per Marshall criteria ○ ≥ 90% of patients with BBS and 100% of patients with Alström syndrome were required to have a genetically confirmed diagnosis • Age ≥ 6 years at the time of randomization • Clinical obesity, defined as BMI ≥ 30 kg/m^2 (for those ≥ 16 years) or weight > 97th percentile for age and sex on growth charts (for those aged 6 to 15 years)	None	Nutritional counseling and monitoring was provided for pediatric patients (< 12 years) to ensure adequate nutritional intake

	on weeks 15 and 16 for open-label period 14 weeks randomized + 52 weeks open-label	Exclusion • > 2% weight loss from diet, exercise program, or both, with or without the use of weight loss agents, in prior 2 months • Use of any obesity medication within prior 3 months. GLP-1 receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus as long as (1) the dose has been stable for ≥ 3 months prior to randomization and is planned to remain stable throughout the study, (2) it is not being prescribed for the treatment of obesity, and (3) the patient has not experienced weight loss during the previous 3 months • > 10% durable weight loss from gastric bypass surgery • Diagnosis of psychiatric disorder that will interfere with study compliance • Patients without neurocognitive defects should not have a Patient Health Questionnaire-9 score ≥ 15, any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale, any lifetime history of a suicide attempt, or any suicidal behavior in prior month • Current pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study • Hemoglobin A1c > 9·0% • History of significant liver (other than NAFLD) or kidney disease or injury		
Haws et al., 2020[101] NCT03013543 Single-arm N = 10 US, Canada, France, Germany, Greece, Netherlands, Spain, the United Kingdom	SC setmelanotide 3.0 mg daily (10) Initiated at 0.5 mg daily for adolescents and 1.0 mg daily for adults, and increased by 0.5 mg every 2 weeks until target dose reached 12 weeks + 52 weeks extension for individuals successful with weight loss of 5 kg or ≥ 5% if baseline body weight was < 100 kg	Inclusion • Adults aged ≥ 18 years with BMI of 30 kg/m^2 or higher • Adolescents aged 12 to 17 years with a body weight > than 97th percentile (adjusted for age and sex) • Diagnosis of BBS Exclusion • Achieved > 2% weight loss from intensive diet or exercise regimens within 2 months of enrollment or > than 10% weight loss durably maintained after gastric bypass surgery • Diagnosis of a mental disorder that could substantially interfere with study adherence • Any suicidal ideation or history of suicide attempt • Clinically significant pulmonary, cardiac or oncologic disease (including dermatologic findings	None	None/NR

| | | Related to melanoma); history of liver disease other than nonalcoholic fatty liver disease; impaired glomerular filtration rate (≤ 30 mL/min/1.73 m^2) Family history of skin cancer, melanoma or oculocutaneous albinism; or an inability to adhere to a once-daily injection. | | |

Name; Author, Yr Number; Design N Randomized Location	Interventions (n) Titration Schedule Duration + Follow-up	Key Participant Inclusion/Exclusion Criteria	Run-In	Background Treatment(s)
Semaglutide vs. liraglutide				
STEP 8[55] Rubino et al., 2022 NCT04074161 RCT – open-label for active treatments; blinded to placebo N = 338 US	• SC semaglutide 2.4 mg weekly (126) • SC liraglutide 3.0 mg daily (127) • Placebo (85) Semaglutide: • Initiated at 0.25 mg and escalated in fixed-dose regimen every 4 weeks until target dose reached Liraglutide: • Initiated at 0.6 mg and escalated by 0.6 mg weekly until target dose reached o 68 weeks + 7 weeks (AEs and pulse only summarized at 75 weeks as descriptive stats only)	Inclusion • Age ≥ 18 years • BMI ≥ 30.0 kg/m² or ≥ 27.0 kg/m² with the presence of at least 1 of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, OSA, or CVD. • History of at least 1 self-reported unsuccessful dietary effort to lose body weight Exclusion • HbA1c ≥ 6.5% (48 mmol/mol) • History of T1DM or T2DM • Treatment with glucose-lowering agent(s) within 90 days before screening • A self-reported change in body weight > 5 kg (11 lb) within 90 days before screening • Treatment with any medication for the indication of obesity within the past 90 days before screening • Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening; (2) lap banding, if the band has been removed > 1 year before screening; (3) intragastric balloon, if the balloon has been removed > 1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year before screening. • Uncontrolled thyroid disease	None	Diet and exercise • Counseling on diet (500 kcal daily deficit) and physical activity (minimum 150 minutes per week)

Liraglutide				
Elkind-Hirsch et al., 2020[66] NCT01234649 RCT N = 153 US	• SC liraglutide 1.8 mg daily (78) • Placebo (75) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 80 to 84 weeks randomized	Inclusion • Postpartum nonpregnant, nondiabetic overweight (BMI ≥ 25) female participants • Aged 18 years to 45 years of age • Experienced GDM during index (within 12 months) pregnancy • Willing to use effective contraception • Not breastfeeding for at least 3 months • Presented with metabolic abnormalities on their postpartum OGTT (inclusive of insulin resistance, impaired beta cell response and glucose intolerance) Exclusion: • Persons with diabetes • Current history of smoking • Taking drugs that affect gastrointestinal motility, carbohydrate metabolism, and lipid-lowering and/or antiobesity drugs within 3 months of the study	None	Diet and exercise • Standardized dietary advice and appropriate written information on a balanced weight-reducing diet and daily exercise (such as walking, using stairs) Metformin • Metformin 2,000 mg per day • Metformin extended-release was initiated at dose 500 mg daily (with dinner) for 2 weeks and increased to 500 mg twice daily (breakfast and dinner) for 2 weeks. The dose was increased to 500mg am, 1000mg pm (with breakfast and dinner) for 2 weeks and then increased to the final dose of 2,000 mg
Ellipse[71] Tamborlane et al., 2019 NCT01541215 RCT N = 135 US, Canada + 33 countries in Europe, Central America, South America, Asia, Africa, and Australia	• SC (up to) liraglutide 1.8 mg daily (66) • Placebo (69) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached as tolerated 26 weeks randomized + 26 open-label (those on placebo discontinued injection but stayed on metformin)	Inclusion • Children and adolescents between the ages of 10 to 17 years • Diagnosis of T2DM and treated for at least 90 days with diet and exercise alone, or diet and exercise in combination with metformin monotherapy • The metformin and/or basal insulin) dose must be stable for at least 30 or 60 days (respectively) prior to screening • HbA1c ≥ 7.0% and ≤ 11% if diet and exercise treated, or ≥ 6.5% and ≤ 11% if treated with metformin • BMI > 85th percentile of the general age and gender matched population *To be randomized, participants had to achieve fasting plasma glucose level between 126 mg and 220 mg per deciliter (7.0 mmol and 12.2 mmol per liter) and with a stable metformin*	Duration 11 to 12 weeks Description 3 to 4 weeks titration of metformin to maximum dose tolerated (between 1,000 and 2,000 mg per day), followed by 8 weeks of	Diet and exercise • Counseling according to local standards Metformin • Maintenance dose after run-in, with or without basal insulin Other • Those who were treated with basal insulin reduced their doses by 20% at the time of randomization; after completion of intervention dose-

			metformin maintenance	escalation basal insulin could be increased to no more than baseline level
		dose (in most patients, 1,000 mg to 2,000 mg per day) for at least 8 weeks		
		Exclusion • T1DM • Maturity-onset diabetes of the young • A fasting C-peptide level of less than 0.6 ng per milliliter, or antibodies against insulinoma-associated 2 or glutamic acid decarboxylase • The use of any antidiabetic agent other than metformin or basal insulin within 90 days before screening • A history of pancreatitis • Serum calcitonin levels of 50 ng or more per liter • A personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 • An alanine aminotransferase level 2.5 times the upper limit of the normal range or higher • Serum creatinine levels greater than the upper limit of the normal range for age • A recent history of heart disease, proliferative retinopathy or maculopathy; and recurrent severe hypoglycemia or hypoglycemic unawareness		
Ghanim et al., 2020[67] NCT01753362 RCT N = 84 US	• SC liraglutide 1.8 mg daily (42) • Placebo (42) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 26 weeks randomized	Inclusion: • T1DM on continuous subcutaneous insulin infusion (i.e., insulin pump) or multiple (four or more) injections of insulin per day • Using CGM device or regularly measuring their blood sugars four times daily • HbA1c of less than 8.5% • Age 18-75 years • BMI≥ 25kg/m² • Age at diagnosis of T1DM should be < 30 years Exclusion: • T1DM for less than 6 months • Coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery or coronary angioplasty) in the previous four weeks • Hepatic disease (transaminase > 3 times normal) or cirrhosis • Renal impairment (serum eGFR < 30ml/min/1.73 m²) • HIV or Hepatitis B or C positive status, history of pancreatitis, gastroparesis, or thyroid carcinoma	Duration 2 weeks Description Baseline testing and monitoring	All participants on basal insulin • Insulin titrations were carried out every 2 to 4 weeks throughout the study and in all patients to target blood sugars between 70 and 180 mg/dL

		• Use of any agent other than insulin for treatment of diabetes (metformin, pramlintide or thiazolidinediones) • Pregnancy or breastfeeding		
Kelly et al., 2020[60] NCT02918279 RCT N = 251 US, Belgium, Mexico, Russia, Sweden	• SC liraglutide 3.0 mg daily (125) • Placebo (126) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks randomized + 26 weeks off treatment	Inclusion: • Pubertal adolescents (12 to < 18 years of age) • Obesity (BMI ≥ 30 kg/m² and ≥ 95th percentile for age and sex) • Stable body weight > 90 days before screening • Poor response to lifestyle therapy alone • Adolescents with T2DM were eligible Exclusion: • Pre-pubertal individuals • T1DM • Body weight ≤ 60 kg • Calcitonin ≥ 50 ng/L • Secondary causes of obesity • Treatment with medications within 90 days before treatment that may cause significant weight change • Antidiabetic treatment other than metformin • Previous surgical treatment or other diet attempt treatments (herbal, OTC medications, organized weight reduction programs)	Duration 12 weeks Description Lifestyle counseling for healthy nutrition and physical activity for weight loss	Diet and exercise • Individualized counseling in healthy nutrition that was performed by a certified dietician • Participants were encouraged to engage in 60 minutes of moderate- to high-intensity physical activity daily
LIDO[72] Dubé, 2017 NCT01787916 RCT crossover N = 15 Canada	• SC liraglutide 1.8 mg daily (15) • Placebo (15) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg after 7 to 10 days (upon tolerance) until target dose reached 24 weeks randomized	Inclusion • Adults with T1D duration who had been treated for more than 5 years with insulin (multiple daily injections or continuous subcutaneous insulin infusion) • Non-smoking • Aged between 18 and 50 years • Without major diabetes-related complications • BMI ≥ 25 kg/m² Exclusion • HbA1c > 8.5% • Personal or familial history of medullary thyroid cancer, pancreatitis, CVD, and gastroparesis.	None	All participants were on insulin • Insulin doses were reduced by 10% to 15% at randomization and then adjusted in accordance with self-measured blood glucose
LIRA-1 Dejgaard et al., 2016[69] NCT01612468 RCT	• SC liraglutide 1.8 mg daily (50) • Placebo (50) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg	Inclusion • Diagnosed with T1DM in accordance with WHO criteria for more than 1 year • Aged 18 years or older • With a BMI more than 25 kg/m² and HbA1c more than 8% (64 mmol/mol).	None	All participants were on insulin (no required type and frequency of insulin use) Insulin type was not allowed to change after randomization

N = 100 Denmark	weekly until target dose reached 24 weeks randomized	Exclusion • Insulin pump treatment • Hypoglycemia unawareness • Gastroparesis • Impaired kidney function • Liver disease with raised alanine aminotransferase more than three times the upper normal range • History of pancreatitis • Pregnancy or lactation		
LOSEIT[64] Gudbergsen et al., 2021 NCT02905864 RCT N = 156 Denmark	• SC liraglutide 3.0 mg daily (80) • Placebo (76) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 52 weeks randomized	Inclusion: • Clinical diagnosis of knee OA • Age ≥ 18 years and < 75 years • BMI ≥ 27 kg/m^2 • Stable body weight during the previous 3 months • Motivated for weight loss *To be randomized, participants had to achieve ≥ 5% weight loss after run-in period* Exclusion: • Ongoing participation, or participation within the last 3 months, in an organized weight loss program • Current or history of treatment with medications that may cause significant weight gain for at least 3 months before this trial • Current use or use within three months before this trial of GLP-1 receptor agonist, pramlintide, sibutramine, orlistat, zonisamide, topiramate, or phentermine • T1DM • T2DM treated with glucose-lowering drugs other than metformin • Alloplasty in target knee joint • End stage disease in target knee joint • Pregnancy, breastfeeding	Duration 8 weeks Description Intensive supervised weight loss program with counseling and low-calorie formula diet from Cambridge Weight Plan (800 to 1,000 kcal per day)	Intensive diet therapy • Those successful with ≥ 5% weight loss during 8-week run-in period continued a tapering dietary intervention for 8 weeks (week 0 to 8) and were randomized to liraglutide or placebo for 52 weeks • The initial 8 weeks after randomization included a dietician-led partial reintroduction of regular meals in combination with formula diet products; all participants (irrespective of random assignment) were scheduled for group sessions every second week • No dietary consultancies were offered after week 8, but patients were instructed to aim for 1,200 kcal/d from week 0 to 8 and for an intake of 1,500 kcal/d from week 8 to 52 • Patients were offered 1 to 2 daily meal replacements with a formula diet from week 8 to 52
SCALE Diabetes[57]	• SC liraglutide 3.0 mg daily (423)	Inclusion • Diagnosed with T2DM (HbA1c level 7.0%-10.0%)	None	Diet and exercise

| Davies et al., 2015 NCT01272232 RCT N = 846 US, France, Germany, Israel, South Africa, Spain, Sweden, Turkey, United Kingdom | • SC liraglutide 1.8 mg daily (211)
• Placebo (212)

Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached

56 weeks + 12 weeks observational off-drug period | • Overweight or obese (BMI ≥ 27.0) adults (age ≥ 18 years)
• With stable body weight (< 5 kg change in the last 3 months)
• Treated with diet and exercise alone, or in combination with 1 to 3 oral hypoglycemic agents (metformin, thiazolidinedione, sulfonylurea)

Exclusion
• Treatment with GLP-1 receptor agonists (including liraglutide or exenatide), dipeptidyl peptidase-4 (DPP-4) inhibitors, or insulin, within the last 3 months prior to screening
• Recurrent major hypoglycemia or hypoglycemic unawareness
• Use of any drug (except for metformin, sulfonylurea or glitazone), including investigational drugs, which in the investigator's opinion | | • Monthly counseling to increase their physical activity to at least 150 minutes of brisk walking per week and to reduce their daily energy intake to 500 kcal below their individualized daily total energy requirements, with food diary |
| SCALE IBT[63] Wadden et al., 2020 NCT02963935 RCT N = 282 US | • SC liraglutide 3.0 mg daily (142)
• Placebo (144)

Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached

56 weeks | Inclusion
• Eligible participants were aged ≥ 18 years, with stable body weight (maximum 5-kg self-reported weight change within 90 days before screening) and BMI ≥ 30 kg/m^2

Exclusion
• Glycated hemoglobin (HbA1c) ≥ 6.5%
• T1DM or T2DM
• Use of medications (in the past 90 days) known to induce significant weight loss or gain
• Inadequately treated hypertension
• Pregnancy or breastfeeding
• History of CVD, severe congestive heart failure, second-degree or greater heart block, medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pancreatitis, major depressive disorder within the past 2 years
• History of suicide attempt, or malignancy within the past 5 years | None | Intensive behavioral therapy
• IBT program followed an abbreviated lifestyle counseling protocol adapted from the Diabetes Prevention Program
• Participants who weighed < 91 kg (< 200 lb) at randomization were prescribed 1,200 calories daily; for those who weighed 91 to 136 kg (200 to 300 lb) daily calories calculated by body weight (lb) × 6 (kcal/lb), and participants who weighed > 136 kg (> 300 lb) were prescribed 1,800 calories daily
• All participants were initially prescribed 100 minutes per week of moderate-intensity physical activity (e.g., brisk walking); physical activity |

				was increased by 25 minutes every 4 weeks, with an ultimate goal of 250 minutes per week
SCALE Insulin[59] Garvey et al., 2020 NCT02963922 RCT N = 396 US, Canada, Germany, Israel, Italy, Mexico, Turkey	• SC liraglutide 3.0 mg daily (198) • Placebo (198) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks randomized	Inclusion • Diagnosed with T2DM with an HbA1c ≥ 6.0 to ≤ 10% (42 to 86 mmol/mol) at screening • Receiving stable treatment with any basal insulin (≥ 90 days; no requirement for minimum or maximum dose) and ≤ 2 oral antidiabetic agents • Aged ≥ 18 years with a BMI of ≥ 27 kg/m^2, stable body weight (maximum 5 kg self-reported weight change within 90 days before screening) Exclusion • T1DM • Recurrent severe hypoglycemic episodes within the last year • Use of dipeptidyl peptidase 4 inhibitors, GLP-1 receptor agonists, bolus insulin, or medications known to induce significant weight change in the previous 90 days • Recent history of cardiovascular event or medullary thyroid carcinoma or multiple • Endocrine neoplasia type 2 • Pregnancy, breastfeeding, or intention to become pregnant • History of pancreatitis	None	Intensive behavioral therapy • Physical activity, reduced energy intake and behavioral counseling, and was based on an abbreviated version of the Diabetes Prevention Program counseling • Behavioral counseling of 23 individual or group sessions over 56 weeks; increased physical activity was of moderate intensity, starting at 100 min/week, and increasing by 25 minutes every 4 weeks to a recommended 250 min/week; energy intake was reduced to 1,200 kcal in individuals < 200 lb, to the sum of body weight (lb) x 6 (kcal/lb) in individuals 200 to 300 lb in weight, or to 1,800 kcal for those > 300 lb All participants on basal insulin • Not to exceed the entry dose within the first 5 weeks • Recommended to reduce basal insulin dose by 15% to 20% • Insulin dose adjusted based on self-measured blood glucose values
SCALE Maintenance[62] Wadden et al., 2013	• SC liraglutide 3.0 mg daily (212)	Inclusion • BMI ≥ 30 kgm-2, or BMI ≥ 27 kgm-2 with presence of comorbidities of treated or untreated dyslipidemia	Duration 4 to 12 weeks	Diet and exercise • At randomization, participants were

NCT00781937 RCT N = 422 US, Canada	• Placebo (210) 56 weeks randomized + 12 weeks off treatment	and/or hypertension. Untreated dyslipidemia was defined as LDL cholesterol ≥ 160 mgdl-1, or triglycerides ≥ 150 mgdl-1, or high-density lipoprotein (HDL) < 40 mgdl-1 for men and < 50 mgdl-1 for women. Untreated hypertension was defined as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg. • Stable body weight during the previous 3 months (< 5 kg self-reported weight change) • Age ≥ 18 years • Previously undergone dietary weight loss and not able to maintain reduced weight *To be randomized, participants had to achieve ≥ 5% weight loss after run-in period* Exclusion • Diagnosis of T1DM or T2DM • Fasting plasma glucose ≥ 7 mmol/L at run-in (week 12) • Treatment with GLP-1 receptor agonists or medications causing significant weight gain/loss • Bariatric surgery • History of idiopathic acute or chronic pancreatitis, major depressive disorder or other severe psychiatric disorders; or clinically significant active CVD	Description Low-calorie diet (1,200 to 1,400 calories per day) with up to 3 liquid meal replacements per day, in-person and telephone lifestyle counseling including exercise	prescribed a 500 kcal per day deficit diet, based on estimated 24-hour energy expenditure (liquid meal replacements not recommended) • Participants were instructed to continue the recommended physical activity • Face-to-face lifestyle counseling visits (15 to 20 minutes) were provided for a total of 17 visits over 56 weeks
SCALE Obesity and Prediabetes Pi-Sunyer et al., 2015[56] Kolotkin et al., 2016[61] le Roux et al., 2017[58] Kolotkin et al., 2018[68] NCT01272219 RCT N = 3,731 US, Canada + 25 countries in Europe, Central America, South America, Asia, Africa, and Australia	• SC liraglutide 3.0 mg daily (2,487) • Placebo (1,244) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 56 weeks randomized + 104 weeks for those with prediabetes at baseline (n = 2254) At week 56, participants assigned to liraglutide and were without prediabetes at baseline were randomized to	Inclusion: • Aged ≥ 18 years • Stable body weight, preceding failed dietary effort • BMI ≥ 30, or ≥ 27 if the patient had treated or untreated dyslipidemia or hypertension Exclusion: • T1DM or T2DM • Medications that cause clinically significant weight gain or loss • Previous bariatric surgery • History of pancreatitis, major depressive or other severe psychiatric disorders • HbA1c ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dl • Family or personal history of multiple endocrine neoplasia syndrome type 2 or familial medullary thyroid carcinoma	None	Diet and exercise • Counseling on diet (500 kcal daily deficit) and physical activity (minimum 150 minutes per week), with 3-day lifestyle diary every other month.

	remain on liraglutide or to PBO and followed for an additional 12-weeks			
S-LiTE[65] Lundgren et al., 2021 NCT04122716 RCT N = 195 Denmark	• Exercise + SC liraglutide 3.0 mg daily (49) • SC liraglutide 3.0 mg daily (49) • Placebo (49) • Exercise (48) Liraglutide initiated at 0.6 gm daily and increased by 0.6 mg weekly until target dose reached 52 weeks randomized	Inclusion: • BMI 32 to 43 (kg/m^2) • Age > 18 and < 65 years • Safe contraceptive method *To be randomized, participants had to achieve ≥ 5% weight loss after run-in period* Exclusion: • Diagnosed with known serious chronic illness including T1DM or T2DM (or a randomly measured fasting plasma glucose > 7 mmol/l), angina pectoris, coronary heart disease, congestive heart disease, severe renal or hepatic impairment, IBD, among other conditions • Pregnancy, expecting pregnancy or breastfeeding	Duration 8 weeks Description Meal replacement therapy diet plan (800 calories per day)	Diet therapy • All participants attended 12 one-on-one consultations with measurement of body weight and dietetic support complying with Danish authorities' dietetic recommendations of sustained weight loss
Semaglutide				
STEP 1 Wilding et al., 2021[80] Wilding et al., 2022[77] NCT03548935 RCT N = 1,961 US, Canada + 14 countries in Asia, Europe, and South America	• SC semaglutide 2.4 mg weekly (1,306) • Placebo (655) Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 68 weeks + 7 weeks off treatment 52-week extension trial off treatment for subgroup who completed treatment throughout primary study	Inclusion • Age ≥ 18 years • BMI ≥ 30.0 or ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, OSA, or CVD • History of at least one self-reported unsuccessful dietary effort to lose body weight Exclusion • Diabetes • Glycated hemoglobin level of 48 mmol per mole (6.5%) or greater History of chronic pancreatitis, acute pancreatitis within 180 days before enrollment, previous surgical obesity treatment, and use of antiobesity medication within 90 days before enrollment method	None	Diet and exercise • Participants received individual counseling sessions every 4 weeks on reduced-calorie diet (500 kcal deficit per day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (with 150 minutes per week of physical activity, such as walking, encouraged) Food and activity diary was reviewed during counseling sessions
STEP 2 Davies et al., 2021[75] NCT03552757 RCT N = 1,210	• SC semaglutide 2.4 mg weekly (404) • SC semaglutide 1.0 mg weekly (403) • Placebo (403)	Inclusion • Diagnosed with T2DM • Age ≥ 18 years • BMI ≥ 27 kg/m^2 • History of at least one self-reported unsuccessful dietary effort to lose body weight • Diagnosed with T2DM ≥ 180 days prior to screening	None	Diet and exercise • Counseling for diet (500 kcal daily calorie reduction) and physical activity (150 minutes per week) with lifestyle change diary

US, Argentina, Canada, Germany, Greece, India, Japan, Russia, South Africa, Spain, United Arab Emirates, United Kingdom	Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 68 weeks	• HbA1c of 7% to 10% (53 to 86 mmol/mol) • Managed with diet and exercise alone, or treated with a stable dose of up to three oral glucose-lowering agents (metformin, sulfonylureas, SGLT2 inhibitors, or thiazolidinediones) for at least 90 days before screening Exclusion • Self-reported change in body weight > 5 kg within 90 days before screening • Previous or planned (during the trial period) obesity treatment with surgery or a weight-loss device • Pregnant, breastfeeding individuals or those who intending to become pregnant, or is of childbearing potential and not using a highly effective contraceptive method		
STEP 3 Wadden et al., 2021[73] NCT03611582 RCT N = 611 US	• SC semaglutide 2.4 mg weekly (407) • Placebo (204) Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 68 weeks + 7 weeks off treatment	Inclusion • 18 years or older • 1 or more unsuccessful dietary efforts to lose weight • BMI of 27 or higher with at least 1 weight-related comorbidity (CVD, dyslipidemia, hypertension, or OSA) or BMI of 30 or higher Exclusion • With diabetes, glycated hemoglobin levels of 6.5% or more (≥ 48 mmol/mol), self-reported bodyweight change greater than 5 kg within 90 days before screening, or prior or planned obesity treatment with surgery or a weight loss device • Treatment with glucose-lowering agent(s) or any medication for the indication of obesity within 90 days before screening Uncontrolled thyroid disease	None	Intensive behavioral therapy • For the first 8 weeks after randomization, participants received a low-calorie diet (1,000 to 1,200 kcal/d) provided as meal replacements (e.g., liquid shakes, meal bars, portion-controlled meals [provided by Nutrisystem, supplied by the sponsor]) • Participants subsequently transitioned to a hypocaloric diet (1,200 to 1,800 kcal/d) of conventional food for the remainder of the 68 weeks, with prescribed calorie intake based on randomization body weight At randomization, participants were prescribed 100 minutes of physical activity per week (spread across 4 to 5 days), which increased by 25 minutes every 4 weeks, to reach 200

				min/wk participants were provided with 30 individual intensive behavioral therapy visits with a registered dietitian, who instructed them in diet, physical activity, and behavioral strategies
STEP 4[74] Rubino et al., 2021 NCT03548987 RCT N = 803 US, Denmark, Israel, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, Ukraine	• SC semaglutide 2.4 mg weekly (535) • Placebo (268) Prior to randomization, all participants started on 0.25 mg semaglutide and increased every 4 weeks to reach 2.4 mg by week 16 and continued on 2.4 mg to week 20 before being randomized to active treatment or placebo 68 weeks + 7 weeks	Inclusion • At least 1 self-reported unsuccessful dietary effort to lose weight • BMI > 30, or a BMI of ≥ 27 with ≥ 1 treated or untreated weight-related comorbidity (hypertension, dyslipidemia, OSA, CVD) Exclusion • T2DM • HbA1c ≥ 6.5% (48 mmol/mol) Self-reported change in body weight of > 5 kg within 90 days of screening	Duration 20 weeks Description All initiated on 0.25 mg semaglutide and titrated up to 2.4 mg by week 16; continued to week 20 before being randomized to active treatment or placebo	Diet and exercise • From trial entry (i.e., week 0) all participants received monthly counseling by qualified health care professionals, prescribed a reduced-calorie diet (500 kcal/d deficit relative to estimated energy expenditure calculated at week 0) and increased physical activity (150 min/wk) Daily records kept by participants (using paper diaries, apps, or other tools) and reviewed during counseling visits.
STEP 5[79] Garvey et al., 2022 NCT03693430 RCT N = 304 US, Canada, Italy, Hungary, Spain	• SC semaglutide 2.4 mg weekly (152) • Placebo (152) Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 104 weeks + 7 weeks off treatment	Inclusion • Aged ≥ 18 years • BMI ≥ 30.0 kg/m² or ≥ 27.0 kg/m² with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, OSA, or CVD • History of at least one self-reported unsuccessful dietary effort to lose body weight Exclusion • HbA1c ≥ 48 mmol/mol (6.5%) • History of T1DM or T2DM • Treatment with glucose-lowering agent(s) within 90 days before screening • A self-reported change in body weight > 5 kg (11 lb) within 90 days before screening • Treatment with any medication for the indication of obesity within the past 90 days before screening	None	Diet and exercise • Behavioral intervention consisted of counseling by a dietitian or similarly qualified healthcare professional every 4 weeks via in-person visits or telephone on adherence to a reduced-calorie diet (500 kcal deficit a day relative to the energy expenditure estimated at randomization) and increased physical activity (150 minutes a week encouraged, for example, walking), both recorded

		• Previous or planned obesity treatment with surgery or weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening; (2) lap banding, if the band had been removed > 1 year before screening; (3) intragastric balloon, if the balloon had been removed > 1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve had been removed > 1 year before screening • Uncontrolled thyroid disease		daily (via a diary, app or other tools, which were reviewed during counseling sessions)
STEP 6[76] Kadowaki et al., 2022 NCT03811574 RCT N = 401 Japan, South Korea	• SC semaglutide 2.4 mg weekly (199) • SC semaglutide 1.7 mg weekly (101) • Placebo (101) Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached 68 weeks + 7 weeks off treatment	Inclusion • Age ≥ 18 • BMI ≥ 27·0 kg/m² with ≥ 2 weight-related comorbidities (treated or untreated) or BMI ≥ 35·0 kg/m² with ≥ 1 weight-related comorbidity (treated or untreated); at least one comorbidity should be hypertension or dyslipidemia (Japan only: or T2DM) • History of at least one self-reported unsuccessful dietary effort to lose body weight • Japanese participants with T2DM at screening, diagnosed ≥ 180 days prior to the day of screening, treated with either diet and exercise alone or stable treatment with up to three oral antidiabetic drugs (metformin, sulphonylurea, SGLT2i, or glitazone), HbA1c 7.0 to 10.0% (53 to 86 mmol/mol) Exclusion • Glycaemia related for participants without T2DM: ○ HbA1c ≥ 48 mmol/mol (6·5%) as measured by the central laboratory at screening ○ History of T1DM or T2DM ○ Treatment with glucose-lowering agent(s) within 90 days before screening ○ Treatment with a glucagon-like peptide-1 receptor agonist within 180 days before screening • Diabetes-related for participants with T2DM (Japan) ○ Treatment with any medication for the indication of diabetes other than stated in the inclusion criteria within the past 90 days prior day of screening only) ○ Receipt of any other antidiabetic investigational drug within 90 days prior to screening for this trial, or receipt of any investigational drugs not	None	Diet and exercise • Participants were counseled every fourth week via visits or telephone contact by a dietician or similar qualified health care professional with regard to diet and exercise • The dietary intervention included a 500kcal deficit per day relative to the estimated total daily energy expenditure • Advised to do 150 minutes of physical activity per week (e.g., walking or climbing the stairs)

		affecting diabetes within 30 days prior to screening for this trial o Treatment with a GLP-1 receptor agonist within 180 days prior to screening • Serious renal impairment • A self-reported change in body weight > 5 kg (11 lb) within 90 days before screening • Treatment with any medication for the indication of obesity within the past 90 days before screening • Previous or planned obesity treatment with surgery or a weight loss device • Uncontrolled thyroid disease		

STEP TEENS[78]
Weghuber et al., 2022
NCT04102189
RCT
N = 201
US, Austria, Belgium, Croatia, Ireland, Mexico, Russian Federation, United Kingdom
	• SC semaglutide 2.4 mg weekly (134)
	• Placebo (67)
	
	Initiated at 0.25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached, or as tolerate
	
	68 weeks + 7 weeks off treatment
		Inclusion
		• Aged 12 to < 18 years at the time of signing
		• Body mass index (BMI) ≥ 95th percentile OR ≥ 85th percentile (on sex- and age-specific growth charts) with ≥ 1 weight-related comorbidity (treated or untreated): hypertension, dyslipidemia, OSA, or T2DM
		• History of at least one self-reported unsuccessful dietary effort to lose weight
		• For participants with T2DM at screening the following inclusion criteria applied:
		    o Participant was treated with either diet and exercise alone or stable treatment for at least 90 days prior to screening with metformin
		    o Glycated hemoglobin ≤ 10.0% (86 mmol/mol) as measured by central laboratory at screening
		Exclusion
		• A self-reported (or by parent[s] where applicable) change in body weight > 5 kg (11 lb) within 90 days before screening, irrespective of medical records
		• Treatment with any medication for the indication of obesity within the past 90 days
		• before screening
		• Previous surgical treatment for obesity (excluding liposuction if performed > 1 year
		• before screening)
		• Uncontrolled thyroid disease at screening, in the opinion of the investigator
		• Participants with secondary causes of obesity (i.e., hypothalamic, monogenic, or endocrine causes)
		• T1DM
		• Prepubertal participants (Tanner stage 1)
			Duration
			12 weeks
			
			Description
			Lifestyle intervention run-in phase according to regulatory guidelines; parents or guardians included
				Diet and exercise
				• Counseling about healthy nutrition and physical activity for weight loss beginning at run-in (week 12) and continuing through the entire trial.
				• Counseling must be done by a certified dietician or a similarly qualified health care professional according to local standards
				• Focus of the counseling in healthy nutrition must be to educate on healthier food choices focus of the counseling in physical activity is to encourage and reinforce a goal of 60 minutes of moderate to high-intensity physical activity per day
				• Activity trackers offered but optional

		• History of major depressive disorder or other severe or serious mental health condition		
Tirzepatide				
SURMOUNT-1[81] Jastreboff et al., 2022 NCT04184622 RCT N = 2,539 US	• SC tirzepatide 15 mg weekly (630) • SC tirzepatide 10 mg weekly (636) • SC tirzepatide 5 mg weekly (630) • Placebo (643) Initiated tirzepatide at 2.5 mg weekly and increased by 2.5 mg every 4 weeks up to target dose 72 weeks + 4 weeks safety period	Inclusion • Have a BMI ≥ 30 or ≥ 27 kg/m^2 and previously diagnosed with at least one of the following weight-related comorbidities: hypertension, dyslipidemia, OSA, CVD • Have a history of at least one self-reported unsuccessful dietary effort to lose body weight • Males willing to use reliable contractive • Females not of childbearing potential Exclusion • T1DM, T2DM • Self-reported change in body weight > 5 kg within 3 months prior to screening • Prior or planned surgical treatment for obesity • Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months • Serious renal impairment • Clinically significant gastric emptying abnormality • History of chronic or acute pancreatitis • Thyroid disease, or secondary obesity	None	Diet and exercise • Lifestyle intervention included regular lifestyle counseling sessions, delivered by a dietitian or a qualified health care professional, to help the participants adhere to healthful, balanced meals, with a deficit of 500 calories per day, and at least 150 minutes of physical activity per week
Exenatide				
Combat-JUDO[83] Weghuber et al., 2020 EudraCT 2015-001628-45 RCT N = 44 Austria, Sweden	• SC exenatide 2.0 mg weekly (33) • Placebo (33) Titration schedule NR 24 weeks + 2 weeks safety follow-up only	Inclusion • Aged age 10 to 18 years • At least 5 months with obesity • Sexually inactive or usage of adequate anticonception, negative pregnancy tests in females, and ability to understand and comply with the requirements of the study • BMI SD score > 2.0 or age-adapted BMI > 30 kg/m^2. Exclusion • Syndromal obesity • Pregnancy or lactation • Gastrointestinal disease, total or partial gastric or small intestine resection • Diabetes mellitus	None	Diet and exercise • 4 sessions each of nutritional, psychological, and physical treatment • Advised participants to follow a traffic light system for diet Psychological sessions aimed to optimize issues related to disturbed eating behavior, sleep pattern, media consumption, and sedentary behavior, exercise at home and at school

		• Kidney disease, hypo-/hyperthyroidism (unless under stable treatment), severe vitamin D insufficiency, or severe sleep apnea • Metformin treatment within 3 months prior to screening or concomitant medication influencing blood glucose or other parameters of the metabolic syndrome • Steroid treatment Concomitant medication addressing attention disorders, antidepressants that can lead to weight gain		
Derosa et al., 2010[84] RCT N = 128 Italy	• SC exenatide 20 µg daily (63) • Oral glibenclamide 15 mg daily (65) Exenatide: 5 µg twice a day for 1 month then increased to 10 µg twice a day for remainder of study Glibenclamide: 2.5mg three times a day for 1 month then glibenclamide 5mg three times a day 52 weeks	Inclusion • With T2DM • Poor glycemic control (i.e., HbA1c level > 8.0%) • Overweight BMI ≥ 25 and < 30 kg/m² receiving therapy with metformin at the mean dosage of 1,500 mg/day (SD, 500) • Intolerant to maximum dose metformin at 3,000 mg per day Exclusion • History of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, impaired hepatic function, impaired renal function, or severe anemia • Serious CVD or cerebrovascular conditions within 6 months before study enrollment • Pregnant or breastfeeding individuals	None	Diet and exercise • Controlled-energy diet (near 600 kcal daily deficit) • Standard diet advice was given by a dietitian or specialist doctor, including feedback on food diaries • Encouraged to increase physical activity by walking briskly or cycling for 20 to 30 minutes, 3 to 5 times per week Metformin • Continued on current dose
Fox et al., 2022[82] NCT02496611 RCT N = 66 US	• SC exenatide 2.0 mg weekly (33) • Placebo (33) Initiated and maintained at 2.0 mg weekly 52 weeks	Inclusion • Ages 12 to 18 years • BMI ≥ 1.2 × 95th percentile for age and sex norms or ≥ 35 kg/m², whichever was lower • Those who achieved reduction ≥ 5% BMI with meal replacement run-in were randomized Exclusion • Less than Tanner stage 2 • T1DM and T2DM • Previous (within 6 months) or current use of medications used primarily for weight loss • History of bariatric surgery • Dose changes in medications for dyslipidemia, prediabetes, or hypertension within the prior 6 months.	Duration 4 to 8 weeks Description • MRT; products included liquid shakes, prepackaged frozen entrée meals, fresh fruit and vegetables	Diet and exercise • Lifestyle therapy delivered monthly by trained coordinators at each in-person study visit and by telephone for the months during which there was no in-person visit • Adapted from the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored TODAY Study lifestyle therapy materials

			of 1,400 kcal/d	
Naltrexone-bupropion				
COR-1[85] Greenway et al., 2010 NCT00532779 RCT N = 1,742 US	• Oral NalBup 32/360 mg daily (583) • Oral NalBup 16/360 mg daily (578) • Placebo (581) High dose: Initiated at 8 mg/90 mg and escalated in fixed dose weekly to reach final dose at week 4 Low dose: Initiated at 4 mg/90 mg and escalated in fixed dose weekly to reach final dose at week 56 weeks	<u>Inclusion</u> • Aged 18 to 65 years • BMI 30 to 45 kg/m² and uncomplicated obesity, or BMI 27 to 45 kg/m² and controlled hypertension or dyslipidemia <u>Exclusion</u> • Obesity of known endocrine origin • T1DM or T2DM • Cerebrovascular, cardiovascular, hepatic, or renal disease • Previous surgical or device intervention for obesity; or loss or gain of more than 4 kg within3 months before randomization • History of seizures or serious psychiatric illness • Treatment with bupropion or naltrexone in the previous 12 months • History of drug or alcohol misuse in the previous 12 months Pregnant or breastfeeding women	None	Diet and exercise Regular instruction to follow hypocaloric diet (500 kcal per day deficit based on the WHO algorithm for calculating resting metabolic rate) and advice on lifestyle modification (including instructions to increase physical activity)
COR-II[86] Apovian et al., 2013 NCT00567255 RCT N = 1,496 US	• Oral NalBup 32/360 mg daily (1,001) • Placebo (495) Initiated at 8 gm/90 mg daily and increased weekly in fixed dose to target dose by week 5 56 weeks	<u>Inclusion</u> • 18 to 65 years of age • BMI ≥ 30 and ≤ 45kg/m² for subjects with uncomplicated obesity, and BMI of ≥ 27 and ≤ 45kg/m² for subjects with obesity and controlled hypertension and/or dyslipidemia • Normotensive (systolic ≤ 140 mmHg; diastolic ≤ 90 mmHg). Antihypertensive medications allowed with the exception of alpha-adrenergic blockers, and clonidine. • Medical regimen must be stable for at least 6 weeks prior to randomization • Medications for treatment of dyslipidemia are allowed as long as medical regimen has been stable for at least 6 weeks prior to randomization <u>Exclusion</u> • Obesity of known endocrine origin (e.g., untreated hypothyroidism, Cushing's syndrome)	None	Diet and exercise • At baseline, 12, 24, 36, and 48 weeks, participants received instructions to follow a hypocaloric diet (500 kcal/day deficit) and increase physical activity, and behavioral modification advice

		• Serious medical condition (including but not limited to renal or hepatic insufficiency; CHF, history of angina pectoris, myocardial infarction, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke) • T1DM or T2DM • History of surgical or device (e.g., gastric banding) intervention for obesity • History of treatment with bupropion, or naltrexone within the preceding 12 months • Use of drugs, herbs, or dietary supplements believed to significantly affect body weight or participation in a weight loss management program within one month prior to randomization • Loss or gain of more than 4.0 kg within 3 months prior to randomization • Pregnant or breastfeeding women		
COR-BMOD[89] Wadden et al., 2011 NCT00456521 RCT N = 793 US	• Oral NalBup 32/36 mg daily (591) • Placebo (202) Initiated at 8mg/90 mg per day and increased weekly in a fixed-dose regimen until target dose at week 4 56 weeks	Inclusion • Aged 18 to 65 years • BMI of 30 to 45 kg/m^2, or BMI of 27 to 45 kg/m^2 in the presence of controlled hypertension and/or dyslipidemia Exclusion • T1DM and T2DM • Significant cerebrovascular, cardiovascular, hepatic, or renal disease • Obesity of known endocrine origin • Previous surgical (or device) intervention for obesity • Loss or gain of > 4 kg within the previous 3 months • Use of medications known to affect body weight • History of seizures • Treatment with bupropion or naltrexone within the previous 12 months • History of drug or alcohol abuse within the previous 12 months • Current smokers and those who had used tobacco or other nicotine products within 6 months before screening Serious psychiatric illness (e.g., bipolar disorder, schizophrenia, bulimia, or conditions requiring psychotropic medications other than low doses of sedative hypnotics).	None	Intensive behavioral modification (BMOD) • Delivered to groups of 10 to 20 persons by registered dietitians, behavioral psychologists, or exercise specialists • Group meetings lasted 90 minutes and were held weekly for the first 16 weeks, every other week for the next 12 weeks, and monthly thereafter (yielding a total of 28 sessions) • All participants were instructed to consume a balanced deficit diet • Participants who weighed ≤ 249 lb were prescribed 1,200 kcal/day, whereas those 250 to 299 lb were prescribed 1,500 kcal/day, with higher allotments for heavier individuals

				Participants were instructed to keep daily records of their activity and aim for up to 360 minutes of activity per week.
COR-Diabetes[88] Hollander et al., 2013 NCT00474630 RCT N = 505 US	• Oral NalBup 32/36 mg daily (335) • Placebo (170) Initiated at 8 mg/90 mg per day and increased weekly in fixed-dose regimen until target dose reached at week 4 56 weeks	Inclusion • 18 to 70 years of age • BMI ≥ 27 and ≤ 45kg/m^2 • WithT2DM and on no injectable hypoglycemic medication or inhaled insulin for more than 3 months • On oral single or combination hypoglycemic medications (biguanides, thiazolidinediones, meglitinides, α-glucosidase inhibitors, sulfonylureas, DPP4 inhibitors) or no medications for the treatment of T2DM; oral hypoglycemic medication must be stable for at least 3 months prior to randomization • Systolic blood pressure < 145 mmHg; diastolic blood pressure < 95 mmHg. Antihypertensive medications are allowed with the exception of alpha-adrenergic blockers, and clonidine • Medications for treatment of dyslipidemia are allowed with the exception of cholestyramine and cholestypol as long as medical regimen has been stable for at least 4 weeks prior to randomization • HbA1c between 7 and 10%, fasting blood glucose < 270 mg/ml, fasting triglycerides < 400 mg/dL. Exclusion • T1DM	None	Diet and exercise • All participants were instructed to follow a hypocaloric diet (500 kcal deficit/day) • Participants received dietary counseling and the "Exchange Lists for Weight Management" booklets in accordance with the ADA guidelines • Participants received advice on behavioral modification, including written instructions, to increase physical activity (to walking for at least 30 minutes most days of the week)

		• Subjects with "brittle-diabetes" or any hospitalization or emergency room visit due to poor diabetic control within the past 6 months, previous history of diabetes-related dehydration leading to hospitalization, history or evidence of ketoacidosis • Obesity of known endocrine origin other than diabetes mellitus (e.g., untreated hypothyroidism, Cushing's syndrome, established PCOS) • Diabetes mellitus secondary to pancreatitis or pancreatectomy • Serious medical conditions (including but not limited to ongoing renal or hepatic insufficiency, heart failure, history of myocardial infarction, angina pectoris, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke • Loss or gain of more than 5.0 kg within previous 3 months • Severe microvascular or macrovascular complications of diabetes • History of surgical or device (e.g., gastric banding) intervention for obesity		
Halseth et al., 2017[90] Halseth et al., 2018[87] NCT01764386 RCT, open-label N = 242 US	• Oral NalBup 32/36 mg daily + CLI (153) • Usual care (89) Initiated at 8 mg/90 mg and increased to final dose over first 3 weeks of study 26 weeks controlled + 52 weeks uncontrolled	Inclusion • Adult male and female subjects, aged 18 to 60 years, had either obesity (BMI 30 to 45 kg/m^2) or overweight (BMI 27 to 45 kg/m^2) with dyslipidemia and/or controlled hypertension. Exclusion • T1DM or T2DM • Myocardial infarction within 6 months before screening; angina pectoris grade III/IV; clinical history of large vessel cortical strokes, including ischemic or hemorrhagic strokes • History of seizures, cranial trauma, bulimia, anorexia nervosa, or other conditions that predispose subjects to seizures • Chronic use or positive screen for opioids • Psychiatric conditions including mania, psychosis, acute depressive illness, or suicide risk • Regular use of tobacco products	None	Diet and exercise • During first 26 weeks NB group received a commercially available comprehensive lifestyle intervention (CLI); usual care received only general advice and recommendations on diet and exercise from their PCP • After 26 weeks all remaining participants received the same NalBup +CLI treatment
Phentermine-topiramate				

CONQUER/SEQUEL	• Oral PhenTop 15/92 mg daily (995)	Inclusion	None	Diet and exercise
Gadde et al., 2011[93] Garvey et al., 2012[95] Davidson et al., 2013[92] Garvey et al., 2014[94] NCT00553787/ NCT00796367 RCT N = 2,487 US	• Oral PhenTop 7.5/46 mg daily (498) • Placebo (994) Initiated at 3·75/23 mg and increased by 3.75/23 mg weekly until target dose reached 56 weeks (CONQUER) + 52 weeks (SEQUEL)	• Adults 18 to 70 years • Overweight or obese with a BMI of 27 to 45 kg/m² (no lower BMI limit for patients diagnosed with diabetes at baseline) • Two or more of the following comorbidities at baseline: o Systolic blood pressure 140 to 160 mmHg o (130 to 160 mmHg in patients with diabetes) o Diastolic blood pressure 90 to 100 mmHg (85 to 100 mmHg in patients with diabetes) o Taking at least two antihypertensive drugs; concentration of triglycerides 2.26 to 4.52 mmol/L o Using at least two lipid-lowering drugs o Fasting blood glucose greater than 5·55 mmol/L o Blood glucose greater than 7.77 mmol/L at 2 hours after oral glucose load during OGTT o Diagnosed with T2DM managed with lifestyle changes or metformin monotherapy o Waist circumference of at least 102 cm for men or at least 88 cm for women For extension study (SEQUEL): • Having completed CONQUER study • Female participants continue with contraception requirements Exclusion • Blood pressure > 160/100 mmHg • Fasting blood glucose > 13·32 mmol/L or triglycerides > 4.52 mmol/L at randomization • T1DM • Use of antidiabetic drugs other than metformin History of nephrolithiasis, recurrent major depression, presence or history of suicidal behavior or ideation with intent to act, and current substantial depressive symptoms For extension study (SEQUEL): • BMI < 22 at the completion of the CONQUER study • Continuously not taking the study drug for .4 week at the completion of the CONQUER study • Developing a condition during the		• Standardized diet and lifestyle modification counseling based on the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) program. At baseline, each patient was provided with written materials and advised to implement lifestyle changes as appropriate, and given instructions to reduce their caloric intake by 500 kcal/day

		• CONQUER study that would interfere with compliance or attainment of study measures Participating in another formal weight-loss program		
EQUIP[91] Allison et al., 2011 RCT N = 1,267 US	• Oral PhenTop 15/92 mg daily (512) • Oral PhenTop 3.75/23 mg daily (241) • Placebo (514) 4-week blinded titration period initiated at 3.75/23 and thereafter increased weekly by 3.75/23 mg increments to the assigned dose 56 weeks	Inclusion • Age 18 to 70 years • BMI ≥ 35 kg/m^2 (no upper limit) • Triglycerides ≤ 200 mg/dl with treatment of 0 to 1 lipid-lowering medication • BP ≤ 140/90 mmHg with treatment of 0 to 2 antihypertensive medications • Fasting serum glucose level ≤ 110 mg/dl. Exclusion • Weight gain or loss > 5 kg within past 3 months • History of eating disorders • Previous bariatric surgery, glaucoma, and nephrolithiasis • Thyroid dysfunction • Chronic systemic glucocorticoid therapy • Bipolar disorder or psychosis history, > 1 lifetime episode of major depression, current depression of moderate or greater severity, presence or history of suicidal behavior or ideation with some intent to act, or antidepressant use that had not been stable for at least 3 months • Stroke, myocardial infarction, life-threatening arrhythmia, or coronary revascularization within past 6 months • Unstable angina, CHF, or known or suspected clinically significant cardiac valvulopathy • Cholelithiasis within past 6 months • Use of any investigational medication or device within the last month	None	Diet and exercise • All patients were provided with standardized lifestyle counseling, based on the LEARN Manual and advised to follow a 500 kcal daily reduction in dietary intake, increased water consumption, and increased physical activity
OB-403[96] Kelly et al., 2022 NCT03922945 RCT N = 223 US	• Oral PhenTop 15/92 mg daily (113) • Oral PhenTop 7.5/46 mg daily (54) • Placebo (56) High dose: • Weeks 1 and 2: 3.75/23 mg daily • Weeks 3 through 12: 7.5/46 mg daily	Inclusion • 12 to less than 17 years of age • BMI in the 95th percentile or greater for age and sex • Tanner stage greater than 1 • Stable body weight • Documented history of insufficient weight loss with lifestyle modification. Exclusion • Treatment with antiobesity medications • History of bariatric surgery or eating disorders	None	Diet and exercise • All participants were instructed to follow a mild hypocaloric diet modification program representing a 500 kcal/day deficit and to implement a family-based lifestyle modification program for adolescents,

	• Weeks 13 and 14: 11.25/69 mg daily • Weeks 15 to end of study: 15/92 mg daily <u>Low dose:</u> • Weeks 1 and 2: phe-top 3.75/23 mg daily • Weeks 3 through end of study: 7.5/46 mg daily 56 weeks	• Stimulant use for treatment of attention-deficit/hyperactivity disorder within 3 months of screening • T1DM • Medical treatment with insulin, sulfonylureas, GLP-1 agonists, SGLT-1 inhibitors, and SGLT-2 inhibitors • Congenital heart disease • Obesity of a known genetic or endocrine origin • Elevated blood pressure • History of bipolar disorder or psychosis, major depressive disorder, current depression of moderate or greater severity, or presence or history of suicidal behavior or ideation with intent to act		as tolerated, throughout the study period • Lifestyle program included physical activity, behavior change, and family support
Setmelanotide				
Clement et al., 2020[100] Kuhnen et al., 2022[99] NCT02896192 NCT03287960 Single-arm N = 22 US, Belgium, France, Germany, the Netherlands, the United Kingdom	SC setmelanotide 3.0 mg daily (22) Initiated at 0.5 mg daily for individuals ≤ 18 and 1.0 mg daily for individuals > 18 years, and increased every 2 weeks by 0.5 mg until target dose 12 weeks at therapeutic dose + 40 weeks of phases (including 4 weeks on PBO in persons with successful weight loss)	<u>Inclusion</u> • Homozygous or compound heterozygous variants in POMC, PCSK1, or LEPR • Age 6 years and above • Obesity with BMI ≥ 30 kg/m^2 (age ≥ 18 years); obesity with BMI ≥ 95th percentile for age on growth chart assessment (age < 18 years) <u>Exclusion</u> • A recent diet or exercise regimen, or both, resulting in weight loss or stabilization and previous gastric bypass surgery resulting in more than 10% weight loss with no evidence of weight regain • Current or history of severe lung, liver, or kidney disease	None	None/NR
Haqq et al., 2022[97] Forsythe et al., 2023[98] NCT03746522 RCT + open-label N = 38 US, Canada, France, Spain, the United Kingdom	SC setmelanotide 3.0 mg daily (19) Placebo (19) Patients < 16 years initiated at 1.0 mg and ≥ 16 years at 2.0 mg and increased by 1.0 mg per week to target dose; dose escalation repeated	<u>Inclusion</u> • BBS clinical diagnosis as per Beales criteria or Alström syndrome diagnosis as per Marshall criteria ○ ≥ 90% of patients with BBS and 100% of patients with Alström syndrome were required to have a genetically confirmed diagnosis • Age ≥ 6 years at the time of randomization • Clinical obesity, defined as BMI ≥ 30 kg/m^2 (for those ≥ 16 years) or weight > 97th percentile for age and sex on growth charts (for those aged 6 to 15 years)	None	Nutritional counseling and monitoring was provided for pediatric patients (< 12 years) to ensure adequate nutritional intake

	on weeks 15 and 16 for open-label period 14 weeks randomized + 52 weeks open-label	Exclusion • > 2% weight loss from diet, exercise program, or both, with or without the use of weight loss agents, in prior 2 months • Use of any obesity medication within prior 3 months. GLP-1 receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus as long as (1) the dose has been stable for ≥ 3 months prior to randomization and is planned to remain stable throughout the study, (2) it is not being prescribed for the treatment of obesity, and (3) the patient has not experienced weight loss during the previous 3 months • > 10% durable weight loss from gastric bypass surgery • Diagnosis of psychiatric disorder that will interfere with study compliance • Patients without neurocognitive defects should not have a Patient Health Questionnaire-9 score ≥ 15, any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale, any lifetime history of a suicide attempt, or any suicidal behavior in prior month • Current pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study • Hemoglobin A1c > 9·0% • History of significant liver (other than NAFLD) or kidney disease or injury		
Haws et al., 2020[101] NCT03013543 Single-arm N = 10 US, Canada, France, Germany, Greece, Netherlands, Spain, the United Kingdom	SC setmelanotide 3.0 mg daily (10) Initiated at 0.5 mg daily for adolescents and 1.0 mg daily for adults, and increased by 0.5 mg every 2 weeks until target dose reached 12 weeks + 52 weeks extension for individuals successful with weight loss of 5 kg or ≥ 5% if baseline body weight was < 100 kg	Inclusion • Adults aged ≥ 18 years with BMI of 30 kg/m^2 or higher • Adolescents aged 12 to 17 years with a body weight > than 97th percentile (adjusted for age and sex) • Diagnosis of BBS Exclusion • Achieved > 2% weight loss from intensive diet or exercise regimens within 2 months of enrollment or > than 10% weight loss durably maintained after gastric bypass surgery • Diagnosis of a mental disorder that could substantially interfere with study adherence • Any suicidal ideation or history of suicide attempt • Clinically significant pulmonary, cardiac or oncologic disease (including dermatologic findings	None	None/NR

		• Related to melanoma); history of liver disease other than nonalcoholic fatty liver disease; impaired glomerular filtration rate (≤ 30 mL/min/1.73 m^2) • Family history of skin cancer, melanoma or oculocutaneous albinism; or an inability to adhere to a once-daily injection.		

Note. Shaded rows are in children and adolescent populations only.

Abbreviations. ADA: American Diabetes Association; AE: adverse event; BBS: Bardet-Biedl syndrome; BMI: body mass index; CGM: continuous glucose monitoring device; CHF: congestive heart failure; CLI: comprehensive lifestyle intervention; CVD: cardiovascular disease; GDM: gestational diabetes; GFR: glomerular filtration rate; GLP-1: glucagon-like peptide-1; HbA1c: hemoglobin A1c; LDL: low-density lipoprotein; NAFLD: non-alcoholic fatty liver disease; NalBup: naltrexone-bupropion; OGTT: oral glucose tolerance test; OSA: obstructive sleep apnea; PCOS: polycystic ovary syndrome; PhenTop: phentermine-topiramate; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation; SGLT: sodium-glucose cotransporter-2; T1DM: type 1 diabetes; T2DM: type 2 diabetes; WHO: World Health Organization; yr: year.

Table B2. Participant Baseline Characteristics: Included Studies for Effectiveness and Harms

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
Semaglutide vs. liraglutide			
STEP 8[55] Rubino et al., 2022 NCT04074161 RCT N = 338 (126 vs. 127 vs. 85)	2.4 mg semaglutide vs. 3.0 mg liraglutide vs. PBO General • Mean age, years (SD): 48 (14) vs. 49 (13) vs. 51 (12) • Female, n (%): 102 (81.0) vs. 97 (76.4) vs. 66 (77.6) • Mean weight, kg (SD): 102.5 (25.3) vs. 103.7 (22.5) vs. 108.8 (23.1) • Mean BMI (SD): 37.0 (7.4) vs. 37.2 (6.4) vs. 38.8 (6.5) • Mean HbA1c % (SD): 5.5 (0.3) vs. 5.5 (0.3) vs. 5.6 (0.4) Other primary condition or comorbidities, n (%) • Prediabetes: 43 (34.1) vs. 45 (35.4) vs. 34 (40.0) • Dyslipidemia: 60 (47.6) vs. 65 (51.2) vs. 36 (42.4) • Hypertension: 48 (38.1) vs. 55 (43.3) vs. 39 (45.9) • Knee osteoarthritis: 23 (18.3) vs. 17 (13.4) vs.22 (25.9) • Obstructive sleep apnea: 24 (19.0) vs. 18 (14.2) vs. 19 (22.4) • NAFLD: 5 (4.0) vs. 12 (9.4) vs. 7 (8.2) • PCOS: 5 (4.9) vs. 6 (6.2) vs. 1 (1.5) • CAD: 4 (3.2) vs. 3 (2.4) vs. 4 (4.7)	2.4 mg sema vs. 3.0 mg lira vs. PBO • Asian: 4 (3.2) vs. 6 (4.7) vs. 3 (3.5) • Black or African American: 25 (19.8) vs. 20 (15.7) vs. 19 (22.4) • Hispanic or Latino: 15 (11.9) vs. 17 (13.4) vs. 7 (8.2) • White: 94 (74.6) vs. 95 (74.8) vs. 60 (70.6) • Other: 3 (2.4) vs. 6 (4.7) vs. 3 (3.5)	2.4 mg sema vs. 3.0 mg lira vs. PBO Glucose-lowering • Exclusion criteria Other • NR
Liraglutide			
Elkind-Hirsch et al., 2020[66] NCT01234649 RCT N = 153 (78 vs. 75)	1.8 mg liraglutide vs. PBO General • Mean age, years (SD): 31.5 (4.4) vs. 31 (4.2) • Female, n (%): 35 (100) vs. 37 (100) • Mean weight, kg (SD): 101.2 (23.5) vs. 94 (19.0) • Mean BMI (SD): 37.7 (7.6) vs. 34.3 (6.0) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • NR	1.8 mg liraglutide vs. PBO • African American: 11(14) vs. 17 (23) • Caucasian: 67 (86) vs. 58 (77)	1.8 mg liraglutide vs. PBO Glucose-lowering: • Exclusion criteria other than metformin (required) Other: • NR
Ellipse[71] Tamborlane et al., 2019	Up to 1.8 mg liraglutide vs. PBO General • Mean age, years (SD): 14.6 (1.7) vs. 14.6 (1.7)	Up to 1.8 mg liraglutide vs. PBO • American Indian or Alaska Native: 2 (3.0) vs. 1 (1.5)	Up to 1.8 mg liraglutide vs. PBO Glucose-lowering:

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
NCT01541215 RCT N = 135 (66 vs. 69)	• Female, n (%): 41 (62.1) vs. 42 (61.8) • Mean weight, kg (SD): 93.3 (31.0) vs. 89.8 (22.1) • Mean BMI (SD): 34.6 (10.9) vs. 33.3 (7.4) • Mean HbA1c % (SD): 7.87 (1.4) vs. 7.69 (1.3) Other primary condition or comorbidities, n (%) • NR	• Asian: 10 (15.2) vs. 8 (11.8) • Black: 9 (13.6) vs. 7 (10.3) • Hispanic or Latinx: 16 (24.2) vs. 23 (33.8) • Native Hawaiian or Other Pacific Islander: 0 (0) vs. 0 (0) • White: 42 (63.6) vs. 45 (66.2) • Other: 3 (4.5) vs. 7 (10.3)	• Metformin: 66 (100) vs. 68 (100) • Basal insulin: 15 (22.7) vs. 10 (14.7) Other: • NR
Ghanim et al., 2020[67] NCT01753362 RCT N = 84 (42 vs. 42)	1.8 mg liraglutide vs. PBO General • Mean age, years (SD): 47 (2) vs. 45 (3) • Female, n (%): 24 (64.9) vs. 16 (59.3) • Mean weight, kg (SD): 94.2 (3.1) vs. 83.3 (3.4) • Mean BMI (SD): 33.3 (1.2) vs. 29.5 (1.3) • Mean HbA1c % (SD): 7.96 (0.2) vs. 7.79 (0.2) Other primary condition or comorbidities, n (%) • T1DM: 37 (100) vs. 27 (100)	1.8 mg liraglutide vs. PBO • NR	1.8 mg liraglutide vs. PBO Glucose-lowering: • Metformin: 3 (8.1) vs. 1 (3.7) Other: • Antihypertensives: 21 (56.8) vs. 15 (55.6) • Statins: 14 (37.8) vs. 13 (48.1)
Kelly et al., 2020[60] NCT02918279 RCT N = 251 (125 vs. 126)	3.0 mg liraglutide vs. PBO General • Mean age, years (SD): 14.6 (1.6) vs. 14.5 (1.6) • Female, n (%): 71 (56.8) vs. 78 (61.9) • Mean weight, kg (SD): 99.3 (19.7) vs. 102.2 (21.6) • Mean BMI (SD): 35.3 (5.1) vs. 35.8 (5.7) • Mean HbA1c % (SD): 5.3 (0.4) vs. 5.3 (0.4) Other primary condition or comorbidities, n (%) • Dysglycemia (prediabetes or T2DM): 32 (25.6) vs. 33 (26.2)	3.0 mg liraglutide vs. PBO • American Indian or Alaska Native: 0 (0) vs. 1 (0.8) • Asian: 2 (1.6) vs. 0 (0) • Black: 14 (11.2) vs. 6 (4.8) • Hispanic or Latino: 32 (25.6) vs. 24 (19.0) • White: 105 (84.0) vs. 115 (91.3) • Other: 4 (3.2) vs. 4 (3.2)	3.0 mg liraglutide vs. PBO Glucose-lowering: • Only metformin allowed, but proportion on with not reported Other: • NR
LIDO[72] Dubé, 2017 NCT01787916 RCT crossover N = 15	1.8 mg liraglutide vs. PBO (n = 15) General • Mean age, years (SD): 35.8 (1.7) • Female, n (%): 8 (53.3) • Mean weight, kg (SD): 89.0 (3.8) • Mean BMI (SD): 30.5 (0.9) • Mean HbA1c % (SD): 7.4 (0.1) Other primary condition or comorbidities, n (%) • T1DM: 15 (100)	1.8 mg liraglutide vs. PBO • NR	1.8 mg liraglutide vs. PBO Glucose-lowering: • NR Other: • Antihypertensives: 2 (13.3)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications

LIRA-1
Dejgaard et al., 2016[69]
NCT01612468
RCT
N = 100 (50 vs. 50)
	1.8 mg liraglutide vs. PBO
	General
	• Mean age, years (SD): 47 (13) vs. 49 (12)
	• Female, n (%): 20 (40) vs. 15 (30)
	• Mean weight, kg (SD): 93·4 (14·2) vs. 94·0 (12·5)
	• Mean BMI (SD): 30·3 (3·5) vs. 29·8 (3·1)
	• Mean HbA1c % (SD): 8·7 (0·7) vs. 8·7 (0·7)
	Other primary condition or comorbidities, n (%):
	• T1DM: 50 (100) vs. 50 (100)
	• Dyslipidaemia: 33 (66) vs. 38 (76)
	• Hypertension: 25 (50) vs. 30 (60)
		1.8 mg liraglutide vs. PBO
		Caucasians: 50 (100) vs. 50 (100)
			1.8 mg liraglutide vs. PBO
			Glucose-lowering:
			• NR
			Other:
			• Antihypertensives:
			  ○ ACE inhibitors: 12 (24) vs. 20 (40)
			  ○ ARBs: 6 (12) vs. 10 (20)
			  ○ Beta blockers: 0 (0) vs. 4 (8)
			  ○ Calcium channel blockers: 6 (12) vs. 5 (10)
			  ○ Diuretics: 11 (22) vs. 15 (30)
			  ○ Other: 4 (8) vs. 5 (10)
			• Aspirin: 11 (22) vs. 17 (34)
			• Lipid-lowering agents: 27 (54) vs. 36 (72)

LOSEIT[64] Gudbergsen et al., 2021 NCT02905864 RCT N = 156 (80 vs. 76)	3.0 mg liraglutide vs. PBO General • Mean age, years (SD): 59.2 (10.8) vs. 59.3 (9.7) • Female, n (%): 52 (65) vs. 49 (64) • Mean weight, kg (SD): 96.3 (18.2) vs. 90.8 (14.3) • Mean BMI (SD): 32.8 (5.5) vs. 31.3 (4.0) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • NR	3.0 mg liraglutide vs. PBO • NR	3.0 mg liraglutide vs. PBO Glucose-lowering: • Exclusion criteria Other: • NR
SCALE Diabetes[57] Davies et al., 2015 NCT01272232 RCT N = 846 (423 vs. 211 vs. 212)	3.0 mg liraglutide vs. 1.8 mg liraglutide vs. PBO General • Mean age, years (SD): 55.0 (10.8) vs. 54.9 (10.7) vs. 54.7 (9.8) • Female, n (%): 203 (48.0) vs. 203 (48.0) vs. 115 (54.2) • Mean weight, kg (SD): 105.7 (21.9) vs. 105.8 (21.0) vs. 106.5 (21.3) • Mean BMI (SD): 37.1 (6.5) vs. 37.0 (6.9) vs. 37.4 (7.1) • Mean HbA1c % (SD): 7.9 (0.8; n = 412) vs. 8.0 (0.8; n = 204) vs.7.9 (0.8)	3.0 mg liraglutide vs. 1.8 mg liraglutide vs. PBO • Asian: 11 (2.6) vs. 4 (1.9) vs.4 (1.9) • Black or African American: 44 (10.4) vs. vs. 27 (12.8) vs. 27 (12.7) • Hispanic or Latino: 46 (10.9) vs. 17 (8.1) vs. 24 (11.3) • White: 353 (83.5) vs. 177 (83.9) vs. 175 (82.5) • Other: 13 (3.1) vs. 3 (1.4) vs. 5 (2.4)	3.0 mg liraglutide vs. 1.8 mg liraglutide vs. PBO Glucose-lowering • Metformin only: 237 (57.5) vs. 111 (54.4) vs. 126 (59.7) • Metformin and glitazone: 22 (5.3) vs. 13 (6.4) vs. 10 (4.7) • Metformin and sulfonylurea: 86 (20.9) vs. 44 (21.6) vs. 48 (22.7) • Metformin, sulfonylurea, and glitazone: 10 (2.4) vs. 4 (2.0) vs. 4 (1.9)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
	• Diet and exercise only: 46 (11.2) vs. 29 (14.2) vs. 20 (9.5) Other primary condition or comorbidities, n (%) • T2DM: 423 (100) vs. 211 (100) vs. 212 (100) • CVD at screening: 69 (16.4) vs. 31 (14.8) vs. 26 (12.3) • Dyslipidemia: 295 (69.7) vs. 143 (67.8) vs. 126 (59.4) • Hypertension: 293 (69.3) vs. 148 (70.1) vs. 145 (68.4)		• Sulfonylurea only: 7 (1.7) vs. 2 (1.0) vs. 2 (0.9) • Sulfonylurea and glitazone: 4 (1.0) vs. 1 (0.5) vs. 1 (0.5) • Concomitant OHA at baseline: 366 (88.8) vs. 175 (85.8) vs.191 (90.5) Other: • NR
SCALE IBT[63] Wadden et al., 2020 NCT02963935 RCT N = 282 (142 vs. 144)	3.0 mg liraglutide vs. PBO General • Mean age, years (SD): 45.4 (11.6) vs. 49.0 (11.2) • Female, n (%): 119 (83.8) vs. 116 (82.9) • Mean weight, kg (SD): 108.5 (22.1) vs. 106.7 (22.0) • Mean BMI (SD): 39.3 (6.8) vs. 38.7 (7.2) • Mean HbA1c % (SD): 5.5 (0.4) vs. 5.5 (0.4) Other primary condition or comorbidities, n (%) • NR	3.0 mg liraglutide vs. PBO • Asian: 2 (1.4) vs. 3 (2.1) • Black: 27 (19.0) vs. 22 (15.7) • Not Hispanic or Latinx: 118 (83.1) vs. 131 (93.6) • White: 112 (78.9) vs. 115 (82.1)	3.0 mg liraglutide vs. PBO Glucose-lowering: • Exclusion criteria Other: • NR
SCALE Insulin[59] Garvey et al., 2020 NCT02963922 RCT N = 396 (198 vs. 198)	3.0 mg liraglutide vs. PBO General • Mean age, years (SD): 55.9 (11.3) vs. 57.6 (10.4) • Female, n (%): 108 (54.5) vs. 99 (50.0) • Mean weight, kg (SD): 100.6 (20.8) vs. 98.9 (19.9) • Mean BMI (SD): 35.9 (6.5) vs. 35.3 (5.8) • Mean HbA1c % (SD): 7.9 (1.1) vs. 8 (1.0) Other primary condition or comorbidities, n (%) • NR	3.0 mg liraglutide vs. PBO • Asian: 3 (1.5) vs. 5 (2.5) • Black: 17 (8.6) vs. 11 (5.6) • Not Hispanic or Latinx: 155 (78.3) vs. 169 (85.4) • White: 174 (87.9) vs. 180 (90.9)	3.0 mg liraglutide vs. PBO Glucose-lowering: • Biguanides: 175 (88.4) vs. 176 (88.9) • Sulfonylureas: 68 (34.3) vs. 71 (35.9) • SGLT2is: 44 (22.2) vs. 44 (22.2) • Thiazolidinediones: 4 (2.0) vs. 6 (3.0) • a-Glucosidase inhibitors: 2 (1.0) vs. 0 (0.0) • Combination oral glucose-lowering drugs: 4 (2.0) vs. 3 (1.5) • Other, excluding insulins: 1 (0.5) vs. 5 (2.5) • Long-acting insulin: 180 (90.9) vs. 184 (92.9)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
			• Intermediate-acting insulin: 18 (9.1) vs. 14 (7.1) Other: • NR
SCALE Maintenance[62] Wadden et al., 2013 NCT00781937 RCT N = 422 (212 vs. 210)	3.0 mg liraglutide vs. PBO General • Mean age, years (SD): 45.9 (11.9) vs. 46.5 (11) • Female, n (%): 178 (84) vs. 166 (79) • Mean weight, kg (SD): 100.4 (20.8) vs. 98.7 (21.2) • Mean BMI (SD): 36.0 (5.9) vs. 35.2 (5.9) • Mean HbA1c % (SD): 5.6 (0.4) vs. 5.6 (0.4) Other primary condition or comorbidities, n (%) • Dyslipidemia: 59 (28) vs. 65 (31) • Hypertension: 71 (33) vs. 61 (29)	3.0 mg liraglutide vs. PBO • Asian or other: 10 (5) vs. 1 (1) • Black or African American: 32 (15) vs. 24 (11) • White: 170 (80) vs. 185 (88)	3.0 mg liraglutide vs. PBO Glucose-lowering: • Exclusion criteria Other: • NR
SCALE Obesity and Prediabetes Pi-Sunyer et al., 2015[56] Kolotkin et al., 2016[61] le Roux et al., 2017[58] Kolotkin et al., 2018[68] NCT01272219 RCT N = 3731 (2.487 vs. 1,244)	3.0 mg liraglutide vs. PBO General • Mean age, years (SD): 45.2 (12.1) vs. 45.0 (12.0) • Female, n (%): 1,957 (78.7) vs. 971 (78.1) • Mean weight, kg (SD): 106.2 (21.2) vs. 106.2 (21.7) • Mean BMI (SD): 38.3 (6.4) vs. 38.3 (6.3) • Mean HbA1c % (SD): 5.6 (0.4) vs. 5.6 (0.4) Other primary condition or comorbidities, n (%) • Prediabetes: 1,528 (61.4) vs. 757 (60.9) • CVD: 216 (8.7) vs. 105 (8.5) • Dyslipidemia: 737 (29.6) vs. 359 (28.9) • Hypertension: 850 (34.2) vs. 446 (35.9) • Dyslipidemia and hypertension: 417 (16.8) vs. 213 (17.1) • Gallbladder disease: 349 (14.0) vs. 163 (13.1)	3.0 mg liraglutide vs. PBO • American Indian or Alaska Native: 5 (0.2) vs. 4 (0.3) • Asian: 90 (3.6) vs. 46 (3.7) • Black: 242 (9.7) vs. 114 (9.2) • Hispanic or Latino: 259 (10.4) vs. 134 (10.8) • Native Hawaiian or other Pacific Islander: 2 (0.08) vs. 2 (0.2) • White: 2,107 (84.7) vs. 1,061 (85.3) • Other: 41 (1.6) vs. 17 (1.4)	3.0 mg liraglutide vs. PBO Glucose-lowering: • NR Other: • Antihypertensive drugs: 754 (30.9) vs. 404 (33.0) • Lipid-lowering drugs: 386 (15.8) vs. 183 (14.9)
S-LiTE Lundgren et al., 2021 NCT04122716 RCT	3.0 mg liraglutide + exercise vs. 3.0 mg liraglutide vs. PBO vs. exercise General • Mean age, years (SD): 42 (12) vs. 43 (12) vs. 43 (12) vs. 43 (12)	3.0 mg liraglutide + exercise vs. 3.0 mg liraglutide vs. PBO vs. exercise • NR	3.0 mg liraglutide + exercise vs. 3.0 mg liraglutide vs. PBO vs. exercise Glucose-lowering: • NR Other:

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
N = 195 (49 vs. 49 vs. 49 vs. 49 vs. 48)	• Female, n (%): 31 (63) vs. 31 (63) vs. 31 (63) vs. 31 (65) • Mean weight, kg (SD): 98.3 (11.5) vs. 95.1 (12.8) vs. 96.7 (12.7) vs. 96.8 (13.2) • Mean BMI (SD): 32.8 (2.4) vs. 32.7 (3.1) vs. 32.3 (3.0) vs. 32.7 (3.0) • Mean HbA1cv mmol/mol (SD): 34 (3) vs. 34 (4) vs. 34 (4) vs. 34 (4) Other primary condition or comorbidities, n (%) • NR		• NR
Semaglutide			
STEP 1 Wilding et al., 2021[80] Wilding et al., 2022[77] NCT03548935 RCT N = 1,961 (1,306 vs. 655)	2.4 mg semaglutide vs. PBO General • Mean age, years (SD): 46 (13) vs. 47 (12) • Female, n (%): 955 (73.1) vs. 498 (76.0) • Mean weight, kg (SD): 105.4 (22.1) vs. 105.2 (21.5) • Mean BMI (SD): 37.8 (6.7) vs. 38.0 (6.5) • Mean HbA1c % (SD): 5.7 (0.3) vs. 5.7 (0.3) Other primary condition or comorbidities, n (%) • Prediabetes: 593 (45.4) vs. 263 (40.2) • Dyslipidemia: 499 (38.2) vs. 226 (34.5) • Hypertension: 472 (36.1) vs. 234 (35.7) • Knee osteoarthritis: 173 (13.2) vs. 102 (15.6) • Obstructive sleep apnea: 159 (12.2) vs. 71 (10.8) • NAFLD: 101 (7.7) vs. 62 (9.5) • PCOS: 62/955 (6.5) vs. 34/498 (6.8) • CAD: 32 (2.5) vs. 17 (2.6)	2.4 mg semaglutide vs. PBO • Asian: 181 (13.9) vs. 80 (12.2) • Black or African American: 72 (5.5) vs. 39 (6.0) • Hispanic or Latino: 150 (11.5) vs. 86 (13.1) • White: 973 (74.5) vs. 499 (76.2) • Other: 80 (6.1) vs. 37 (5.6)	2.4 mg semaglutide vs. PB Glucose-lowering • Exclusion criteria Other • NR
STEP 2[75] Davies et al., 2021 NCT03552757 RCT N = 1,210 (404 vs. 403 vs. 403)	2.4 mg semaglutide vs. 1.0 mg semaglutide vs. PBO General • Mean age, years (SD): 55 (11) vs. 56 (10) vs. 55 (11) • Female, n (%): 223 (55.2) vs. 203 (50.4) vs. 190 (47.1) • Mean weight, kg (SD): 99.9 (22.5) vs. 99.0 (21.1) vs. 100·5 (20.9) • Mean BMI (SD): 35.9 (6.4) vs. 35.3 (5.9) vs. 35.9 (6.5) • Mean HbA1c % (SD): 8.1 (0.8) vs. 8.1 (0.8) vs. 8.1 (0.8)	2.4 mg semaglutide vs. 1.0 mg semaglutide vs. PBO • Asian: 112 (27.7) vs. 97 (24.1) vs. 108 (26.8) • Black or African American: 35 (8.7) vs. 28 (6.9) vs. 37 (9.2) • Hispanic or Latino: 47 (11.6) vs. 59 (14.6) vs. 49 (12.2) • White: 237 (58.7) vs. 272 (67.5) vs. 242 (60.0)	2.4 mg semaglutide vs. 1.0 mg semaglutide vs. PBO Glucose-lowering • Biguanides: 370 (91.6) vs. 379 (94.0) vs. 62 (89.8) • Sulfonylureas: 110 (27.2) vs. 99 (24.6) vs. 99 (24.6) • SGLT2 inhibitors: 99 (24.5) vs. 96 (23.8) vs. 105 (26.1)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
	Other primary condition or comorbidities, n (%) • CAD: 26 (6.4%) vs. 40 (9.9%) vs. 33 (8.2) • Dyslipidemia: 265 (65.6) vs. 277 (68.7) vs. 284 (70.5) • Hypertension: 276 (68.3) vs. 285 (70.7) vs. 287 (71.2) • Knee osteoarthritis: 73 (18.1) vs. 73 (18.1) vs. 67 (16.6) • Obstructive sleep apnea: 68 (16.8) vs. 54 (13.4) vs. 54 (13.4) • NAFLD: 85 (21.0) vs. 82 (20.3) vs. 94 (23.3) • PCOS: 7 of 223 (3.1) vs. 8 of 203 (3.9) vs. 10 of 190 (5.3)	• Other: 20 (5.0) vs. 6 (1.5) vs. 16 (4.0)	• Thiazolidinediones: 19 (4.7) vs. 16 (4.0) vs. 9 (4.7) • DPP-4 inhibitors: 2 (0.5) vs. 3 (0.7) vs. 1 (0.2) • α-Glucosidase inhibitors: 1 (0.2) vs. 1 (0.2) vs. 0 (0) • GLP-1 receptor agonists: 0 (0) vs. 1 (0.2) vs. 0 (0) • Fast-acting insulins and insulin analogues: 0 (0) vs. 0 (0) vs. 1 (0.2) • Other: 1 (0.2) vs. 0 (0) vs. 0 (0) Other • NR
STEP 3[73] Wadden et al., 2021 NCT03611582 RCT N = 611 (407 vs. 204)	2.4 mg semaglutide vs. PBO General • Mean age, years (SD): 46 (13) vs. 46 (13) • Female, n (%): 315 (77.4) vs. 180 (88.2) • Mean weight, kg (SD): 106.9 (22.8) vs. 103.7 (22.9) • Mean BMI (SD): 38.1 (6.7) vs. 37.8 (6.9) • Mean HbA1c % (SD): 5.7 (0.3) vs. 5.8 (0.3) Other primary condition or comorbidities, n (%) • Dyslipidemia: 145 (35.6) vs. 67 (32.8) • Hypertension: 145 (35.6) vs. 67 (32.8) • Knee osteoarthritis: 76 (18.7) vs. 31 (15.2) • Obstructive sleep apnea: 58 (14.3) vs. 19 (9.3) • NAFLD: 23 (5.7) vs. 12 (5.9) • PCOS: 17 (5.4) vs. 10 (5.6) • CAD: 6 (1.5) vs. 4 (2.0)	2.4 mg semaglutide vs. PBO • American Indian or Alaska Native: 1 (0.2) vs. 0 (0) • Asian: 5 (1.2) vs. 6 (2.9) • Black or African American: 80 (19.7) vs. 36 (17.6) • Hispanic or Latino: 75 (18.4) vs. 46 (22.5) • Native Hawaiian or other Pacific Islander: 3 (0.7) vs. 0 (0) • White: 307 (75.4) vs. 158 (77.5) • Other: 11 (2.7) vs. 4 (2.0)	2.4 mg semaglutide vs. PBO Glucose-lowering • Exclusion criteria Other • NR
STEP 4[74] Rubino et al., 2021 NCT03548987 RCT N = 803 (535 vs. 268)	2.4 mg semaglutide vs. PBO General • Mean age, years (SD): 47 (12) vs. 46 (12) • Female, n (%): 429 (80.2) vs. 205 (76.5) • Mean weight, kg (SD): 96.5 (22.5) vs. 95.4 (22.7) • Mean BMI (SD): 34.5 (6.9) vs. 34.1 (7.1) • Mean HbA1c % (SD): 5.4 (0.3) vs. 5.4 (0.3) Other primary condition or comorbidities, n (%)	2.4 mg semaglutide vs. PBO • Asian: 15 (2.8) vs. 4 (1.5) • Black or African American: 69 (12.9) vs. 35 (13.1) • Hispanic or Latino ethnicity: 42 (7.9) vs. 21 (7.8) • White: 446 (83.4) vs. 226 (84.3) • Other: 5 (0.9) vs. 3 (1.1)	2.4 mg semaglutide vs. PBO Glucose-lowering • NR Other • Antihypertensive medication: 149 (27.9%) vs. 67 (25.0%) • Lipid-lowering medication: 70 (13.1%) vs. 36 (13.4%)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
	• CAD: 4 (0.7) vs. 3 (1.1) • Dyslipidemia: 189 (35.3) vs. 99 (36.9) • Hypertension: 199 (37.2) vs. 99 (36.9) • Knee osteoarthritis: 72 (13.5) vs. 27 (10.1) • Nonalcoholic fatty liver disease: 37 (6.9) vs. 18 (6.7) • Obstructive sleep apnea: 61 (11.4) vs. 33 (12.3) • Polycystic ovary syndrome: 15 (3.5) vs. 10 (4.9)		
STEP 5[79] Garvey et al., 2022 NCT03693430 RCT N = 304 (152 vs. 152)	2.4 mg semaglutide vs. PBO General • Mean age, years (SD): 47.3 (11.7) vs. 47.4 (10.3) • Female, n (%): 123 (80.9) vs. 113 (74.3) • Mean weight, kg (SD): 105.6 (20.8) vs. 106.5 (23.1) • Mean BMI (SD): 38.6 (6.7) vs. 38.5 (7.2) • Mean HbA1c % (SD): 5.7 (0.3) vs. 5.7 (0.4) Other primary condition or comorbidities, n (%) • Dyslipidemia: 58 (38.2) vs. 49 (32.2) • Hypertension: 56 (36.8) vs. 62 (40.8) • Knee osteoarthritis: 21 (13.8) vs. 25 (16.4) vs. 24 (15.8) • Obstructive sleep apnea: 56 (36.8) vs. 24 (15.8) • NAFLD: 16 (10.5) vs. 15 (9.9) • PCOS: 10/123 (8.1) vs. 5/113 (4.4) • CAD: 2 (1.3) vs. 3 (2.0)	2.4 mg semaglutide vs. PBO • American Indian or Alaska Native: 2 (1.3) vs. 1 (0.7) • Asian: 2 (1.3) vs. 0 (0.0) • Black or African American: 7 (4.6) vs. 5 (3.3) • Hispanic or Latino: 18 (11.8) vs. 21 (13.8) • White: 141 (92.8) vs. 142 (93.4) • Other: 0 (0.0) vs. 4 (2.6)	2.4 mg semaglutide vs. PBO Glucose-lowering • Exclusion criteria Other • NR

STEP 6[76]
Kadowaki et al., 2022
NCT03811574
RCT
N = 401 (199 vs. 101 vs. 101)
	2.4 mg semaglutide vs. 1.7 mg semaglutide vs. PBO
	General
	• Mean age, years (SD): 52 (12) vs. 51 (10) vs. 50 (9)
	• Female, n (%): 85 (43) vs. 37 (37) vs. 26 (26)
	• Mean weight, kg (SD): 86·9 (16·5) vs. 86·1 (11·9) vs. 90·2 (15·1)
	• Mean BMI (SD): 32·0 (4·6) vs. 31·6 (3·7) vs. 31·9 (4·2)
	• Mean HbA1c % (SD): 6·4 (1·2) vs. 6·4 (1·1) vs. 6·4 (1·1)
	Other primary condition or comorbidities, n (%)
	• T2DM: 49 (25) vs. 25 (25) vs. 25 (25)
	• Dyslipidemia: 178 (90) vs. 88 (87) vs. 80 (79)
	• Hypertension: 152 (76) vs. 74 (73) vs. 73 (72)
	• Knee osteoarthritis: 22 (11) vs. 9 (9) vs. 9 (9)
		2.4 mg semaglutide vs. 1.7 mg vs. PBO
		• All (100%) reported as Asian
			2.4 mg semaglutide vs. 1.7 mg vs. PBO
			Glucose-lowering
			• Exclusion criteria for participants in South Korea
			• For participants from Japan with T2DM:
			  ○ Biguanides: 26 (53·1) vs. 15 (60·0) vs. 18 (72·0)
			  ○ SGLT2 inhibitors: 20 (40·8) vs. 11 (44·0) vs. 13 (52·0)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
	• Obstructive sleep apnea: 17 (9) vs. 13 (13) vs. 10 (10) • NAFLD: 93 (47) vs. 40 (40) vs. 46 (46) • Kidney disease: 28 (14) vs. 15 (15) vs. 13 (13)		o Sulfonylureas: 7 (14·3) vs. 6 (24·0) vs. 8 (32·0) o Thiazolidinediones: 8 (16·3) vs. 4 (16·0) vs. 3 (12·0) Other • NR
STEP TEENS[78] Weghuber et al., 2022 NCT04102189 RCT N = 201 (134 vs. 67)	2.4 mg semaglutide vs. PBO <u>General</u> • Mean age, years (SD): 15.5 (1.5) vs. 15.3 (1.6) • Female, n (%): 84 (63) vs. 41 (61) • Mean weight, kg (SD): 109.9 (25.2) vs. 102.6 (22.3) • Mean BMI (SD): 37.7 (6.7) vs. 35.7 (5.4) • Mean HbA1c % (SD): 5.5 (0.4) vs. 5.5 (0.4) <u>Other primary condition or comorbidities, n (%)</u> • T2DM: 5 (3.7) vs. 3 (4.5) • Dyslipidemia: 27 (20.1) vs. 10 (14.9) • Hypertension: 18 (13.4) vs. 9 (13.4) • Obstructive sleep apnea: 2 (1.5) vs. 2 (1.5)	NR	NR
Tirzepatide			
SURMOUNT-1[81] Jastreboff et al., 2022 NCT04184622 RCT N = 2539 (630 vs. 636 vs. 630 vs. 643)	15 mg tirzepatide vs. 10 mg vs. 5 mg vs. PBO <u>General</u> • Mean age, years (SD): 44.9 (12.3) vs. 44.7 (12.4) vs. 45.6 (12.7) vs. 44.4 (12.5) • Female, n (%): 425 (67.5) vs. 427 (67.1) vs. 426 (67.6) vs. 436 (67.8) • Mean weight, kg (SD): 105.6 (22.9) vs. 105.8 (23.3) vs. 102.9 (20.7) vs. 104.8 (21.4) • Mean BMI (SD): 38.1 (6.7) vs. 38.2 (7.0) vs. 37.4 (6.6) vs. 38.2 (6.9) • Mean HbA1c % (SD): 5.6 (0.4) vs. 5.6 (0.4) vs. 5.6 (0.4) vs. 5.6 (0.4) <u>Other primary condition or comorbidities, n (%)</u> • Prediabetes: 253 (40.2) vs. 262 (41.2) vs. 247 (39.2) vs. 270 (42.0)	15 mg tirzepatide vs. 10 mg vs. 5 mg vs. PBO • American Indian or Alaska Native: 59 (9.4) vs. 58 (9.1) vs. 56 (8.9) vs. 58 (9.0) • Asian: 66 (10.5) vs. 71 (11.2) vs. 68 (10.8) vs. 71 (11.0) • Black or African American: 51 (8.1) vs. 47 (7.4) vs. 48 (7.6) vs. 55 (8.6) • Hispanic or Latino: 299 (47.5) vs. 297 (46.7) vs. 308 (48.9) vs. 310 (48.2) • Native Hawaiian or other Pacific Islander: 3 (0.5) vs. 2 (0.3) vs. 2 (0.3) vs. 2 (0.3 • White: 443 (70.3) vs. 452 (71.1) vs. 447 (71.0) vs. 450 (70.0)	NR

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
	• Dyslipidemia: 182 (28.9) vs. 188 (29.6) vs. 201 (31.9) vs. 186 (28.9) • Hypertension: 207 (32.9) vs. 208 (32.7) vs. 205 (32.5) vs. 199 (30.9) • Osteoarthritis: 77 (12.2) vs. 86 (13.5) vs. 87 (13.8) vs. 76 (11.8) • Obstructive sleep apnea: 46 (7.3) vs. 51 (8.0) vs. 41 (6.5) vs. 59 (9.2) • NAFLD: 48 (7.6) vs. 44 (6.9) vs. 42 (6.7) vs. 46 (7.2) • PCOS: 6/429 (1.4) vs. 13/427 (3.0) vs. 7/426 (1.6) vs. 13/436 (3.0) • CVD: 21 (3.3) vs. 20 (3.1) vs. 16 (2.5) vs. 21 (3.3)	• Multiple: 8 (1.3) vs. 6 (0.9) vs. 9 (1.4) vs. 7 (1.1)	
Exenatide			
Combat-JUDO[83] Weghuber et al., 2020 EudraCT 2015-001628-45 RCT N = 44 (22 vs. 22)	2.0 mg exenatide vs. PBO General • Mean age, years (SD): 14.5 (2.3) vs. 13.5 (2.3) • Female, n (%): 13 (59.1) vs. 9 (40.9) • Mean weight, kg (SD): 106.2 (19.7) vs. 102.5 (24.5) • Mean BMI (SD): 36.0 (4.8) vs. 36.2 (5.0) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • NR	2.0 mg exenatide vs. PBO • Asian: 0 (0) vs. 1 (4.5) • Black: 0 (0) vs. 1 (4.5) • White: 22 (100) vs. 19 (86.4) • Other: 0 (0) vs. 1 (4.5)	NR
Derosa et al., 2010[84] RCT N = 128 (63 vs. 65)	20 µg exenatide daily vs. 15 mg glibenclamide General • Mean age, years (SD): 57 (8) vs. 56 (7) • Female, n (%): 33 (52.4) vs. 32 (49.2) • Mean weight, kg (SD): 82.0 (8.3) vs. 82.4 (9.1) • Mean BMI (SD): 28.7 (1.5) vs. 28.5 (1.4) • Mean HbA1c % (SD): 8.8 (0.7) vs. 8.9 (0.8) Other primary condition or comorbidities, n (%) • T2D: 63 (100) vs. 65 (100)	20 mg exenatide vs. 15 mg glibenclamide • White: 63 (100) vs. 65 (100)	20 mg exenatide vs. 15 mg glibenclamide Glucose-lowering • Metformin: 63 (100) vs. 65 (100) Other • NR
Fox et al., 2022[82] NCT02496611 RCT N = 66 (33 vs. 33)	2.0 mg exenatide vs. PBO General • Mean age, years (SD): 15.9 (1.6) vs. 16.1 (1.5) • Female, n (%): 18 (54.5) vs. 13 (39.4) • Mean weight, kg (SD): 105.6 (17.7) vs. 111.4 (17.2)	2.0 mg exenatide vs. PBO • American Indian: 0 (0) vs. 0 (0) • Asian: 0 (0) vs. 0 (0) • Black or African American: 3 (9) vs. 2 (6)	NR

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
	• Mean BMI (SD): 36.5 (4.3) vs. 37.3 (4.6) • Mean HbA1c % (SD): 5.2 (0.2) vs. 5.2 (0.3) Other primary condition or comorbidities, n (%) • NR	• Hispanic: 5 (15) vs. 2 (6) • White: 26 (79) vs. 28 (85) • Multiple: 3 (9) vs.2 (6)	
Naltrexone-bupropion			
COR-1[85] Greenway et al., 2010 NCT00532779 RCT N = 1,742 (583 vs. 578 vs. 581)	32/360 mg NalBup vs. 16/360 mg NalBup vs. PBO General • Mean age, years (SD): 44.4 (11.1) vs. 44.4 (11.3) vs. 43.7 (11.1) • Female, n (%): 496 (85) vs. 490 (85) vs. 496 (85) • Mean weight, kg (SD): 99.7 (15.9) vs. 99.5 (14.8) vs. 99.5 (14.3) • Mean BMI (SD): 36.1 (4.4) vs. 36.2 (4.3) vs. 36.2 (4.0) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • Dyslipidemia: 284 (49) vs. 287 (50) vs. 113 (19) • Hypertension: 130 (22) vs. 117 (20) vs. 288 (50)	32/360 mg NalBup vs. 16/360 mg NalBup vs. PBO • Black: 106 (18) vs. 122 (21) vs. 110 (19) • White: 440 (75) vs. 427 (74) vs. 440 (76) • Other: 37 (6) vs. 29 (5) vs. 31 (5)	NR
COR-II[86] Apovian et al., 2013 NCT00567255 RCT N = 1,496 (1001 vs. 495)	32/360 mg NalBup vs. PBO General • Mean age, years (SD): 44.3 (11.2) vs. 44.4 (11.4) • Female, n (%): 847 (84.6) vs. 420 (84.8) • Mean weight, kg (SD): 100.3 (16.6) vs. 99.2 (15.9) • Mean BMI (SD): 36.2 (4.5) vs. 36.1 (4.3) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • Hypertension: 212 (21.2) vs. 106 (21.4) • Dyslipidemia: 560 (55.9) vs. 263 (53.1	32/360 mg NalBup vs. PBO • Black: 130 (13) vs. 74 (15) • White: 831 (83) vs. 416 (84) • Other: 30 (3) vs. 10 (2)	NR
COR-BMOD[89] Wadden et al., 2011 NCT00456521 RCT N = 793 (591 vs. 202)	32/360 mg NalBup vs. PBO General • Mean age, years (SD): 46.1 (9.7) vs. 47.0 (10.0) • Female, n (%): 125 (81.7) vs. 77 (86.5) • Mean weight, kg (SD): 101.4 (15.1) vs. 100.2 (16.6) • Mean BMI (SD): 36.33 (4.2) vs. 36.26 (4.4) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • NR	32/360 mg NalBup vs. PBO • American Indian or Alaska Native: 0 (0) vs. 1 (1.1) • Asian: 1 (0.7) vs. 0 (0) • Black or African American: 28 (18.3) vs. 24 (27.0) • Hispanic or Latino: 4 (2.6) vs. 5 (5.6) • White: 124 (81.0) vs. 64 (71.9)	NR

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
COR-Diabetes[88] Hollander et al., 2013 NCT00474630 RCT N = 505 (335 vs. 170)	32/360 mg NalBup vs. PBO General • Mean age, years (SD): 45.9 (10.4) vs. 45.6 (11.4) • Female, n (%): 528 (89.3) vs. 185 (91.6) • Mean weight, kg (SD): 100.2 (15.4) vs. 101.9 (15.0) • Mean BMI (SD): 36.3 (4.2) vs. 37.0 (4.2) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • NR	32/360 mg NalBup vs. PBO • African American: 145 (24.5) vs. 44 (21.8) • White: 405 (68.5) vs. 149 (73.8) • Other: 41 (6.9) vs. 9 (4.5)	32/360 mg NalBup vs. PBO Glucose-lowering • Metformin: 263 (78.5) vs. 130 (76.5) • Sulfonylureas: 156 (46.6) vs. 83 (48.8) • Thiazolidinedione: 103 (30.7) vs. 52 (30.6) Other • NR
Halseth et al., 2017[90] Halseth et al., 2018[87] NCT01764386 RCT N = 242 (153 vs. 89)	32/360 mg NalBup + CLI vs. usual care General • Mean age, years (SD): 54.0 (9.1) vs. 53.5 (9.8) • Female, n (%): 195 (58.2) vs. 90 (52.9) • Mean weight, kg (SD): 104.2 (18.9) vs. 105.1 (17.0) • Mean BMI (SD): 36.4 (4.8) vs. 36.4 (4.5) • Mean HbA1c % (SD): 8.0 (0.8) vs. 8.0 (0.9) Other primary condition or comorbidities, n (%) • Dyslipidemia: 280 (83.6) vs. 145 (85.3)	32/360 mg NalBup + CLI vs. usual care • Black: 63 (18.8) vs. 18 (10.6) • White: 261(77.9) vs. 140 (82.4) • Other: 10 (3.3) vs. 12 (7.0)	NR
Phentermine-topiramate			
CONQUER/SEQUEL Gadde et al., 2011[93] Garvey et al., 2012[95] Davidson et al., 2013[92] Garvey et al., 2014[94] NCT00553787/ NCT00796367 RCT N = 2,487 (995 vs. 498 vs. 994)	15/92 mg PhenTop vs. 7.5/46 mg PhenTop vs. PBO General • Mean age, years (SD): 51.0 (10.7) vs. 51.1 (10.4) vs. 51.2 (10.3) • Female, n (%): 693 (70) vs. 349 (70) vs. 695 (70) • Mean weight, kg (SD): 103·0 (17.6) vs. 102.6 (18.2) vs. 103.3 (18.1) • Mean BMI (SD): 36.6 (4.5) vs. 36.2 (4.4) vs. 36.7 (4.6) • Mean HbA1c % (SD): 5.9 (0.8) vs. 5.8 (0.7) vs. 5.9 (0.8) Other primary condition or comorbidities, n (%) • T2DM: 166 (16.7) vs. 68 (13.7) vs. 159 (16.0) • Dyslipidemia: 363 (36) vs. 180 (36) vs. 354 (36) • Hypertension: 520 (52) vs. 261 (52) vs. 524 (53) • 3 or more comorbidities: 500 (50) vs. 259 (52) vs. 675 (68)	15/92 mg PhenTop vs. 7.5/46 mg PhenTop vs. PBO • African: 122 (12) vs. 56 (11) vs. 114 (11) • Asian: 11 (1) vs. 5 (1) vs. 6 (< 1) • Native American or Alaska Native: 8 (< 1) vs. 6 (1) vs. 4 (< 1) • Native Hawaiian or other Pacific Islander: 3 (< 1) vs. 2 (< 1) vs. 2 (< 1) • White: 850 (85) vs. 429 (86) vs. 861 (87) • Other: 8 (< 1) vs. 5 (1) vs. 12 (1)	15/92 mg PhenTop vs. 7.5/46 mg PhenTop vs. PBO Glucose-lowering • NR Other • Antidepressants, n (%): 144 (14) vs. 83 (17) vs. 170 (17)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
EQUIP[91] Allison et al., 2011 RCT N = 1,267 (512 vs. 241 vs. 514)	15/92 mg PhenTop vs. 3.75/23 mg PhenTop vs. PBO General • Mean age, years (SD): 41.9 (12.2) vs. 43.0 (10.9) vs. 43.0 (11.8) • Female, n (%): 424 (82.8) vs. 201 (83.4) vs. 425 (82.7) • Mean weight, kg (SD): 115.2 (20.7) vs. 118.5 (21.9) vs. 115.8 (21.5) • Mean BMI (SD): 41.9 (6.0) vs. 42.6 (6.5) vs. 42.0 (6.2) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • NR	15/92 mg PhenTop vs. 3.75/23 mg PhenTop vs. PBO • American Indian or Alaskan Native: 7 (1.4) vs. 2 (0.8) vs. 6 (1.2) • Asian American: 1 (0.2) vs. 2 (0.8) vs. 3 (0.6) • Black: 93 (18.2) vs. 39 (16.2) vs. 93 (18.1) • Hispanic/Latino: 81 (15.8) vs. 29 (12.0) vs. 74 (14.4) • Native Hawaiian or other Pacific Islander: 2 (0.4 vs. 1 (0.4) vs. 2 (0.4) • White: 408 (79.7) vs. 192 (79.7) vs. 413 (80.4) • Other: 7 (1.4) vs. 5 (2.1) vs. 4 (0.8)	15/92 mg PhenTop vs. 3.75/23 mg PhenTop vs. PBO Glucose-lowering • NR Other • Antidepressants, n (%): 65 (12.7) vs. 36 (14.9) vs. 68 (13.2)
OB-403[96] Kelly et al., 2022 NCT03922945 RCT N = 223 (113 vs. 54 vs. 56)	15/92 mg PhenTop vs. 7.5/46 mg PhenTop vs. PBO General • Mean age, years (SD): 13.9 (1.4) vs. 14.1 (1.3) vs. 14.0 (1.4) • Female, n (%): 63 (55.8) vs. 28 (51.9) vs. 30 (53.6) • Mean weight, kg (SD): 108.5 (25.0) vs. 105.2 (22.4) vs. 102.2 (21.8) • Mean BMI (SD): 39.0 (7.4) vs. 36.9 (6.8) vs. 36.4 (6.4) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • NR	15/92 mg PhenTop vs. 7.5/46 mg PhenTop vs. PBO • American Indian or Alaska Native: 1 (0.9) vs. 0 (0) vs. 0 (0) • Asian: 1 (0.9) vs. 0 (0) vs. 0 (0) • Black or African American: 36 (31.9) vs. 14 (25.9) vs. 10 (17.9) • Hispanic or Latino: 34 (30.1) vs. 25 (46.3) vs. 13 (23.2) • Native Hawaiian or Other Pacific Islander: 0 (0) vs. 0 (0) vs. 0 (0) • White: 71 (62.8) vs. 36 (66.7) vs. 42 (75.0) • Other: 4 (3.5) vs. 4 (7.4) vs. 4 (7.1)	NR
Setmelanotide			
Clement et al., 2020[100] Kuhnen et al., 2022[99] NCT02896192 NCT03287960	3.0 mg setmelanotide General POMC • Mean age, years (SD; range): 18.4 (6.2; 11.0 to 30.0) • Female, n (%): 5 (50) • Mean weight, kg (SD; range): 118·7 (37.5; 55.9 to 186·7)	3.0 mg setmelanotide POMC: • Hispanic or Latino: 1 (10) • White: 7 (70) • Other: 3 (30) LEPR:	3.0 mg setmelanotide Glucose-lowering POMC: • Insulin glargine: 2 (20) • Metformin: 2 (20) • Other insulin: 1 (10)

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
Single-arm N = 22 (10 with POMC, 11 with LEPR)	• Mean BMI (SD; range): 40.4 (9.0; 26.6 to 53.3) • Mean HbA1c % (SD): NR LEPR: • Mean age, years (SD; range): 23.7 (8.4; 13.0 to 37.0) • Female, n (%): 8 (73) • Mean weight, kg (SD; range): 133·3 (26·0; 89·4 to 170·4) • Mean BMI (SD; range): 48·2 (10·4; 35·8 to 64·6) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) POMC: • T2DM: 1 (10) • T1DM: 2 (20) • Adrenocorticotropic hormone deficiency: 9 (90) • Hypothyroidism: 5 (50) LEPR: • T2DM: 2 (18) • Hypogonadotropic hypogonadism: 2 (18)	• Hispanic or Latino: 0 (0) • White: 10 (91) • Other: 1 (9)	LEPR: • Metformin: 2 (18) Other POMC: • Hydrocortisone: 9 (90) • Levothyroxine sodium: 5 (50) • Supradyn: 4 (40) • Omeprazole: 2 (20) • Ramipril: 2 (20) LEPR: • Estrogen replacement therapy: 2 (18)
Haqq et al., 2022[97] Forsythe et al., 2023[98] NCT03746522 RCT N = 38 (19 vs. 19)	3.0 mg setmelanotide vs. PBO General • Median age overall, 16.5 year (IQR, 12 to 24) • Mean age, years (SD): 19.3 (10.5) vs. 20.3 (10.2) • Female, n (%): 10 (52.6) vs. 13 (68.4) • Mean weight, kg (SD): 114.9 (34.3) vs. 108.5 (26.5) • Mean BMI (SD): 43.3 (13.3) vs. 41.2 (8.4) • Mean HbA1c % (SD): NR Other primary condition or comorbidities, n (%) • Alström syndrome: 3 (15.8) vs. 3 (15.8) • Bardet-Biedl syndrome: 16 (84.2) vs. 16 (84.2)	3.0 mg setmelanotide vs. PBO • Asian: 1 (5.3) vs. 0 (0) • Black or African American: 1 (5.3) vs. 2 (10.5) • Hispanic or Latino: 1 (5.3) vs. 0 (0) • White: 14 (73.7) vs. 17 (89.5 • Other: 3 (15.8) vs. 0 (0)	NR
Haws et al., 2020[101] NCT03013543 Single-arm N = 10	3.0 mg setmelanotide General • Mean age, years (SD): 22.5 (14.7) • 12 to 18 years, n (%): 6 (60) • > 18 years, n (%): 4 (40) • Female, n (%): 6 (60) • Mean weight, kg (SD): 128.1 (28.6) • Mean BMI (SD): 44.8 (4.1)	3.0 mg setmelanotide • Black or African American: 1 (10) • Hispanic or Latino: 1 (10) • White: 9 (90)	NR

Name; Author, Yr Number; Design N Randomized	General	Race and Ethnicity	Medications
	• Mean HbA1c % (SD): 5.8 (1.5) Other primary condition or comorbidities, n (%) • NR		

Note. Shaded rows are in children and adolescent populations only.

Abbreviations. BMI: body mass index; CAD: coronary artery disease; CLI: comprehensive lifestyle intervention; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase 4; HbA1c: hemoglobin A1c; IQR: interquartile range; LEPR: leptin receptor; NAFLD: non-alcoholic fatty liver disease; NalBup: naltrexone-bupropion; NR: not reported; PBO: placebo; PCOS: polycystic ovary syndrome; PhenTop: phentermine-topiramate; POMC: proopiomelanocortin; RCT: randomized controlled trial; SD: standard deviation; SGLT: sodium-dependent glucose cotransporters; T1DM: type 1 diabetes; T2DM: type 2 diabetes; yr: year.

Appendix C. Liraglutide: Full Evidence Tables

Table C1. Weight Change, %: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
Elkind-Hirsch, 2020[66]	History of GDM	84	Placebo	37	−3.1 (1.4)	1.8 mg/d	35	−7.2 (1.3)	NR; P = .04
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	2.37 (0.95)	3.0 mg/d	125	−2.65 (0.93)	−5.01 (95% CI, −7.63 to −2.39)
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	211	−2.0 (SD, 7.2)[a]	3.0 mg/d	412	−5.9 (SD, 7.2)[a]	−4.00 (95% CI, −5.1 to −2.9); P < .001
						1.8 mg/d	204	−4.6 (SD, 7.2)[a]	−2.71 (95% CI, −4.0 to −1.4); P < .001
			Liraglutide, 1.8 mg/d	202	−4.6 (NR)	3.0 mg/d	411	−5.9 (NR)	−1.35 (95% CI, −2.23 to −0.48); P = .002
		56 to 68, off treatment	Placebo	211	-4.7 (SD, 5.0)	3.0 mg/d, off treatment	412	-2.7 (SD, 5.8)	NR
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	−4.0 (SD, 7.9)[a]	3.0 mg/d	142	−7.5 (SD, 7.9)[a]	−3.4 (95% CI, −5.3 to −1.6); P < .001
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	−1.5 (SD, 5.8)[a]	3.0 mg/d	198	−5.8 (SD, 5.8)[a]	−4.3 (95% CI, −5.5 to −3.2); P < .001
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	−0.2 (SD, 7.0)	3.0 mg/d	207	−6.2 (SD, 7.3)	−6.1 (95% CI, −7.5 to −4.6); P < .001
		56 to 68, off treatment	Placebo, off treatment	144	-4.1 (SD, 8.2)[b]	3.0 mg/d, off treatment	159	0.3 (SD, 7.7)[b]	-4.2 (-6.0 to -2.4); P < .001[b]
	No diabetes	56	Placebo	1,225	−2.6 (SD, 5.7)	3.0 mg/d	2,473	−8.0 (SD, 6.7)	−5.4 (95% CI, −5.8 to −5.0); P < .001

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes, no prediabetes	56 to 68, off treatment	Placebo, off treatment	304	0.30 (SD, 2.43)[b]	3.0 mg/d, off treatment	351	0.61 (SD, 2.42)[b]	NR
	Prediabetes	160	Placebo	738	−1.9 (SD, 6.3)	3.0 mg/d	1,472	−6.1 (SD, 7.3)	−4.3 (95% CI, −4.9 to −3.7); P < .001
		160 to 172, off treatment	Placebo, off treatment	326	−2.1 (SD, 7.3)[b]	3.0 mg/d, off treatment	783	−5.2 (SD, 8.3)[b]	−3.2 (95% CI, −4.3 to −2.2)[b]; P < .001

Notes. Shaded rows indicate studies with pediatric populations. [a] Standard deviation calculated by Center researchers; [b] Change from baseline, not post-treatment.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; GDM: gestational diabetes; mg/d: milligrams per day; NR: not reported; SD: standard deviation; SE: standard error; T2DM: type 2 diabetes.

Table C2. Weight Change, kg: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, kg (95% CI)
			Type	n	Mean CFB, kg (SD)	Dose	n	Mean CFB, kg (SD)	
Elkind-Hirsch, 2020[66]	History of GDM	84	Placebo	37	o Baseline (kg): 94 (19.0) o At week 84 (kg): 91.3 (20.0) o Center calculated: −2.7 (SD, 7.8)	1.8 mg/d	35	o Baseline (kg): 100.6 (23.0) o At week 84 (kg): 94.2 (18.6) o Center calculated: −6.4 (SD, 7.8); P < .001	−3.7[a] (NR); P = .048
Ellipse Tamborlane, 2019[71]	T2DM	26	Placebo	68	−0.99 (NR)	≤ 1.8 mg/d	66	−2.3 (NR)	NR
		52	Placebo	68	0.87 (NR)	≤ 1.8 mg/d	66	−1.91 (NR)	
Ghanim, 2020[67]	T1DM	26	Placebo	27	0.4 (SE, NR)	1.8 mg/d	37	−4.2 (SE, 0.6)	Adjusted: −4.0 (95% CI, 0.5); P = .003
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	2.25 (SE, 0.98)	3.0 mg/d	125	−2.26 (SE, 0.94)	−4.50 (95% CI, −7.17 to −1.84); P, NR
LIDO Dubé, 2017[72] Crossover RCT	T1DM	24	Placebo	15	o Baseline: 89.0 (3.8) o Post-treatment: 88.3 (4.2) o Center calculated: −0.7 (SD, 3.6)	1.8 mg/d	15	o Baseline: 89.0 (3.8) o Post-treatment: 83.4 (4.2) o Center calculated: −5.6 (SD, 3.6)	−4.83 (95% CI, NR); P < .001
LIRA-1 Dejgaard, 2016[69]	T1DM	24	Placebo	50	o Baseline: 93.1 (95% CI, 89.3 to 96.9)	1.8 mg/d	50	o Baseline: 92.4 (95% CI, 88.6 to 96.2)	−6.8 (95% CI, −12.2 to −1.4); P = .01

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, kg (95% CI)
			Type	n	Mean CFB, kg (SD)	Dose	n	Mean CFB, kg (SD)	
					o Post-treatment: 93.3 (95% CI, 89.5 to 97.1)			o Post-treatment: 86.5 (95% CI, 82.7 to 90.3)	
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	1.2 (95% CI, −1.2 to 3.6)	3.0 mg/d	80	−2.8 (95% CI, −5.3 to −0.2)	−3.9 (95% CI, −6.9 to −1.0); P = .008
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	−0.1 (6.9)	3.0 mg/d	207	−6.0 (7.3)	−5.9 (95% CI, −7.3 to −4.4); P < .001
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,225	−2.8 (6.5)	3.0 mg/d	2,473	−8.4 (7.3)	−5.6 (95% CI, −6.0 to −5.1); P < .001
	Prediabetes	160	Placebo	738	−2.0 (7.3)	3.0 mg/d	1,472	−6.5 (8.1)	−4.6 (95% CI, −5.3 to −3.9); P < .001
		172	Placebo	326	−2.2 (8.4)	3.0 mg/d	783	−5.6 (9.2)	−3.5 kg (95% CI, −4.7 to −2.4); P < .001
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	6.1 (95% CI, 3.5 to 8.7)	3.0 mg/d	49	−0.7 (95% CI, −3.2 to 1.8)	-6.8 (95% CI, -10.4 to -3.1)
						3.0 mg/d + exercise	49	-3.4 (95% CI, -5.9 to -0.9)	-9.5 (95% CI, -13.1 to -5.9)
			Exercise	48	2.0 (95% CI, −0.7 to 4.6)	3.0 mg/d	49	−0.7 (95% CI, −3.2 to 1.8)	NR

Notes. Shaded rows indicate studies with pediatric populations. [a] Calculated by Center researchers.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; GDM: gestational diabetes; mg/d: milligrams per day; NR: not reported; SD: standard deviation; SE: standard error; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Table C3. Change in Body Mass Index: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
BMI, kg/m^2									
Elkind-Hirsch, 2020[66]	History of GDM	84	Placebo	37	o Baseline: 33.8 kg/m^2 (SD, 5.2) o At week 84: 32.8 kg/m^2 (SD, 6.0) o Center calculated: −1.0 kg/m^2 (SD, 5.03); P, NR	1.8 mg/d	35	o Baseline): 37.2 kg/m^2 (SD, 8.3) o At week 84: 33.8 kg/m^2 (SD, 5.2) o Center calculated: −3.4 kg/m^2 (SD, 5.03); P < .001	[a]−2.4 kg/m^2; P = .047
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	0.19 kg/m^2 (SE, 0.33)	3.0 mg/d	125	−1.39 kg/m^2 (SE, 0.31)	−1.58 kg/m^2 (95% CI, −2.47 to −0.69); P, NR
		56 to 82, off treatment	Placebo, off treatment	102	0.8 kg/m^2 (SE, 4.0)	3.0 mg/d, off treatment	112	−0.2 kg/m^2 (SE, 3.5)	NR
LIDO Dubé, 2017[72] Crossover RCT	T1DM	24	Placebo	15NR	o Baseline: 30.5 kg/m^2 (SE, 0.9) o Mean, 30.2 kg/m^2 (SE, 1.0) o Center calculated: −0.3 kg/m^2 (SD 12.4)	1.8 mg/d	15	o Baseline: 30.5 kg/m^2 (SE, 0.9) o Post-treatment: 28.5 kg/m^2 (SE, 1.0) o Center calculated: −2.0 kg/m^2 (SD 12.4)	−1.68 kg/m^2 (95% CI, NR); P < .001

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	0.3 kg/m² (95% CI, −0.5 to 1.2)	3.0 mg/d	80	−1.0 kg/m² (95% CI, −1.8 to −0.1)	−1.3 kg/m² (95% CI, −2.3 to −0.3); P = 0.01
SCALE Diabetes Davies, 2015[57]	T2DM	56	Liraglutide, 1.8 mg/d	204	−1.7 kg/m² (SD, 2.1)	3.0 mg/d	411	−2.2 kg/m² (SD, 2.1)	−0.56 kg/m² (95% CI, −0.89 to −0.23); P = .001
			Placebo	211	−0.8 kg/m² (SD, 1.7)	3.0 mg/d	411	−2.2 kg/m² (SD, 2.1)	−1.50 kg/m² (95% CI, −1.83 to −1.18); P < .001
						1.8 mg/d	204	−1.7 kg/m² (SD, 2.1)	−0.95 kg/m² (95% CI, −1.33 to −0.57); P < .001
		56 to 68, off treatment	Placebo, off treatment	211	-2.5 (2.2)[b]	3.0 mg/d, off treatment	411	-1.1 (2.0)[b]	NR
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	−0.0 kg/m² (SD, 2.3)	3.0 mg/d	207	−2.1 kg/m² (SD, 2.6)	−2.1 kg/m² (95% CI, −2.5 to −1.6); P < .001
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,225	−1.0 kg/m² (SD, 2.3)	3.0 mg/d	2,473	−3.0 kg/m² (SD, 2.6)	−2.0 kg/m² (95% CI, −2.2 to −1.9); P < .001
	Prediabetes	160	Placebo	738	−0.7 kg/m² (SD, 2.6)	3.0 mg/d	1,472	−2.4 kg/m² (SD, 2.9)	−1.7 kg/m² (95% CI, −1.9 to −1.4); P < .001
BMI change, %									
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	0.35% (SE, 0.91)	3.0 mg/d	125	−4.29% (SE, 0.88)	−4.64% (95% CI, −7.14 to −2.14); P, NR
BMI z score									
Ellipse Tamborlane, 2019[71]	T2DM	26	Placebo + metformin	68	−0.21 (SD, 0.31)[a]	Lira 1.8 mg + metformin	66	−0.25 (SD, 0.31)[a]	−0.05 (95% CI, −0.2 to −0.1); P = .39

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
		52	Placebo x 6 mo + Metformin	68	−0.16 (SD, 0.443)[a]	Lira 1.8 mg + metformin	66	−0.34 (SD, 0.443)[a]	−0.18 (95% CI, −0.33 to −0.03); P, NR
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	−0.00 (SE, 0.05)[a]	3.0 mg/d	125	−0.23 (SE, 0.05)[a]	−0.22 (95% CI, −0.37 to −0.08); P = .002

Notes. Shaded rows indicate studies with pediatric populations. [a] Calculated by Center researchers; [b] Change from baseline, not post-treatment.
Abbreviations. BMI: body mass index; Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; GDM: gestational diabetes; mg/d: milligrams per day; NR: not reported; SD: standard deviation; SE: standard error; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Table C4. Weight Loss ≥ 5% or ≥ 10%: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, OR (95% CI)
			Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Proportion With ≥ 5% weight loss									
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	105	At least 5% loss of BMI: 20 (19.0)	3.0 mg/d	113	At least 5% loss of BMI: 51 (45.1)	NR
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	13 (17.1)	3.0 mg/d	80	28 (35.0)	2.5 (95% CI, 1.1 to 5.6); P = .02
SCALE Diabetes Davies, 2015[57]	T2DM	56	Liraglutide 1.8 mg/d	204	72 (35.6)	3.0 mg/d	412	205 (49.9)	1.84 (95% CI, 1.29 to 2.64); P < .001
			Placebo	211	29 (13.8)	3.0 mg/d	412	205 (49.9)	6.81 (95% CI, 4.34 to 10.68); P < .001
						1.8 mg/d	204	72 (35.6)	3.69 (95% CI, 2.24 to 6.09); P < .001
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	54 (38.8)	3.0 mg/d	142	87 (61.5)	2.5 (95% CI, 1.5 to 4.1); P < .001
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	24 (NR)	3.0 mg/d	198	51.8 (NR)	3.4 (95% CI, 2.2 to; 5.3); P < .001
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	45 (21.8)	3.0 mg/d	207	105 (50.5)	3.9 (95% CI, 95% CO. 2.4 to 6.1); P < .001
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,225	332 (27.1)	3.0 mg/d	2,473	1,540 (63.2)	4.8 (95% CI, 4.1 to 5.6); P < .001
	Prediabetes	160	Placebo	738	175 (23.7)	3.0 mg/d	1,472	730 (49.6)	3.2 (95% CI, 2.6 to 3.9); P < .001
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	40	28 (70)	3.0 mg/d	41	36 (88)	NR
						3.0 mg/d + exercise	45	39 (87)	
			Exercise	40	32 (80)	3.0 mg/d	41	36 (88)	

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, OR (95% CI)
			Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Proportion with ≥ 10% weight loss									
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	105	At least 10% loss of BMI: 9 (8.6)	3.0 mg/d	113	At least 10% loss of BMI: 33 (29.2)	NR
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	7 (9.6)	3.0 mg/d	80	17 (21.3)	2.3 (95% CI, 0.9 to 6.1); *P* = .1
SCALE Diabetes Davies, 2015[57]	T2DM	56	Liraglutide, 1.8 mg/d	204	29 (14.4)	3.0 mg/d	411	96 (23.4)	7.10 (95% CI, 3.48 to 14.48); *P* < .001
			Placebo	211	9 (4.3)	3.0 mg/d	411	96 (23.4)	1.85 (95% CI, 1.16 to 2.95); *P* = .001
						1.8 mg/d	204	29 (14.4)	3.84 (95% CI, 1.75 to 8.41); *P* < .001
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	28 (19.8)	3.0 mg/d	142	43 (30.5)	1.8 (95% CI, 1.0 to 3.0); *P* = 0.05
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	13 (6.6)	3.0 mg/d	198	45 (22.8)	4.2 (95% CI, 2.2 to 8.2); *P* < .001
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	13 (6.3)	3.0 mg/d	207	54 (26.1)	5.3 (95% CI, 2.8 to 10.1); *P* < .001
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,225	130 (10.6)	3.0 mg/d	2,473	807 (33.1)	4.3 (95% CI, 3.5 to 5.3); *P* < .001
	Prediabetes	160	Placebo	738	73 (9.9)	3.0 mg/d	1,472	365 (24.8)	3.1 (95% CI, 2.3 to 4.1); *P* < .001
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	40	11 (28)	3.0 mg/d	41	24 (59)	NR
						3.0 mg/d + exercise	45	31 (69)	
			Exercise	40	18 (45)	3.0 mg/d	41	24 (59)	
			Liraglutide, 3.0 mg/d + exercise	45	31 (69)				

Notes. Shaded rows indicate studies with pediatric populations.

Abbreviations. CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; N/A: not applicable; NR: not reported; OR, odds ratio; SD: standard deviation; SE: standard error; T2DM: type 2 diabetes.

Table C5. Change in Systolic Blood Pressure: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, mmHg (95% CI)
			Type	n	Mean CFB, mmHg (SD)	Dose	n	Mean CFB, mmHg (SD)	
Elkind-Hirsch, 2020[66]	History of GDM	84	Placebo	37	o Baseline: 126 (14.0) At 84 weeks: 123 (SD, 12.0); P, NR	1.8 mg/d	35	o Baseline: 126 (12.0) At 84 weeks: 122 (SD, 12.0); P = .02	NR
Ellipse Tamborlane, 2019[71]	T2DM	26	Placebo	68	o NR	1.8 mg/d	66	o NR	0.03 (95% CI, −3.40 to 3.47); P > .05
		52	Placebo	68	o NR	1.8 mg/d	66	o NR	−2.07 (95% CI, −5.48 to 1.33); P > .05
Ghanim, 2020[67]	T1DM	26	Placebo	27	o Baseline: 123 (SE, 3) o Post-treatment: 121 (SE, 3) Center calculated: −2 (9.176)	1.8 mg/d	37	−5 (SE, 3)	Adjusted: −4 (SE, 2); P = .09
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	0.84 (SE, 0.90)	3.0 mg/d	125	−1.21 (SE, 0.90)	−2.05 (95% CI, −4.53 to 0.43); P, NR
LIDO Dubé, 2017[72] Crossover RCT	T1DM	24	Placebo	15	o Baseline: 126.5 (2.5) Post-treatment: 122.3 (2.5)	1.8 mg/d	15	o Baseline: 126.5 (2.5) Post-treatment: 116.3 (2.3)	−5.92 (95% CI, NR); P = .007
LIRA-1 Dejgaard, 2016[69]	T1DM	24	Placebo	50	130 (95% CI, 125 to 134)	1.8 mg/d	50	125 (95% CI, 121 to 130)	−4.2 (−95% CI, -10.2 to 1.8); P = .17

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, mmHg (95% CI)
			Type	n	Mean CFB, mmHg (SD)	Dose	n	Mean CFB, mmHg (SD)	
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	211	−0.4 (13.4)	3.0 mg/d	411	−2.8 (13.5)	−2.59 (95% CI, −4.56 to −0.62); *P* = .01
						1.8 mg/d	204	−3.5 (12.7)	−2.68 (−4.98 to −0.38); *P* = .02
		56 to 68, off treatment	Placebo, off treatment	211	-2.6 (13.8)[b]	3.0 mg/d, off treatment	411	-0.5 (13.5)[b]	NR
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	○ −0.6 (11.57)[a]	3.0 mg/d	142	○ −2.8 (11.57)[a]	−2.2 (95% CI, −4.9 to 0.5); *P* = .11
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	−1.6 (12.44)[a]	3.0 mg/d	198	−5.6 (12.44)[a]	−4.0 (95% CI, −6.4 to −1.5); *P* = .001
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	○ 2.8 (10.4)	3.0 mg/d	207	0.2 (12.0)	−2.7 (95% CI, −4.7 to −0.8); *P* < .01
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,225	−1.5 (12.4)	3.0 mg/d	2,437	−4.2 (12.2)	−2.8 (95% CI, −3.56 to −2.09); *P* < .001
	No diabetes and no prediabetes	56 to 68, off treatment	Placebo	304	0.21 (10.98)[b]	3.0 mg/d, off treatment	351	0.06 (10.52)[b]	NR
	Prediabetes	160	Placebo	738	−0.5 (13.7)	3.0 mg/d	1,472	−3.2 (13.0)	−2.8 (95% CI, −3.8 to −1.8); *P* < .001
		160 to 172, off treatment	Placebo, off treatment	326	−0.35 (13.9)[b]	3.0 mg/d, off treatment	783	−1.6 (13.5)[b]	−1.5 (95% CI, −3.0 to 0.05)[b]; *P* = .06
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	4.4 (95% CI, 0.1 to 8.8)	3.0 mg/d	49	−1.1 (95% CI, −5.4 to 3.2)	-5.5 (95% CI, -11.7 to 0.6)
						3.0 mg/d + exercise	49	−0.1 (95% CI, −4.4 to 4.1)	-1.8 (95% CI, -2.8 to -0.8)

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, mmHg (95% CI)
			Type	n	Mean CFB, mmHg (SD)	Dose	n	Mean CFB, mmHg (SD)	
			Exercise	48	3.5 (95% CI, −1.0 to 7.9)	3.0 mg/d	49	−1.1 (95% CI, −5.4 to 3.2)	NR

Notes. Shaded rows indicate studies with pediatric populations. [a] Standard deviation calculated by Center researchers; [b] Change from baseline, not post-treatment.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; GDM: gestational diabetes; mg/d: milligrams per day; mmHg: millimeters of mercury; NR: not reported; SD: standard deviation; SE: standard error; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Table C6. Change in LDL Cholesterol: Liraglutide

| Study Name Author, Year | Baseline Diabetes Status | Time Point, Weeks | Comparator | | | Liraglutide | | | Liraglutide vs. Comparator, Between-Group Difference, mmol/L (95% CI) |
			Type	n	Mean CFB, mmol/L (SD)	Dose	n	Mean CFB, mmol/L (SD)	
Ellipse Tamborlane, 2019[71]	T2DM	26	Placebo	68	Geometric mean, ratio to baseline: 1.00 (SE, 0.03)	1.8 mg/d	66	Geometric mean, ratio to baseline: 0.99 (SE, 0.03)	Treatment ratio: 1.00 (95% CI, 0.93 to 1.08); P, NR
		52	Placebo	68	Geometric mean, ratio to baseline: 1.04 (SE, 0.04)	1.8 mg/d	66	Geometric mean, ratio to baseline: 1.02 (SE, 0.04)	Treatment ratio: 0.98 (95% CI, 0.89 to 1.09); P, NR
Elkind-Hirsch, 2020[66]	No diabetes	84	Placebo	37	Baseline: 2.88 (0.59) At 84 weeks: 2.8 (0.65); P, NR MC, -0.08[a] (SD, 0.21)[a]	1.8 mg/d	35	Baseline: 3.02 (0.97) At 84 weeks: 2.84 (0.83); P = .05 MC, -0.18[a] (SD, 0.21)[a]	P = .048
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	Geometric mean, ratio to baseline: 1.00 (CV, 0.02)	3.0 mg/d	125	Geometric mean, ratio to baseline: P1.00 (CV, 0.02)	Treatment ratio: 1.00 (95% CI, 0.94 to 1.05); P, NR
LIDO Dubé, 2017[72] Crossover RCT	T1DM	24	Placebo	15	Baseline: 2.16 (0.16) Post-treatment: 2.16 (0.16)	1.8 mg/d	15	Baseline: 2.16 (0.16) Post-treatment: 2.08 (0.18)	−0.09 (95% CI, NR); P > .05
LIRA-1 Dejgaard, 2016[69]	T1DM	24	Placebo	50	2.7 (95% CI, 2.5 to 3.0	1.8 mg/d	50	2.4 (95% CI, 2.2 to 2.7)	−0.3 (95% CI, −0.6 to 0.1); P = .11

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, mmol/L (95% CI)
			Type	n	Mean CFB, mmol/L (SD)	Dose	n	Mean CFB, mmol/L (SD)	
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	211	Geometric mean: 5.02% (CV, 27.3)	3.0 mg/d	411	Geometric mean: 0.58% (CV, 38.8)	Ratio: 0.98 (95% CI, 0.93 to 1.03); P = .36
						1.8 mg/d	204	Geometric mean: −3.07 (CV, 30.5)	Ratio, 0.95 (95% CI, 0.90 to 1.01); P = .10
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	0.04 (NR) 0.578	3.0 mg/d	142	−0.04 (NR) 0.578	−0.07 (95% CI, −0.21 to 0.06); P = .27
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	Treatment ratio: 1.01 (NR)	3.0 mg/d	198	Treatment ratio: 0.97 (NR)	OR, 0.96 (95% CI, 0.91 to 1.01); P = .10
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	0.3 (0.6)	3.0 mg/d	207	0.2 (0.6)	−0.09 (95% CI, −0.2 to 0.02); P = 0.11
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,225	−1.0% (NR)	3.0 mg/d	2,437	−3.0% (NR)	−2.4% (95% CI, −4.0 to −0.9); P = .002
	Prediabetes	160	Placebo	738	−3.3% (NR)	3.0 mg/d	1,472	−4.2% (NR)	−2% (95% CI, −4 to 0); P = .10
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	0.3 mmol/mol (95% CI, 0.09[b] to 0.5)	3.0 mg/d	49	0.2 mmol/mol (95% CI, −0.1 to 0.4)	-0.2 (95% CI, -0.5 to 0.2)
						3.0 mg/d + exercise	49	0.3 (95% CI, 0.1 to 0.6)	0.0 (95% CI, -0.2 to 0.3)
			Exercise	48	0.4 (95% CI, 0.2 to 0.6)	3.0 mg/d	49	0.2 (95% CI, −0.1 to 0.4)	NR

Notes. Shaded rows indicate studies with pediatric populations; [a] Calculated by Center researchers; [b] Error in publication and corrected here.
Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; LDL: low-density lipoprotein; mg/d: milligrams per day; mmol/L: millimoles per liter; NR: not reported; SD: standard deviation; SE: standard error; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Table C7. Change in HbA1c: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (SD)	Dose	n	Mean CFB, % (SD)	
Ellipse Tamborlane, 2019[71]	T2DM	26	Placebo	68	0.42 (NR)	1.8 mg/d	66	−0.64 (NR)	−1.06 (95% CI, −1.65 to −0.46); $P < .001$
		52	Placebo	68	0.80 (NR)	1.8 mg/d	66	−0.50 (NR)	−1.30% (95% CI, −1.89 to −0.70); $P < .001$
Ghanim, 2020[67]	T1DM	26	Placebo	27	o Baseline: 7.79 (0.18) o Post-treatment: 7.67 (0.19) o Center calculated: −0.12% (0.66)	1.8 mg/d	37	o Baseline: 7.96 (0.19) o Post-treatment: 7.55 (0.18) o Center calculated: −0.41 (0.18)	Adjusted[b]: 0.25% (95% CI, SE, 0.17); $P = .14$
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	o −0.03 (SE, 0.03)	3.0 mg/d	125	o −0.10 (SE, 0.03)	−0.06 (95% CI, −0.14 to 0.01)
LIDO Dubé, 2017[72] Crossover RCT	T1DM	24	Placebo	15	o Baseline: 7.4 (0.1) o Post-treatment: 7.2 (0.2)	1.8 mg/d	15	o Baseline: 7.4 (0.1) o Post-treatment: 7.1 (0.2)	−0.09 (95% CI, NR); $P > .05$
LIRA-1 Dejgaard, 2016[69]	T1DM	24	Placebo	50	o Baseline: 8.7 o Post-treatment: 8.4 (95% CI, 8.1 to 8.6) o Center calculated: −0.3 (0.74)	1.8 mg/d	50	o Baseline: 8.7 o Post-treatment: 8.2 (95% CI, 7.9 to 8.4) o Center calculated: −0.5 (0.74)	−0.2 (95% CI, −0.5 to 0.1); $P = .18$
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	211	−0.3 (0.9)	3.0 mg/d	411	−1.3 (0.9)	−0.93 (95% CI, −1.08 to −0.78); $P < .001$

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (SD)	Dose	n	Mean CFB, % (SD)	
						1.8 mg/d	204	−1.1 (1.0)	−0.74 (95% CI, −0.91 to −0.57); P < .001
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	−0.06 (0.34)[a]	3.0 mg/d	142	o −0.16 (0.34)[a]	−0.10 (95% CI, −0.2 to −0.04); P < .001
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	−0.6% (1.27)[a]	3.0 mg/d	198	−1.1 (1.27)[a]	−0.5 (95% CI, −0.8 to −0.3); P < .001
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	206	0.1 (0.3)	3.0 mg/d	207	o −0.1 (0.3)	−0.3 (95% CI, −0.3 to −0.2); P < .001
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,225	−0.06 (0.30)	3.0 mg/d	2,437	−0.30 (0.28)	−0.23 (95% CI, −0.25 to −0.21); P < .001
	Prediabetes	160	Placebo	738	−0.14 (0.34)	3.0 mg/d	1,472	−0.35 (0.32)	−0.21 (95% CI, −0.24 to −0.18); P < .001
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	o 0.8 mmol/mol (95% CI, 0.1 to 1.5) Center calculated: 2.2%[b] (2.1 to 2.3)	3.0 mg/d	49	o -1.4 mmol/mol (95% CI, -2.1 to -0.7) Center calculated: −2.3% (−2.4 to −2.2)	-2.2 mmol/mol (95% CI, -3.2 to -1.2)
						3.0 mg/d + exercise	49	-0.9 mmol/mol (95% CI, -1.6 to -0.3)	-1.8 mmol/mol (95% CI, -2.8 to -0.8)
			Exercise	48	0.6 mmol/mol (95% CI, -0.2 to 1.3)	3.0 mg/d	49	-1.4 mmol/mol (95% CI, -2.1 to -0.7)	NR

Notes. Shaded rows indicate studies with pediatric populations. [a] Standard deviation calculated by Center researchers. [b] Adjusted for baseline body weight as a covariate because this was significantly different between groups at baseline

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; HbA1c: hemoglobin A1c; mg/d: milligrams per day; mmol/mol: millimoles per mole; N/A: not applicable; NR: not reported; SD: standard deviation; SE: standard error; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Table C8. Quality of Life: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
SF-36: physical function score [a]									
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	Physical function score: 3.8 (SD, NR)	3.0 mg/d	142	Physical function score: 4.0 (SD, NR)	Physical function score: 0.2 (95% CI, −1.2 to 1.5); P = .81
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	Physical function score: 2.3 (SD, NR)	3.0 mg/d	198	Physical function score: 2.7 (SD, NR)	Physical function score: 0.4 (95% CI, −1.0 to 1.8); P = 0.57
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	799	Mental component summary score: −0.76 points (SE, 0.25)	3.0 mg/d	1,690	Mental component summary score: 0.14 points (SE, 0.17)	Mental component summary score: 0.90 points (95% CI, 0.30 to 1.50); P = .003
					Physical component summary score: 1.93 points (SE, 0.21)			Physical component summary score: 3.66 points (SE, 0.15)	Physical component summary score: 1.73 (95% CI, 1.22 to 2.24); P < .001
	Prediabetes	160	Placebo	469	Mental component summary score: −1.28 points (SD, NR)	3.0 mg/d	993	Mental component summary score: −0.51 points (SD, NR)	Mental component summary score: 0.77 (95% CI, −0.09 to 1.63); P = .08

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
					Physical component summary score: 2.35 points (SD, NR)			Physical component summary score: 3.22 points (SD, NR)	Physical component summary score: 0.87 (95% CI, 0.17 to 1.58); P = .02
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	Physical function: −1.0 (95% CI, −3.6 to 1.6)	3.0 mg/d	49	Physical function: 0.2 (95% CI, −2.3 to 2.8)	NR
						3.0 mg/d + exercise	49	Physical function: 2.9 (95% CI, 0.5 to 5.3)	NR
			Exercise	48	Physical function: 2.6 (95% CI, −0.1 to 5.3)	3.0 mg/d	49	Physical function: 0.2 (95% CI, −2.3 to 2.8)	NR
IWQoL-Lite: physical function score [a]									
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	211	Total score: 7.58 (SD, 12.57)	3.0 mg/d	411	Total score: 11.68 (SD, 14.67)	Total score: 2.75 (95% CI, 0.57 to 4.93); P = .01
						1.8 mg/d	204	Total score: 9.07 (SD, 14.1)	Total score: 0.78 (95% CI, −1.74 to 3.31); P = .54
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	Physical function score: 14.1 (SD, NR)	3.0 mg/d	142	Physical function score: 14.9 (SD, NR)	Physical function score: 0.9 (95% CI, −3.4 to 5.1); P = .69
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	Physical function score: 5.7 (SD, NR)	3.0 mg/d	198	Physical function score: 8.2 (SD, NR)	Physical function score: 2.5 (95% CI, −1.5 to 6.4); P = 0.15

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	890	Total score: 7.54 points (SE, 0.37)	3.0 mg/d	1,891	Total score: 10.66 points (SE, 0.25)	Total score: 3.13 points (95% CI, 2.24 to 4.01); *P* < .001
	Prediabetes	160	Placebo	517	Total score: 7.76 points (SD, NR)	3.0 mg/d	1,117	Total score: 11.11 points (SD, NR)	Total score: 3.35 (95% CI, 2.04 to 4.66); *P* < .001
IWQoL-Kids: total score									
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	6.57 (SE, 1.06)	3.0 mg/d	125	7.88 (SE, 1.04)	1.31 (95% CI, −1.57 to 4.20); *P*, NR
KOOS									
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	Pain score: −0.6 (95% CI, −4.4 to 3.3)	3.0 mg/d	80	Pain score: 0.4 (95% CI, −3.3 to 4.0)	Pain score: 0.9 (95% CI, −3.9 to 5.7); *P* = 0.71
					Knee-related QoL: 0.7 (95% CI, −3.4 to 4.8)			Knee-related QoL: 3.1 (95% CI, −0.8 to 7.1)	Knee-related QoL: 2.4 (95% CI, −2.7 to 7.6); *P* = 0.35

Notes. Shaded rows indicate studies with pediatric populations. [a] Larger values (higher scores) indicated higher levels of quality of life.

Abbreviations. CFB: change from baseline; CI: confidence interval; IWQoL: impact of weight on quality of life; KOOS: knee injury and osteoarthritis outcomes score; mg/d: milligrams per day; N/A: not applicable; NR: not reported; QoL: quality of life; SD: standard deviation; SE: standard error; SF-36: Short-Form Health Survey, 36 questions; T2DM: type 2 diabetes.

Table C9. Withdrawals Due to AEs, Any AE, and AEs Occurring in ≥ 10%: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
Withdrawals due to AEs									
Elkind-Hirsch, 2020[66]	History of GDM	84	Placebo	75	3	1.8 mg/d	78	4	NR
Ellipse Tamborlane, 2019[71]	T2DM	52	Placebo	68	1 (1.5)	≤ 1.8 mg/d	66	1 (1.5)	RR, 1.03 (95% CI, 0.07 to 16.13); *P*, NR
Ghanim, 2020[67]	T1DM	26	Placebo	27	3 (11.1)	1.8 mg/d	37	2 (5.4)	NR
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	0 (0)	3.0 mg/d	125	13 (10.4)	NR; *P* < .001
LIDO Dubé, 2017[72] Crossover RCT	T1DM	24	Placebo	15	0	1.8 mg/d	15	0	NR
LIRA-1 Dejgaard, 2016[69]	T1DM	24	Placebo	50	2 (4.0)	1.8 mg/d	50	3 (6.0)	NR
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	4 (5.3)	3.0 mg/d	80	10 (12.5)	NR
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	212	7 (3.3)	3.0 mg/d	422	39 (9.2)	NR
						1.8 mg/d	210	18 (4.3)	
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	6 (4.3)	3.0 mg/d	142	12 (8.5)	NR
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	198	6 (3.0)	3.0 mg/d	198	15 (7.7)	NR
SCALE Maintenance	No diabetes	56	Placebo	210	18 (8.6)	3.0 mg/d	212	18 (8.5)	NR

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
Wadden, 2013[62]									
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,244	47 (3.8%)	3.0 mg/d	2,487	246 (9.9%)	NR
	Prediabetes	160	Placebo	747	46 (6%)	3.0 mg/d	1,501	199 (13%)	
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	0	3.0 mg/d	49	1 (2)	NR
						3.0 mg/d + exercise	49	1 (2)	
			Exercise	48	3 (6)	3.0 mg/d	49	1 (2)	
Any AEs									
Elkind-Hirsch, 2020[66]	History of GDM		Placebo	75	14 (19.0)	1.8 mg/d	78	30 (38.5)	NR
Ellipse Tamborlane, 2019[71]	T2DM	52	Placebo	68	55 (80.9)	≤ 1.8 mg/d	66	56 (84.8)	RR, 1.05 (95% CI, 0.90 to 1.22); P, NR
Kelly, 2020[60] N/A	~ 33% with T2DM and prediabetes	56	Placebo	126	107 (84.9)	3.0 mg/d	125	111 (88.8)	NR; P = .07
LIRA-1 Dejgaard, 2016	T1DM	24	Placebo	50	23 (46%)	1.8 mg/d	50	45 (90%)	NR
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	71 (93)	3.0 mg/d	80	77 (96)	Crude risk difference, 0.03 (95% CI, −0.04 to 0.10)
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	212	182 (85.8)	3.0 mg/d	422	392 (92.9)	NR
						1.8 mg/d	210	190 (90.5)	

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	124 (88.6)	3.0 mg	142	136 (95.8)	NR
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	197	175 (88.8)	3.0 mg/d	195	180 (92.3)	NR
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	210	186 (88.6)	3.0 mg/d	212	194 (91.5)	NR
SCALE Obesity and Prediabetes[a] Pi-Sunyer, 2015[56]	No diabetes	58	Placebo	1,242	786 (63.3%)	3.0 mg/d	2,481	1,992 (80.3%)	NR
	Prediabetes	160	Placebo	747	668 (89.4%)	3.0 mg/d	1,501	1,421 (94.7%)	
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	42 (86)	3.0 mg/d	49	49 (100)	NR
						3.0 mg/d + exercise	49	45 (92)	
			Exercise	48	39 (81)	3.0 mg/d	49	49 (100)	
AEs occurring in≥ 10%									
Ellipse Tamborlane, 2019[71]	T2DM	52	Placebo	68	o Nausea: 9 (13.2) o Vomiting: 6 (8.8) o Diarrhea: 11 (16.2) o Headache: 13 (19.1) o Abdominal pain: 5 (7.4) o Congestion: 19 (27.9) o Dizziness: 2 (2.9) o Gastroenteritis: 2 (2.9)	≤ 1.8 mg/d	66	o Nausea: 19 (28.8) o Vomiting: 17 (25.8) o Diarrhea: 15 (22.7) o Headache: 14 (21.2) o Abdominal pain: 12 (18.2) o Congestion: 11 (16.7)	o Nausea: 2.18 (95% CI, 1.06 to 4.46) o Vomiting: 2.92 (95% CI, 1.23 to 6.95) o Diarrhea: 1.40 (95% CI, 0.70 to 2.83) o Headache: 1.11 (95% CI, 0.57 to 2.18)

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
					o Hypoglycemia, minor: 7 (10.3)			o Dizziness: 8 (12.1) o Gastroenteritis: 7 (10.6) o Hypoglycemia, minor: 16 (24.2)	o Abdominal pain: 2.47 (95% CI, 0.92 to 6.63) o Congestion: 0.60 (95% CI, 0.31 to 1.16) o Dizziness: 4.12 (95% CI, 0.91 to 18.69) o Gastroenteritis: 3.61 (95% CI, 0.78 to 16.73) Hypoglycemia, minor: 2.35 (95% CI, 1.04 to 5.35)
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	o Congestion: 38 (30.2) o Nausea: 18 (14.3) o Headache: 35 (27.8) o Vomiting: 5 (4.0) o Diarrhea: 18 (14.3) o Upper abdominal pain: 17 (13.5) o Gastroenteritis: 6 (4.8) o Dizziness: 4 (3.2)	3.0 mg/d	125	o Congestion: 34 (27.2) o Nausea: 53 (42.4) o Headache: 29 (23.2) o Vomiting: 43 (34.4) o Diarrhea: 28 (22.4) o Upper abdominal pain: 17 (13.6) o Gastroenteritis: 16 (12.8) o Dizziness: 13 (10.4)	o Nausea: $P < .001$ o Vomiting: $P < .001$ o Gastroenteritis: $P = .02$ Dizziness: $P = .02$

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
LIRA-1 Dejgaard, 2016[69]	T1DM	24	Placebo	50	o Nausea: 5 (10%)	1.8 mg/d	50	o Nausea: 29 (58%) o Dyspepsia: 11 (22%) o Diarrhea: 10 (20%) o Decreased appetite: 7 (14%) o Vomiting: 7 (14%)	NR
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	212	o Gastrointestinal disorders: 83 (39.2) o Nausea: 29 (13.7) o Diarrhea: 27 (12.7)	3.0 mg/d	422	o Gastrointestinal disorders: 275 (65.2) o Dyspepsia: 47 (11.1) o Nausea: 138 (32.7) o Vomiting: 66 (15.6) o Constipation: 68 (16.1) o Diarrhea 108 (25.6)	NR
					o Gastrointestinal disorders: 118 (56.2) o Nausea: 29 (13.7) o Vomiting: 21 (10.0) o Diarrhea: 37 (17.6)	1.8 mg/d	210	o Nausea: 66 (31.4) o Vomiting: 21 (10.0)	

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	o Nausea: 25 (17.9) o Constipation: 26 (18.6) o Diarrhea: 23 (16.4) o Upper RTI: 15 (10.7) o Vomiting: 7 (5.0)	3.0 mg/d	142	o Nausea: 68 (47.9) o Constipation: 43 (30.3) o Diarrhea: 31 (21.8) o Upper RTI: 32 (22.5) o Vomiting: 33 (23.2) o Headache: 20 (14.1)	NR
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	197	o Diarrhea: 30 (15.2) o Headache: 29 (14.7) o Hypoglycemic episodes: 140 (71.1) o Nasopharyngitis: 36 (18.3) o Nausea: 23 (11.7) o Upper RTI: 29 (14.7)	3.0 mg/d	195	o Constipation: 28 (14.4) o Diarrhea: 45 (23.1) o Headache: 29 (14.9) o Nasopharyngitis: 58 (29.7) o Nausea: 58 (29.7) o Upper RTI: 24 (12.3) o Vomiting: 32 (16.4) o Hypoglycemic episodes: 140 (71.8)	NR
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	210	o Nausea: 36 (17.1) o Constipation: 26 (12.4)	3.0 mg/d	212	o Nausea: 101 (47.6) o Constipation: 57 (26.9)	o NR

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
					o Diarrhea: 26 (12.4) o Vomiting: 5 (2.4) o Congestion: 47 (22.4) o Sinusitis: 27 (12.9) o Upper RTI: 23 (11.0) o Headache: 26 (12.4) o Injection-site hematoma: 24 (11.4)			o Diarrhea: 38 (17.9) o Vomiting: 35 (16.5) o Congestion: 36 (17.0) o Upper RTI: 26 (12.3) o Headache: 27 (12.7) o Dizziness: 22 (10.4)	
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	58	Placebo	1,242	o Nausea: 183 (14.7%) o Nasopharyngitis: 234 (18.8%) o Headache: 154 (12.4%)	3.0 mg/d	2,481	o Nausea: 997 (40.2%) o Diarrhea: 518 (20.9%) o Constipation: 495 (20.0%) o Vomiting: 404 (16.3%) o Nasopharyngitis: 427 (17.2%) o Headache: 327 (13.2%) o Decreased appetite: 267 (10.8%)	NR
	Prediabetes	160	Placebo	747	o Nausea, n (%): 125 (17%) o Diarrhea, n (%): 107 (14%)	3.0 mg/d	1,501	o Nausea: 614 (41%) o Diarrhea: 379 (25%)	NR

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
					o Constipation, n (%): 85 (11%) o Nasopharyngitis: 209 (28%) o Upper RTI: 119 (16%) o Influenza: 79 (11%) o Back pain: 120 (16%) o Arthralgia: 97 (13%) o Headache: 122 (16%)			o Constipation: 331 (22%) o Vomiting: 295 (20%) o Dyspepsia: 154 (10%) o Fatigue: 152 (10%) o Nasopharyngitis: 396 (26%) o Upper RTI: 235 (16%) o Influenza: 181 (12%) o Lipase increased: 146 (10%) o Decreased appetite: 164 (11%) o Back pain: 200 (13%) o Arthralgia: 184 (12%) o Headache: 270 (18%) o Dizziness: 146 (10%)	
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	o Nausea: 8 (16) o Upper RTI: 13 (27) o Flu or flu-like symptoms: 8 (16)	3.0 mg/d	49	o Nausea: 32 (65) o Upper RTI: 12 (24) o Abdominal pain: 18 (37)	NR

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
					o Headache: 9 (18) o Constipation: 6 (12) o Flatulence or abdominal distention: 5 (10)			o Flu or flu-like symptoms: 11 (22) o Headache: 10 (20) o Diarrhea: 13 (27) o Constipation: 9 (18) o Vomiting: 11 (22) o Fever: 7 (14) o Dizziness: 15 (31) o Fatigue: 15 (31) o Flatulence or abdominal distention: 5 (10) o GI upset: 9 (18) o UTI: 6 (12) o Heart palpitations: 6 (12)	
			Exercise	48	o Nausea: 15 (31) o Upper RTI: 17 (35) o Abdominal pain: 13 (27) o Flu or flu-like symptoms: 8 (17) o Headache: 10 (21)	3.0 mg/d + exercise	49	o Nausea: 26 (53) o Upper RTI: 13 (27) o Abdominal pain: 12 (24) o Flu or flu-like symptoms: 13 (27) o Headache: 11 (22)	

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
					o Diarrhea: 7 (15) o Constipation: 7 (15) o Vomiting: 6 (12) o Fever: 9 (19) o Fatigue: 6 (12) o UTI: 5 (10)			o Diarrhea: 14 (29) o Constipation: 12 (24) o Vomiting: 15 (31) o Fever: 14 (29) o Dizziness: 11 (22) o Fatigue: 8 (16) o Flatulence or abdominal distention: 8 (16) o GI upset: 9 (18)	

Notes. Shaded rows indicate studies with pediatric populations. ᵃ Pi-Sunyer and colleagues did not report number of participants that experienced at least 1 AE, instead they reported total AEs where at least 5% of study cohort experienced a specific AE (e.g., injection site hematoma).

Abbreviations. AE: adverse event; CI: confidence interval; mg/d: milligrams per day; GDM: gestational diabetes; GI: gastrointestinal; N/A: not applicable; NR: not reported; RR: risk ratio; RTI: respiratory tract infection; SD: standard deviation; SE: standard error; T2DM: type 2 diabetes; UTI: urinary tract infection.

Table C10. Serious Adverse Events and Deaths: Liraglutide

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
Any SAE									
Ellipse Tamborlane, 2019[71]	T2DM	52	Placebo	68	4 (5.9)	≤ 1.8 mg/d	66	9 (13.6)	RR, 2.32 (95% CI, 0.75 to 7.16); P, NR
Kelly, 2020[60]	~ 33% with T2DM and prediabetes	56	Placebo	126	5 (4.0)	3.0 mg/d	125	3 (2.4)	P = .72
LIRA-1 Dejgaard, 2016[69]	T1DM	24	Placebo	50	2 (4)	1.8 mg/d	50	3 (6)	NR
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	6 (8)	3.0 mg/d	80	7 (9)	Crude risk difference, 0.01 (95% CI, −0.08 to 0.10)
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	212	13 (6.1)	3.0 mg/d	422	37 (8.8)	NR
						1.8 mg/d	210	18 (8.6)	
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	2 (1.4)	3.0 mg	142	8 (4.2)	NR
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	197	19 (9.6)	3.0 mg/d	195	16 (8.2)	NR
SCALE Maintenance Wadden, 2013[62]	No diabetes	56	Placebo	210d	5 (2.4)	3.0 mg/d	212	9 (4.2)	NR
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	58	Placebo	1,242	75 (6.0) events	3.0 mg/d	2,481	194 (7.8) events	NR
	Prediabetes	160	Placebo	747	96 (13)	3.0 mg/d	1,501	227 (15)	NR
S-LiTE Lundgren, 2021[65]	No diabetes	52	Placebo	49	2 (4)	3.0 mg/d	49	6 (12)	NR

Study Name Author, Year	Baseline Diabetes Status	Time Point, Weeks	Comparator			Liraglutide			Liraglutide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n %	Dose	n	Proportion, n %	
						3.0 mg/d + exercise	49	4 (8)	
			Exercise	48	4 (8)	3.0 mg/d	49	6 (12)	
Deaths									
LOSEIT Gudbergsen, 2021[64]	NR	52	Placebo	76	0 (0)	3.0 mg/d	80	0 (0)	N/A
SCALE Diabetes Davies, 2015[57]	T2DM	56	Placebo	212	0 (0)	3.0 mg/d	422	0 (0)	NR
						1.8 mg/d	210	1 (44 days after stopping drug)	
SCALE IBT Wadden, 2020[63]	No diabetes	56	Placebo	140	0 (0)	Placebo	142	0 (0)	N/A
SCALE Insulin Garvey, 2020[59]	T2DM	56	Placebo	197	0 (0)	3.0 mg/d	195	0 (0)	N/A
SCALE Obesity and Prediabetes Pi-Sunyer, 2015[56]	No diabetes	56	Placebo	1,242	2 (0.16; pulmonary fibrosis and cardiorespiratory arrest)	3.0 mg/d	2,481	1 (0.04; cardiomegaly and hypertensive heart disease)	NR

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. CI: confidence interval; mg/d: milligrams per day; N/A: not applicable; NR: not reported; RR: risk ratio; SAE: serious adverse event; SD: standard deviation; SE: standard error; T2DM: type 2 diabetes.

Appendix D. Semaglutide: Full Evidence Tables

Table D1. Weight Change, %: Semaglutide

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, % (95% CI)
		Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
STEP 1 Wilding, 2021[80] Wilding, 2022[77]	68	Placebo	655	−2.41 (SD, 10.12)[a]	2.4 mg/week	1,306	−14.85 (SD, 10.12)[a]	−12.44 (95% CI, −13.4 to −11.5)
	0 to 120, off treatment starting at week 68	Placebo, off treatment	93	1.9 (SD, 4.8)	2.4 mg/week, off treatment	197	11.6 (SD, 7.7)	NR
	68 to 120, off treatment			2.1 (SD, 4.9)			14.8 (SD, 10.7)	
STEP 2 Davies, 2021[75]	68	Placebo	403	−3.42 (0.4)	2.4 mg/week	404	−9.64 (0.4)	−6.21 (95% CI, −7.28 to −5.15); P < .001
		Semaglutide, 1.0 mg/d	403	−6.99 (0.4)				−2.65 (95% CI, −3.66 to −1.64); P < .001
STEP 3 Wadden, 2021[73]	68	Placebo	204	−5.7 (SD, 10.11)[a]	2.4 mg/week	407	−16.0 (SD, 10.11)[a]	−10.3 (95% CI, −12.0 to −8.6); P < .001
STEP 4 Rubino, 2021[74]	68	Placebo	268	6.9 (95% CI, 5.8 to 7.9)	2.4 mg/week	535	−7.9 (95% CI, −8.6 to −7.2)	−14.8 (95% CI, −16.0 to −13.5); P < .001
STEP 5 Garvey, 2022[79]	52	Placebo	152	−3.0 (0.7)	2.4 mg/week	152	−15.6 (0.7)	−12.6 (95% CI, −14.5 to −10.7); P, NR
	104	Placebo	152	−2.6 (1.1)	2.4 mg/week	152	−15.2 (0.9)	−12.6 (95% CI, −15.3 to −9.8); P <.001
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	−2·1 (0·8)	2.4 mg/week	199	−13·2 (0·5)	−11·06 (95% CI, −12·88 to −9·24); P < ·001
					1.7 mg/week	101	−9·6 (0·8)	−7·52 (95% CI, −9·62 to −5·43); P < ·001
STEP 8 Rubino, 2022[55]	68	Liraglutide, 3.0 mg/d	117	−6.4 (95% CI, −8.2 to −4.6)	2.4 mg/week	117	−15.8 (95% CI, −17.6 to −13.9)	−9.4 (95% CI, −12.0 to −6.8); P < .001

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, % (95% CI)
		Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
		Placebo	78	−1.9 (95% CI, −4.0 to 0.2)	2.4 mg/week	117	−15.8 (95% CI, −17.6 to −13.9)	−13.9 (95% CI, −16.7 to −11.0); P, NR
					Liraglutide 3.0 mg/d	117	−6.4 (95% CI, −8.2 to −4.6)	−4.5 (95% CI, −7.3 to −1.7); P, NR

Note. [a] Standard deviation calculated by Center researchers.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; NR: not reported; SD: standard deviation; SE: standard error.

Table D2. Weight Change, kg: Semaglutide

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, kg (95% CI)
		Type	n	Mean CFB, kg (SE)	Dose	n	Mean CFB, kg (SE)	
STEP 1 Wilding, 2021[80]	68	Placebo	655	−2.6 (SD, 10.66)[a]	2.4 mg/week	1,306	−15.3 (SD, 10.66)[a]	−12.7 (95% CI, −13.7 to −11.7); *P*, NR
	68 to 120, off treatment	Placebo, off treatment	93	2.0 (SD, 4.8)	2.4 mg/week, off treatment	197	12.0 (SD, 8.4)	NR
STEP 3 Wadden, 2021[73]	68	Placebo	204	−6.2 (SD, 11.0)[a]	2.4 mg/week	407	−16.8 (SD, 11.0)[a]	−10.6 (95% CI, −12.5 to −8.8); *P* < .001
STEP 4 Rubino, 2021[74]	68	Placebo	268	6.1 (95% CI, 5.1 to 7.0)	2.4 mg/week	535	−7.1 (95% CI, −7.8 to −6.5)	−13.2 (95% CI, −14.3 to −12.0); *P* < .001
STEP 5 Garvey, 2022[79]	104	Placebo	152	−3.2 (1.2)	2.4 mg/week	152	−16.1 (1.0)	−12.9 (95% CI, −16.1 to −9.8); *P*, NR
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	−1·70 (0·65)	2.4 mg/week	199	−11·25 (0·46)	−9·55 (95% CI, −11·12 to −7·99); *P*, NR
					1.7 mg/week	101	−8·19 (0·65)	−6·50 (95% CI, −8·30 to −4·69); *P*, NR
STEP 8 Rubino, 2022[55]	68	Liraglutide 3.0 mg/d	117	−6.8 (95% CI, −8.8 to −4.9)	2.4 mg/week	117	−15.3 (95% CI, −17.3 to −13.4)	−8.5 (95% CI, −11.2 to −5.7); *P*, NR
		Placebo	78	−1.6 (95% CI, −3.9 to 0.8)	2.4 mg/week	117	−15.3 (95% CI, −17.3 to −13.4)	−13.8 (95% CI, −16.8 to −10.7); *P*, NR
					Liraglutide 3.0 mg/d	117	−6.8 (95% CI, −8.8 to −4.9)	−5.3 (95% CI, −8.3 to −2.3); *P*, NR
STEP TEENS Weghuber, 2022[78]	68	Placebo	67	2.4 (NR)	2.4 mg/week	134	−15.3 (NR)	−17.7 (95% CI, −21.8 to −13.7); *P*, NR

Notes. Shaded rows indicate studies with pediatric populations. [a] Standard deviation calculated by Center researchers.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; NR: not reported; SD: standard deviation; SE: standard error.

Table D3. Change in Body Mass Index: Semaglutide

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			B Semaglutide vs. Comparator, Between-Group Difference, kg/m² (95% CI)
		Type	n	Mean CFB	Dose	n	Mean CFB	
BMI, kg/m²								
STEP 1 Wilding, 2021[80]	68	Placebo	655	−0.92 kg/m² (SD, 3.68)[a]	2.4 mg/week	1,306	−5.54 kg/m² (SD, 3.68)[a]	−4.61 (95% CI, −4.96 to −4.27); *P*, NR
	68 to 120, off treatment	Placebo, off-treatment	93	0.7 kg/m² (SD, 1.7)	2.4 mg/week, off-treatment	197	4.3 kg/m² (SD, 2.9)	NR
STEP 3 Wadden, 2021[73]	68	Placebo	204	−2.2 (SD, 3.87)[a]	2.4 mg/week	407	−6.0 (SD, 3.87)[a]	−3.8 (95% CI, −4.4 to −3.1); *P* < .001
STEP 4 Rubino, 2021[74]	68	20 weeks 2.4 mg/week, 48 weeks placebo	268	2.2 kg/m² (95% CI, 1.8 to 2.5)	2.4 mg/week	535	−2.6 kg/m² (95% CI, −2.8 to −2.4)	−4.7 (95% CI, −5.2 to −4.3); *P* < .001
STEP 5 Garvey, 2022[79]	104	Placebo	152	−1.6 kg/m² (SE, 0.6)	2.4 mg/week	152	−5.9 kg/m² (SE, 0.4)	−4.3 (95% CI, −5.7 to −2.9); *P*, NR
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	−0·61 kg/m² (SE, 0·24)	2.4 mg/week	199	−4·21 kg/m² (SE, 0·17)	−2.49 (95% CI, −3·17 to −1·82); *P*, NR
					1.7 mg/week	101	−3·10 kg/m² (SE, 0·24)	−2.49 (95% CI, −3·17 to −1·82); *P*, NR
STEP TEENS Weghuber, 2022[78]	68	Placebo	67	0.1 kg/m² (NR)	2.4 mg/week	134	−5.8 kg/m² (NR)	−6.0 (95% CI, −7.3 to −4.6); *P*, NR
BMI, %								
STEP TEENS Weghuber, 2022[78]	68	Placebo	67	0.6% (SD, 12.1)[a]	2.4 mg/week	134	−16.1% (SD, 12.1)[a]	−16.7% (95% CI, −20.3 to −13.2); *P* < .001
	75, off treatment	Placebo, off-treatment	64	1.2% (SD, 11.4)[a]	2.4 mg/week, off-treatment	132	−13.2% (SD, 11.4)[a]	−14.4% (95% CI, −17.8 to −11.0); *P*, NR

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			B Semaglutide vs. Comparator, Between-Group Difference, kg/m² (95% CI)
		Type	n	Mean CFB	Dose	n	Mean CFB	
BMI z/SD score								
STEP TEENS Weghuber, 2022[78]	68	Placebo	67–	−0.1 (SD, 2.08)[a]	2.4 mg/week	134	−1.1 (SD, 2.08)[a]	−1.0 (95% CI, −1.3 to −0.8); P, NR

Notes. Shaded rows indicate studies with pediatric populations. [a] Standard deviation calculated by Center researchers.

Abbreviations. BMI: body mass index; Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; NR: not reported; SD: standard deviation; SE: standard error.

Table D4. Weight Loss ≥ 5% or ≥ 10%: Semaglutide

Author, Year Study Name	Time Point, weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, OR (95% CI)
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Weight change ≥ 5%								
STEP 1 Wilding, 2021[80]	68	Placebo	577	182 (31.5)	2.4 mg/week	1,212	1,047 (86.4)	11.2 (8.9 to 14.2); P < .001
STEP 2 Davies, 2021[75]	68	Placebo	376	107 (28.5)	2.4 mg/week	388	267 (68.8)	4.88 (3.58 to 6.64); P < .001
		Semaglutide, 1.0 mg/d	380	217 (57.1)				1.62 (1.21 to 2.18); P = .001
STEP 3 Wadden, 2021[73]	68	Placebo	204	97 (47.6)	2.4 mg/week	407	352 (86.6)	6.1 (4.0 to 9.3); P < .001
STEP 4 Rubino, 2021[74]	68	20 weeks 2.4 mg/week, 48 weeks placebo	268	128 (47.6)	2.4 mg/week	535	475 (88.7)	NR
STEP 5 Garvey, 2022[79]	104	Placebo	128	44 (34.4)	2.4 mg/week	144	111 (77.1)	5.0 (3.0 to 8.4); P < .001
STEP 6 Kadowaki, 2022[76]	68	Placebo	100	21 (21)	2.4 mg/week	193	160 (83)	21·72 (11·27 to 41·86); P < .001
					1.7 mg/week	98	71 (72)	11·08 (5·53 to 22·22); P < .001

Author, Year Study Name	Time Point, weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, OR (95% CI)
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
STEP TEENS Weghuber, 2022[78]	68	Placebo	62	11 (18)	2.4 mg/week	131	95 (73)	14.0 (6.3 to 31.0); P < .001
Weight change ≥ 10%								
STEP 1 Wilding, 2021[80]	68	Placebo	577	69 (12.0)	2.4 mg/week	1,212	837 (69.1)	14.7 (95% CI, 11.1 to 19.4); P < .001
STEP 2 Davies, 2021[75]	68	Placebo	376	31 (8.2)	2.4 mg/week	388	177 (45.6)	7.41 (4.89 to 11.24); P < .001
		Semaglutide, 1.0 mg/d	380	109 (28.7)				2.07 (1.53 to 2.80); P, NR
STEP 3 Wadden, 2021[73]	68	Placebo	204	55 (27.0)	2.4 mg/week	407	306 (75.3)	7.4 (95% CI, 4.9 to 11.0); P < .001
STEP 4 Rubino, 2021[74]	68	20 weeks 2.4 mg/week, 48 weeks placebo	268	55 (20.4)	2.4 mg/week	535	423 (79.0)	NR
STEP 5 Garvey, 2022[79]	104	Placebo	128	17 (13.3)	2.4 mg/week	144	89 (61.8)	5.0 (3.0 to 8.4); P < .001
STEP 6 Kadowaki, 2022[76]	68	Placebo	100	5 (5)	2.4 mg/week	193	117 (61)	31·67 (12·15 to 82·58); P < .001
					1.7 mg/week	98	41 (42)	13·57 (5·01 to 36·74); P < .001
STEP 8 Rubino, 2022[55]	68	Liraglutide 3.0 mg/d	117	30 (25.6)	2.4 mg/week	117	83 (70.9)	6.3 (95% CI, 3.5 to 11.2); P < .001
		Placebo	78	12 (15.4)	2.4 mg/week	117	83 (70.9)	NR
					Liraglutide 3.0 mg/d	117	30 (25.6)	
STEP TEENS Weghuber, 2022[78]	68	Placebo	62	5 (8)	2.4 mg/week	131	81 (62)	23.0 (95% CI, 8.3 to 63.7; P, NR)

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; NR: not reported; SD: standard deviation; SE: standard error.

Table D5. Change in Systolic Blood Pressure: Semaglutide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, mmHg (95% CI)
			Type	n	Mean CFB, mmHg (SE)	Dose	n	Mean CFB, mmHg (SE)	
STEP 1 Wilding, 2021[80]	No diabetes	68	Placebo	655	−1.06 (SD, 13.158)[a]	2.4 mg/week	1,306	−6.16 (SD, 13.158)[a]	−5.10 (95% CI, −6.34 to −3.87); $P < .001$
		120	Placebo, off treatment	93	4 (SD, 15)	2.4 mg/week, off treatment	197	9 (SD, 14)	NR
STEP 2 Davies, 2021[75]	T2DM	68	Semaglutide, 1.0 mg/week	403	−2.9 (0.9)	2.4 mg/week	404	−3.9 (0.7)	−1.0 (95% CI, −3.3 to 1.2)
			Placebo	403	−0.5 (0.8)				−3.4 (95% CI, −5.6 to −1.3); $P < .01$
STEP 3 Wadden, 2021[73]	No diabetes	68	Placebo	204	−1.6 (SD, 14.57)[a]	2.4 mg/week	407	−5.6 (SD, 14.57)[a]	−3.9 (95% CI, −6.4 to −1.5); $P = .001$
STEP 4 Rubino, 2021[74]	No diabetes	68	20 weeks 2.4 mg/week, 48 weeks placebo	268	4.4 (95% CI, 2.9 to 6.0)	2.4 mg/week	535	0.5 (95% CI, −0.6 to 1.6)	−3.9 (95% CI, −5.8 to −2.0); $P < .001$
STEP 5 Garvey, 2022[79]	No diabetes	104	Placebo	152	−1.6 (1.2)	2.4 mg/week	152	−5.7 (1.1)	−4.2 (95% CI, −7.3 to −1.0); $P = 0.01$
STEP 6 Kadowaki, 2022[76]	Mixed diabetes	68	Placebo	101	−5.31 (1.24)	2.4 mg/week	199	−10.83 (0.90)	−5.53 (95% CI, −8.53 to −2.52)
						1.7 mg/week	101	−10.76 (1.26)	−5.45 (95% CI, −8.93 to −1.97)
STEP 8 Rubino, 2022[55]	No diabetes	68	Liraglutide 3.0 mg/d	112	−2.9 (95% CI, −5.3 to −0.5)	2.4 mg/week	114	−5.7 (95% CI, −8.1 to −3.3)	−2.8 (95% CI, −6.1 to 0.6); P, NR
			Placebo	[77]	3.2 (95% CI, 0.3 to 6.1)	2.4 mg/week	114	−5.7 (95% CI, −8.1 to −3.3)	NR
						Liraglutide 3.0 mg/d	112	−2.9 (95% CI, −5.3 to −0.5)	
STEP TEENS	Mixed diabetes	68	Placebo	67	−0.8 (SD, 10.399)[a]	2.4 mg/week	134	−2.7 (SD, 10.399)[a]	−1.9 (95% CI, −5.0 to 1.1)

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, mmHg (95% CI)
			Type	n	Mean CFB, mmHg (SE)	Dose	n	Mean CFB, mmHg (SE)	
Weghuber, 2022[78]									

Notes. Shaded rows indicate studies with pediatric populations. [a] Standard deviation calculated by Center researchers.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; mmHg: millimeters of mercury; NR: not reported; SD: standard deviation; SE: standard error.

Table D6. Change in LDL Cholesterol: Semaglutide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
STEP 1 Wilding, 2021[80]	No diabetes	68	Placebo	655	Geometric mean ratio: 1.01 (SD, NR)	2.4 mg/week	1,306	Geometric mean ratio: 0.97 (SD, NR)	Ratio, 0.96 (95% CI, 0.94 to 0.98)
		68 to 120, off treatment	Placebo, off treatment	92	Geometric mean ratio: 0.95 (SD, 25.6)	2.4 mg/week, off treatment	194	Geometric mean ratio: 1.01 (SD, 20.5)	NR
STEP 3 Wadden, 2021[73]	No diabetes	68	Placebo	204	2.6% (SD, NR)	2.4 mg/week	407	−4.7% (SD, NR)	ETD, −7.1 (95% CI, −10.9 to −3.2); P < .001
STEP 4 Rubino, 2021[74]	No diabetes	68	20 weeks 2.4 mg/week, 48 weeks placebo	268	8% (95% CI, 5 to 10)	2.4 mg/week	535	1% (95% CI, −1 to 3)	−6% (95% CI, −9 to −3); P < .001
STEP 5 Garvey, 2022[79]	No diabetes	104	Placebo	152	−2.7% (SD, NR)	2.4 mg/week	152	−6.1% (SD, NR)	−3.4% (95% CI, −9.1 to 2.6); P, NR
STEP 6 Kadowaki, 2022[76]	Mixed diabetes	68	Placebo	101	Geometric mean ratio: 0.96 (SD, NR)	2.4 mg/week	199	Geometric mean ratio: 0.85 (SD, NR)	Geometric mean ratio: 0.89 (95% CI, 0.84 to 0.94); P, NR
						1.7 mg/week	101	Geometric mean ratio: 0.90 (SD, NR)	Geometric mean ratio: 0.94 (95% CI, 0.88 to 1.00); P, NR
STEP 8 Rubino, 2022[55]	No diabetes	68	Liraglutide 3.0 mg/d	127	0.9% (95% CI, −4.4 to 6.5)	2.4 mg/week	126	−6.5% (95% CI, −12.4 to −0.1)	−7.3% (95% CI, −14.9 to 1.0); P, NR
			Placebo	85	−1.1% (95% CI, −11.4 to 10.4)	2.4 mg/week	126	−6.5% (95% CI, −12.4 to −0.1)	NR

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
						Liraglutide 3.0 mg/d	127	0.9% (95% CI, −4.4 to 6.5)	NR
STEP TEENS Weghuber, 2022[78]	Mixed diabetes	68	Placebo	67	−3.4% (SD, NR)	2.4 mg/week	134	−10.2% (SD, NR)	−7.0% (95% CI, −11.9 to −1.8)

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. CFB: change from baseline; CI: confidence interval; LDL: low-density lipoprotein; mg/d: milligrams per day; NR: not reported; SD: standard deviation.

Table D7. Change in HbA1c: Semaglutide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
STEP 1 Wilding, 2021[80]	No diabetes	68	Placebo	655	−0.15 (SD, 0.32)[a]	2.4 mg/week	1,306	−0.45% (SD, 0.32)[a]	−0.29 (95% CI, −0.32 to −0.26); P, NR
		120	Placebo, off treatment	90	0.1 (0.3)	2.4 mg/week, off treatment	195	0.4 (0.3)	NR
STEP 2 Davies, 2021[75]	T2DM	68	Semaglutide, 1.0 mg/week	403	−1.5 (0.1)	2.4 mg/week	404	−1.6 (0.1)	−0.2% (95% CI, −0.3 to 0.0); P, NR
			Placebo	403	−0.4 (0.1)				−1.2 (95% CI, −1.4 to −1.0); P < .001
STEP 3 Wadden, 2021[73]	No diabetes	68	Placebo	204	−0.27 (SD, 2.974)[a]	2.4 mg/week	407	−0.51 (SD, 2.974)[a]	−0.24 (95% CI, −0.29 to −0.19); P < .001
STEP 4 Rubino, 2021[74]	No diabetes	68	20 weeks 2.4 mg/week, 48 weeks placebo	268	0.1 (95% CI, 0.1 to 0.1)	2.4 mg/week	535	−0.1 (95% CI, −0.2 to −0.1)	−0.2 (95% CI, −0.3 to −0.2); P < .001
STEP 6 Kadowaki, 2022[76]	Mixed diabetes types	68	Placebo	101	−0.03 (0.07)	2.4 mg/week	199	−0.93 (0.05)	−0.90 (95% CI, −1.05 to −0.74); P, NR
						1.7 mg/week	101	−0.89 (0.07)	−0.86 (95% CI, −1.04 to −0.68); P, NR
STEP 8 Rubino, 2022[55]	No diabetes	68	Liraglutide 3.0 mg/d	127	−0.1 (95% CI, −0.1 to 0.0)	2.4 mg/week	126	−0.2 (95% CI, −0.3 to −0.2)	−0.2 (95% CI, −0.2 to −0.1); P, NR

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
			Placebo	85	0.1 (95% CI, 0.1 to 0.2)	2.4 mg/week	126	−0.2 (95% CI, −0.2 to −0.005)	NR
						Liraglutide 3.0 mg/d	127	−0.1 (95% CI, −0.3 to −0.2)	NR
STEP TEENS Weghuber, 2022[78]	Mixed diabetes types	68	Placebo	67	−0.1 (SD, 0.17)[a]	2.4 mg/week	134	−0.4 (SD, 0.17)[a]	−0.3 (95% CI, −0.3 to −0.2); *P*, NR

Notes. Shaded rows indicate studies with pediatric populations. [a] Standard deviation calculated by Center researchers.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; HbA1c: hemoglobin A1c; mg/d: milligrams per day; NR: not reported; SD: standard deviation.

Table D8. Quality of Life: Semaglutide

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, (95% CI)
		Type	n	Mean CFB	Dose	n	Mean CFB	
SF-36: physical function score [a]								
STEP 1 Wilding, 2021[80]	68	Placebo	655	0.41 (SD, NR)	2.4 mg/week	1,306	2.21 (SD, NR)	1.80 (95% CI, 1.18 to 2.42); P < .001
STEP 2 Davies, 2021[75]	68	Placebo	403	1.0 (SE, 0.4)	2.4 mg/week	404	2.5 (SE, 0.4)	1.5 (95% CI, 0.4 to 2.6); P = .006
		Semaglutide, 1.0 mg/week	403	2.4 (SE, 0.4)				0.1 (95% CI, −1.0 to 1.2); P, NR
STEP 3 Wadden, 2021[73]	68	Placebo	204	1.6 (SD, NR)	2.4 mg/week	409	2.4 (SD, NR)	0.8 (95% CI, −0.2 to 1.9); P = .12
STEP 4 Rubino, 2021[74]	68	20 weeks 2.4 mg/week, 48 weeks placebo	268	−1.5 (95% CI, −2.2 to −0.7)	2.4 mg/week	535	1.0 (95% CI, 0.6 to 1.4)	2.5 (95% CI, 1.6 to 3.3); P < .001
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	−0·33 (SE, 0·44)	2.4 mg/week	199	0·83 (SE, 0·33)	1·16 (95% CI, 0·09 to 2·22); P, NR
					1.7 mg/week	101	−0·07 (SE, 0·46)	0·26 (95% CI, −0·98 to 1·49); P, NR
IWQoL-Lite-CT: physical function score [a]								
STEP 1 Wilding, 2021[80]	68	Placebo	655	5.25 (SD, NR)	2.4 mg/week	1,306	14.67 (SD, NR)	9.43 (95% CI, 7.50 to 11.35); P < .001
STEP 2 Davies, 2021[75]	68	Placebo	403	5.3 (SE, 1.1)	2.4 mg/week	404	10.1 (SE, 1.0)	4.8 (95% CI, 1.8 to 7.9); P = ·002
		Semaglutide, 1.0 mg/week	403	8.7 (SE, 1.1)				1.4 (95% CI, −1.5 to 4.3); P, NR
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	0·84 (SE, 1·44)	2.4 mg/week	199	4·21 (SE, 1·06)	3·37 (95% CI, −0·12 to 6·87); P, NR
					1.7 mg/week	101	2·84 (SE, 1·48)	2·00 (95% CI, −2·03 to 6·03); P, NR

Note. ᵃ Larger values (higher scores) indicated higher levels of quality of life.

Abbreviations. CFB: change from baseline; CI: confidence interval; IWQoL-Lite-CT: impact of weight on quality of life-lite for clinical trials version; NR: not reported; QoL: quality of life; SD: standard deviation; SE: standard error; SF-36: Short-Form Health Survey, 36 questions.

Table D9. Withdrawals Due to AEs, Any AEs, and AEs occurring in ≥ 10%: Semaglutide

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Withdrawals due to AEs								
STEP 1 Wilding, 2021[80]	75	Placebo	655	20 (3.1)	2.4 mg/week	1,306	92 (7.0)	NR
STEP 2 Davies, 2021[75]	68	Placebo	402	14 (3·5%)	2.4 mg/week	403	25 (6.2%)	NR
		Semaglutide, 1.0 mg/week	402	20 (5·0%)				
STEP 3 Wadden, 2021[73]	68	Placebo	204	6 (2.9)	2.4 mg/week	407	24 (5.9)	NR
STEP 4 Rubino, 2021[74]	75	20 weeks 2.4 mg/week, 48 weeks placebo	268	6 (2.2%)	2.4 mg/week	535	13 (2.4%)	NR
STEP 5 Garvey, 2022[79]	104	Placebo	152	7 (4.6)	2.4 mg/week	152	9 (5.9)	NR
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	1 (1)	2.4 mg/week	199	5 (3)	NR
					1.7 mg/week	100	3 (3)	
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	16 (12.6)	2.4 mg/week	126	4 (3.2)	NR
		Placebo	85	3 (3.5)				
STEP TEENS Weghuber, 2022[78]	68	Placebo	67	3 (4)	2.4 mg/week	133	6 (5)	NR
Any AE								
STEP 1 Wilding, 2021[80]	75	Placebo	655	566 (86.4)	2.4 mg/week	1,306	1171 (89.7)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
STEP 2 Davies, 2021[75]	68	Placebo	402	309 (76.9)	2.4 mg/week	403	353 (87.6)	NR
		Semaglutide, 1.0 mg/week	402	329 (81.8)				
STEP 3 Wadden, 2021[73]	68	Placebo	204	196 (96.1)	2.4 mg/week	407	390 (95.8)	NR
STEP 4 Rubino, 2021[74]	75	20 weeks 2.4 mg/week, 48 weeks placebo	268	201 (75.0)	2.4 mg/week	535	435 (81.3)	NR
STEP 5 Garvey, 2022[79]	104	Placebo	152	136 (89.5)	2.4 mg/week	152	146 (96.1)	NR
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	80 (79.0)	2.4 mg/week	199	171 (86)	NR
					1.7 mg/week	100	82 (82)	NR
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	122 (96.1)	2.4 mg/week	126	120 (95.2)	NR
		Placebo	85	81 (95.3)				
STEP TEENS Weghuber, 2022[78]	68	Placebo	67	55 (82)	2.4 mg/week	133	105 (79)	NR
AEs occurring in ≥ 10%								
STEP 1 Wilding, 2021[80]	75	Placebo	655	• Nausea: 114 (17.4) • Diarrhea: 104 (15.9) • Headache: 80 (12.2) • Congestion: 133 (20.3) • Upper RTI: 80 (12.2)	2.4 mg/week	1,306	• Nausea: 577 (44.2) • Constipation: 306 (23.4) • Diarrhea: 412 (31.5) • Vomiting: 324 (24.8) • Headache: 198 (15.2) • Dyspepsia: 135 (10.3) • Congestion: 281 (21.5	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
							• Abdominal pain: 130 (10.0)	
STEP 2 Davies, 2021[75]	68	Placebo	402	• Nausea: 37 (9.2) • Vomiting: 11 (2.7) • Diarrhea: 48 (11.9) • Constipation: 22 (5.5) • Nasopharyngitis: 59 (14.7) • Upper RTI: 38 (9.5)	2.4 mg/week	403	• Nausea: 136 (33.7) • Vomiting: 88 (21.8) • Diarrhea: 86 (21.3) • Constipation: 70 (17.4) • Nasopharyngitis: 68 (16.9) • Upper RTI: 42 (10.4)	NR
		Semaglutide, 1.0 mg/week	402	• Nausea: 129 (32.1) • Vomiting: 54 (13.4); 93 events • Diarrhea: 89 (22.1) • Constipation: 51 (12.7) • Nasopharyngitis: 47 (11.7) • Upper RTI: 37 (9.2)				
STEP 3 Wadden, 2021[73]	68	Placebo	204	• Nausea: 45 (22.1) • Constipation: 50 (24.5) • Diarrhea: 45 (22.1) • Vomiting: 22 (10.8) • Flatulence: 23 (11.3) • Congestion: 49 (24.0) • Upper RTI: 44 (21.6) • Sinusitis: 26 (12.7) • Back pain: 22 (10.8)	2.4 mg/week	407	• Nausea: 237 (58.2) • Constipation: 150 (36.9) • Diarrhea: 147 (36.1) • Vomiting: 111 (27.3) • Headache: 78 (19.2) • Flatulence: 47 (11.5) • Fatigue: 52 (12.8) • Congestion: 90 (22.1) • Upper RTI: 85 (20.9) • Sinusitis: 39 (9.6) • Back pain: 54 (13.3) • Abdominal pain: 54 (13.3)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
							• Dizziness: 52 (12.8) • UTI: 42 (10.3)	
STEP 4 Rubino, 2021[74]	75	20 weeks 2.4 mg/week, 48 weeks placebo	268	• Nasopharyngitis: 39 (14.6) 54 • Gastrointestinal disorders: 70 (26.1); 124 events • Psychiatric disorders: 35 (13.1) 50 events • Cardiovascular disorders: 30 (11.2); 40 events	2.4 mg/week	535	• Diarrhea: 77 (14.4); 114 events • Nausea: 75 (14.0); 105 events • Constipation: 62 (11.6); 75 events • Nasopharyngitis: 58 (10.8); 77 events • Vomiting: 55 (10.3); 88 events • Gastrointestinal disorders: 224 (41.9); 607 events	NR
STEP 5 Garvey, 2022[79]	104	Placebo	152	• Nausea: 33 (21.7) • Constipation: 17 (11.2) • Diarrhea: 36 (23.7) • Headache: 16 (10.5) • Congestion: 23 (15.1) • Upper RTI: 23 (15.1) • Back pain: 19 (12.5) • Influenza: 16 (10.5)	2.4 mg/week	152	• Nausea: 81 (53.3) • Constipation: 47 (30.9) • Diarrhea: 53 (34.9) • Vomiting: 46 (30.3) • Headache: 16 (10.5) • Flatulence: 20 (13.2) • Burping: 17 (11.2) • Dyspepsia: 20 (13.2) • Congestion: 24 (15.8) • Gastroenteritis: 20 (13.2) • Influenza: 20 (13.2) • Upper RTI: 20 (13.2) • Back pain: 15 (9.9) • Abdominal pain: 20 (13.2)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
							• Abdominal pain, upper: 22 (14.5)	
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	• Congestion: 18 (18)	2.4 mg/week	199	• Nausea: 35 (18) • Constipation: 52 (26) • Diarrhea: 32 (16) • Congestion: 53 (27)	NR
					1.7 mg/week	100	• Nausea: 18 (18) • Constipation: 19 (19) • Diarrhea: 22 (22 • Congestion: 24 (24) • Vomiting: 10 (10) • Abdominal discomfort: 11 (11)	
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	• Nausea: 75 (59.1) • Constipation: 40 (31.5) • Diarrhea: 23 (18.1) • Vomiting: 26 (20.5) • Headache: 18 (14.2) • Decreased appetite: 16 (12.6) • Fatigue: 14 (11.0) • Dyspepsia: 15 (11.8) • Upper RTI: 19 (15.0) • Joint pain: 14 (11.0) • Influenza: 14 (11.0)	2.4 mg/week	126	• Nausea: 77 (61.1) • Constipation: 49 (38.9) • Diarrhea: 35 (27.8) • Vomiting: 32 (25.4) • Headache: 20 (15.9) • Burping: 17 (13.5) • Decreased appetite: 15 (11.9)	NR
		Placebo	85	• Nausea: 19 (22.4) • Constipation: 20 (23.5) • Diarrhea: 22 (25.9) • Headache: 10 (11.8) • Congestion: 9 (10.6)				

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
				• Upper RTI: 18 (21.2) • Sinusitis: 13 (15.3) • Back pain: 9 (10.6)				
STEP TEENS Weghuber, 2022[78]	68	Placebo	67	• Nausea: 12 (18) • Constipation: 1 (1) • Diarrhea: 13 (19) • Vomiting: 7 (10) • Headache: 11 (16) • Congestion: 7 (10) • Abdominal pain: 4 (6)	2.4 mg/week	133	• Nausea: 56 (42) • Diarrhea: 29 (22) • Vomiting: 48 (36) • Headache: 22 (17) • Congestion: 16 (12) • Abdominal pain: 20 (15)	NR

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. AE: adverse event; mg/d: milligrams per day; NR: not reported; RTI: respiratory tract infection; UTI: urinary tract infection.

Table D10. Serious Adverse Events and Deaths: Semaglutide

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Notes
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Any SAE								
STEP 1 Wilding, 2021[80]	75	Placebo	655	42 (6.4)	2.4 mg/week	1,306	128 (9.8)	NR
STEP 2 Davies, 2021[75]	68	Placebo	402	37 (9.2)	2.4 mg/week	403	40 (9.9)	NR
		Semaglutide, 1.0 mg/week	402	1 (7.7)				
STEP 3 Wadden, 2021[73]	68	Placebo	204	6 (2.9)	2.4 mg/week	407	37 (9.1)	NR
STEP 4 Rubino, 2021[74]	75	20 weeks 2.4 mg/week, 48 weeks placebo	268	15 (5.6)	2.4 mg/week	535	41 (7.7)	NR
STEP 5 Garvey, 2022[79]	104	Placebo	152	18 (11.8)	2.4 mg/week	152	12 (7.9)	NR
STEP 6 Kadowaki, 2022[76]	68	Placebo	101	7 (7)	2.4 mg/week	199	10 (5)	NR
					1.7 mg/week	100	7 (7)	
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	14 (11.0)	2.4 mg/week	126	10 (7.9)	NR
		Placebo	85	6 (7.1)				
STEP TEENS Weghuber, 2022[78]	68	Placebo	67	6 (9)	2.4 mg/week	133	15 (11)	For SAEs, 3 (2.3%) experienced cholelithiasis in sema group, vs. 0 in placebo; 2 (1.5%) experienced appendicitis vs. 0 in placebo group
Deaths								
STEP 1 Wilding, 2021[80]	75	Placebo	655	1 (0.2)	2.4 mg/week	1,306	1 (0.1)	Serious gastrointestinal disorders (1.4% of participants in the

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Notes
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
								semaglutide group and 0% in the placebo group) and hepatobiliary disorders (1.3% with semaglutide and 0.2% with placebo)
STEP 2 Davies, 2021[75]	68	Placebo	402	1 (0·2%)	2.4 mg/week	403	1 (0.2%)	NR
		Semaglutide, 1.0 mg/week	402	1 (0·2%)				
STEP 4 Rubino, 2021[74]	75	20 weeks 2.4 mg/week, 48 weeks placebo	268	1 (0.4%)	2.4 mg/week	535	1 (0.2%)	For semaglutide: "natural causes with underlying chronic obstructive pulmonary disease" For placebo: malignant lung cancer and malignant pericardial effusion in a participant who had discontinued placebo
STEP 5 Garvey, 2022[79]	104	Placebo	152	0 (0.0)	2.4 mg/week	152	1 (0.7)	Death considered by the independent external event adjudication committee to be unrelated to the trial product
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	0	2.4 mg/week	126	0	NR
		Placebo	85	0				

Note. Shaded rows indicate studies with pediatric populations.
Abbreviations. mg/d: milligrams per day; NR: not reported; SAE: serious adverse event.

Appendix E. Semaglutide vs. Liraglutide: Full Evidence Tables

Table E1. Weight Change, %: Semaglutide vs. Liraglutide

Author, Year Study Name	Time Point. Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, % (95% CI)
		Type	n	% Mean CFB (95% CI)	Dose	n	% Mean CFB (95% CI)	
STEP 8 Rubino, 2022[55]	68	Liraglutide, 3.0 mg/d	127	−6.4 (95% CI, −8.2 to −4.6)	2.4 mg/week	126	−15.8 (95% CI, −17.6 to −13.9)	−9.4 (95% CI, −12.0 to −6.8); *P* < .001
		Placebo	85	−1.9 (95% CI, −4.0 to 0.2)	2.4 mg/week	126	−15.8 (95% CI, −17.6 to −13.9)	−13.9 (95% CI, −16.7 to −11.0); *P, NR*
					Liraglutide 3.0 mg/d	127	−6.4 (95% CI, −8.2 to −4.6)	−4.5 (95% CI, −7.3 to −1.7); *P, NR*

Abbreviations. CFB: change from baseline; CI: confidence interval; NR: not reported.

Table E2. Weight Change, kg: Semaglutide vs. Liraglutide

Author, Year Study Name	Time Point. Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, kg (95% CI)
		Type	n	Mean CFB, kg (95% CI)	Dose	n	Mean CFB, kg (95% CI)	
STEP 8 Rubino, 2022[55]	68	Liraglutide 3.0 mg/d	127	−6.8 (95% CI, −8.8 to −4.9)	2.4 mg/week	126	−15.3 (95% CI, −17.3 to −13.4)	−8.5 (95% CI, −11.2 to −5.7); *P, NR*
		Placebo	85	−1.6 (95% CI, −3.9 to 0.8)	2.4 mg/week	126	−15.3 (95% CI, −17.3 to −13.4)	−13.8 (95% CI, −16.8 to −10.7); *P, NR*
					Liraglutide 3.0 mg/d	127	−6.8 (95% CI, −8.8 to −4.9)	−5.3 (95% CI, −8.3 to −2.3); *P, NR*

Abbreviations. CFB: change from baseline; CI: confidence interval; NR: not reported.

Table E3. Weight Loss ≥ 10%: Semaglutide vs. Liraglutide

Author, Year Study Name	Time Point. Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, OR (95% CI)
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
STEP 8 Rubino, 2022[55]	68	Liraglutide 3.0 mg/d	117	30 (25.6)	2.4 mg/week	117	83 (70.9)	6.3 (95% CI, 3.5 to 11.2); P < .001
		Placebo	78	12 (15.4)	2.4 mg/week	117	83 (70.9)	NR
					Liraglutide 3.0 mg/d	117	30 (25.6)	

Abbreviations. CI: confidence interval; mg/d: milligrams per day; NR: not reported.

Table E4. Change in Systolic Blood Pressure: Semaglutide vs. Liraglutide

Author, Year Study Name	Time Point. Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference, mmHg (95% CI)
		Type	n	Mean CFB, mmHg (95% CI)	Dose	n	Mean CFB, mmHg (95% CI)	
STEP 8 Rubino, 2022[55]	68	Liraglutide 3.0 mg/d	127	−2.9 (95% CI, −5.3 to −0.5)	2.4 mg/week	126	−5.7 (95% CI, −8.1 to −3.3)	−2.8 (95% CI, −6.1 to 0.6); P, NR
		Placebo	85	3.2 (95% CI, 0.3 to 6.1)	2.4 mg/week	126	−5.7 (95% CI, −8.1 to −3.3	NR
					Liraglutide 3.0 mg/d	127	−2.9 (95% CI, −5.3 to −0.5)	

Abbreviations. CFB: change from baseline; CI: confidence interval; NR: not reported; mg/d: milligrams per day; mmHg: millimeters of mercury.

Table E5. Change in LDL Cholesterol, %: Semaglutide vs. Liraglutide

| Author, Year Study Name | Time Point. Weeks | Comparator | | | Semaglutide | | | Semaglutide vs. Comparator, Between-Group Difference, % (95% CI) |
		Type	n	Mean CFB, % (95% CI)	Dose	n	Mean CFB, % (95% CI)	
STEP 8 Rubino, 2022[55]	68	Liraglutide 3.0 mg/d	127	0.9 (95% CI, −4.4 to 6.5)	2.4 mg/week	126	−6.5 (95% CI, −12.4 to −0.1)	−7.3 (95% CI, −14.9 to 1.0); *P*, NR
		Placebo	85	−1.1 (95% CI, −11.4 to 10.4)	2.4 mg/week	126	−6.5 (95% CI, −12.4 to −0.1)	NR
					Liraglutide 3.0 mg/d	127	0.9 (95% CI, −4.4 to 6.5)	NR

Abbreviations. CFB: change from baseline; CI: confidence interval; LDL: low-density lipoprotein; mg/d: milligrams per day; NR: not reported.

Table E6. Change in HbA1c, %: Semaglutide vs. Liraglutide

| Author, Year Study Name | Time Point. Weeks | Comparator | | | Semaglutide | | | Semaglutide vs. Comparator, Between-Group Difference, % (95% CI) |
		Type	n	Mean CFB, % (95% CI)	Dose	n	Mean CFB, % (95% CI)	
STEP 8 Rubino, 2022[55]	68	Liraglutide 3.0 mg/d	127	−0.1 (95% CI, −0.1 to 0.0)	2.4 mg/week	126	−0.2 (95% CI, −0.3 to −0.2)	−0.2 (95% CI, −0.2 to −0.1); *P*, NR
		Placebo	85	0.1 (95% CI, 0.1 to 0.2)	2.4 mg/week	126	−0.2 (95% CI, −0.3 to −0.2)	NR
					Liraglutide 3.0 mg/d	127	−0.1 (95% CI, −0.1 to 0.0)	NR

Abbreviations. CFB: change from baseline; CI: confidence interval; HbA1c: hemoglobin A1c; mg/d: milligrams per day; NR: not reported.

Table E7. Withdrawals Due to AEs, Any AE, and AEs Occurring in ≥ 10%: Semaglutide vs. Liraglutide

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Withdrawals due to AEs								
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	16 (12.6)	2.4 mg/week	126	4 (3.2)	NR
		Placebo	85	3 (3.5)				
Any AE								
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	122 (96.1)	2.4 mg/week	126	120 (95.2)	NR
		Placebo	85	81 (95.3)				
AEs occurring in ≥ 10%								
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	• Nausea: 75 (59.1) • Constipation: 40 (31.5) • Diarrhea: 23 (18.1) • Vomiting: 26 (20.5) • Headache: 18 (14.2) • Decreased appetite: 16 (12.6) • Fatigue: 14 (11.0) • Dyspepsia: 15 (11.8) • Upper RTI: 19 (15.0) • Joint pain: 14 (11.0) • Influenza: 14 (11.0)	2.4 mg/week	126	• Nausea: 77 (61.1) • Constipation: 49 (38.9) • Diarrhea: 35 (27.8) • Vomiting: 32 (25.4) • Headache: 20 (15.9) • Burping: 17 (13.5) • Decreased appetite: 15 (11.9)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
		Placebo	85	- Nausea: 19 (22.4) - Constipation: 20 (23.5) - Diarrhea: 22 (25.9) - Headache: 10 (11.8) - Congestion: 9 (10.6) - Upper RTI: 18 (21.2) - Sinusitis: 13 (15.3) - Back pain: 9 (10.6)				

Abbreviations. AE: adverse event; mg/d: milligrams per day; NR: not reported; RTI: respiratory tract infection.

Table E8. Serious Adverse Events and Deaths: Semaglutide vs. Liraglutide

Author, Year Study Name	Time Point. Weeks	Comparator			Semaglutide			Semaglutide vs. Comparator, Between-Group Difference
Any SAE								
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	14 (11.0)	2.4 mg/week	126	10 (7.9)	NR
		Placebo	85	6 (7.1)				
Deaths								
STEP 8 Rubino, 2022[55]	75	Liraglutide 3.0 mg/d	127	0	2.4 mg/week	126	0	NR
		Placebo	85	0				

Abbreviations. mg/d: milligrams per day; NR: not reported; SAE: serious adverse event.

Appendix F. Tirzepatide: Full Evidence Tables

Table F1. Weight Change, %: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (95% CI)	Dose	n	Mean CFB, % (95% CI)	
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	−3.1 (95% CI, −4.3 to −1.9)	15 mg/week	630	−20.9 (95% CI, −21.8 to −19.9)	−17.8 (95% CI, −19.3 to −16.3); *P* < .001
						10 mg/week	636	−19.5 (95% CI, −20.4 to −18.5)	−16.4 (95% CI, −17.9 to −14.8); *P* < .001
						5 mg/week	630	−15.0 (95% CI, −15.9 to −14.2)	−11.9 (95% CI, −13.4 to −10.4); *P* < .001

Abbreviations. CFB: change from baseline; CI: confidence interval.

Table F2. Weight Loss ≥ 5% or ≥ 10%: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference, OR (95% CI)
			Type	n	Proportion, n (%; 95% CI of LS MC)	Dose	n	Proportion, n (%; 95% CI of LS MC)	
Weight loss ≥ 5%									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	222 (34.5; 95% CI, 29.8 to 39.2)	15 mg/week	630	573 (90.9; 95% CI; 88.0 to 93.8)	NR; *P* < .001
						10 mg/week	636	565 (88.9; 95% CI, 85.9 to 91.9)	
						5 mg/week	630	536 (85.1; 95% CI, 81.6 to 88.6)	
Weight loss ≥ 10%									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	121 (18.8; 95% CI, 14.9 to 22.7)	15 mg/week	630	526 (83.5; 95% CI, 80.0 to 86.9)	NR; *P* < .001
						10 mg/week	636	497 (78.1; 95% CI, 74.4 to 81.7)	
						5 mg/week	630	432 (68.5; 95% CI, 64.5 to 72.5)	

Abbreviations. CFB: change from baseline; CI: confidence interval; LS MC: least square mean change; NR: not reported; OR: odds ratio.

Table F3. Change in Systolic Blood Pressure: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Control			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (95% CI)	Dose	n	Mean CFB, % (95% CI)	
SURMOUNT−1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	−1.0 (95% CI, −2.3 to −0.3)	5, 10, or 15 mg/week	1,896	−7.2 (95% CI, −7.8 to −6.7)	−6.2 (95% CI, −7.7 to −4.8); P < .001

Abbreviations. CFB: change from baseline; CI: confidence interval.

Table F4. Change in LDL Cholesterol: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference, mg/dl (95% CI)
			Type	n	Mean CFB, mg/dl (95% CI)	Dose	n	Mean CFB, mg/dl (95% CI)	
SURMOUNT−1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	−1.7 (95% CI, −4.6 to 1.3)	5, 10, or 15 mg/week	1,896	−5.8 (95% CI, −6.9 to −4.6)	−4.2 (95% CI, −7.2 to −1.0); P, NR

Abbreviations. CFB: change from baseline; CI: confidence interval; LDL: low-density lipoprotein.

Table F5. Change in HbA1c: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference
			Type	n	Mean CFB, % (95% CI)	Dose	n	Mean CFB, % (95% CI)	
SURMOUNT−1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	−0.07 (95% CI, −0.09 to −0.05)	15 mg/week	630	−0.51 (95% CI, −0.53, −0.49)	NR
						10 mg/week	636	−0.49 (95% CI, −0.51, −0.47)	
						5 mg/week	630	−0.40 (95% CI, −0.42 to −0.38)	

Abbreviations. HbA1c: hemoglobin A1c; NR: not reported.

Table F6. Quality of Life: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference, Points (95% CI)
			Type	n	Mean CFB, points (95% CI)	Dose	n	Mean CFB, points (95% CI)	
SF-36: physical function score									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	+1.7 (95% CI, 0.8 to 2.6)	10 or 15 mg/week	1,266	+3.6 (95% CI, 3.2 to 4.0)	+1.9 (95% CI, 1.0 to 2.9); P, NR

Note. An increase in score indicates that the participant perceived an improvement in their physical function.[81]

Abbreviations. CFB: change from baseline; CI: confidence interval; NR: not reported; SF-36: Short-Form Health Survey, 36 questions.

Table F7. Withdrawals Due to AEs, Any AEs, and AEs occurring in ≥ 10%: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Withdrawals due to AEs									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	17 (2.6)	15 mg/week	630	39 (6.2)	NR
						10 mg/week	636	45 (7.1)	
						5 mg/week	630	27 (4.3)	
Any AE									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	463 (72.0)	15 mg/week	630	497 (78.9)	NR
						10 mg/week	636	520 (81.8)	
						5 mg/week	630	510 (81.0)	
AEs occurring in ≥ 10%									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	None	15 mg/week	630	• Nausea: 195 (31.0) • Constipation: 74 (11.7) • Diarrhea: 145 (23.0) • Vomiting: 77 (12.2) • Dyspepsia: 71 (11.3)	NR
						10 mg/week	636	• Nausea: 212 (33.3) • Constipation: 109 (17.1) • Diarrhea: 135 (21.2) • Vomiting: 68 (10.7)	NR
						5 mg/week	630	• Nausea: 155 (24.6) • Constipation: 106 (16.8) • Diarrhea: 118 (18.7)	NR

Abbreviations. AE: adverse event; NR: not reported.

Table F8. Serious Adverse Events and Deaths: Tirzepatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Tirzepatide			Tirzepatide vs. Comparator, Between-Group Difference
			Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Any SAE									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	44 (6.8)	15 mg/week	630	32 (5.1)	NR
						10 mg/week	636	44 (6.9)	
						5 mg/week	630	40 (6.3)	
Deaths									
SURMOUNT-1 Jastreboff, 2022[81]	No diabetes	72	Placebo	643	4 (0.6)	15 mg/week	630	1 (0.2)	NR
						10 mg/week	636	2 (0.3)	
						5 mg/week	630	4 (0.6)	

Abbreviations. NR: not reported; SAE: serious adverse event.

Appendix G. Exenatide: Full Evidence Tables

Table G1. Weight Change, kg: Exenatide

Study Name Author, Year	Time Point, Weeks	Comparator			Exenatide			Exenatide vs. Comparator, Between-Group Difference, kg (95% CI)
		Type	n	Mean CFB, kg (SD)	Dose	n	Mean CFB, kg (SD)	
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	• Baseline: 102.5 (24.5) • Post-treatment: 105.0 (24.0)	2 mg/week	22	• Baseline: 106.2 (19.7) • Post-treatment: 105.7 (21.7)	−3.0 (95% CI, −5.8, −0.1); *P* < .05
Derosa, 2010[84]	52	Glibenclamide, 5 mg three times/d	57	Post-treatment: 86.7 (11.2)	10 μg twice/d	59	Post-treatment: 74.0 (4.1)	Center calculated: −12.7 (95% CI, −15.78 to −9.62); *P* < .001
Fox, 2022[82]	52	Placebo	33	12.4 (10)	2 mg/week	33	6.1 (11.4)	−4.4 (95% CI, −9.5 to 0.6); *P* = .09

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; NR: not reported; μg twice/d: micrograms twice per day.

Table G2. Change in Body Mass Index: Exenatide

Study Name Author, Year	Time Point, Weeks	Comparator			Exenatide			Exenatide vs. Comparator, Between-Group Difference
		Type	n	Mean CFB (SD)	Dose	n	Mean CFB (SD)	
BMI, kg/m^2 change (SE)								
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	• Baseline: 36.2 (5.0) • Post-treatment: (36.7)	2 mg/week	22	• Baseline: 36 (4.8) • Post-treatment: 35.7 (5.7)	-0.83 (95% CI, -1.68 to 0.01); $P < .05$
Derosa, 2010[84]	52	Glibenclamide, 5 mg three times/d	57	30.0 (1.9)	10 µg twice/d	59	25.9 (0.7)	Center calculated: −4.1 kg/m^2 (95% CI, −4.62 to −3.58); $P < .001$
Fox, 2022[82]	52	Placebo	33	9.6 (11.5)	2 mg/week	33	2.7 (13.2)	−4.8 kg/m^2 (95% CI, −10.6 to 0.9); $P = .098$
BMI, % change (SE)								
Fox, 2022[82]	52	Placebo	33	10.1 (9.0)	2 mg/week	33	4.6 (10.5)	−4.1% (95% CI, −8.6 to 0.5); $P = .08$
Change in percent of 95th BMI percentile								
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	• Baseline: 131.8 (SD, 17.9) • Post-treatment: 128.9 (SD, 20.8)	2 mg/week	22	• Baseline: 136.6 (SD, 15.8) • Post-treatment: 136.6 (SD, 15.9)	−2.9% (95% CI, -5.4 to −0.3); $P < .05$
Fox, 2022[82]	52	Placebo	33	3.7 (3.2)	2 mg/week	33	1.8 (SE, 3.9)	-1.4% (95% CI, -3.0 to 0.2); $P = .096$
BMI z/SD score								
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	• Baseline: 3.3 (0.4) • Post-treatment: 3.3 (0.4) • Center calculated: 0 (0.148)	2 mg/week	22	• Baseline: 3.1 (0.5) • Post-treatment: 3.0 (0.6) • Center calculated: −0.1 (0.148)	BMI z: −0.09 (95% CI, −0.18 to −0.00); $P < .05$

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. BMI: body mass index; Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; SD: standard deviation; SE: standard error; µg twice/d: micrograms twice per day.

Table G3. Change in Systolic Blood Pressure: Exenatide

Study Name Author, Year	Time Point, Weeks	Comparator			Exenatide			Exenatide vs. Comparator, Between-Group Difference, mmHg (95% CI)
		Type	n	Mean CFB, mmHg (SD)	Dose	n	Mean CFB, mmHg (SD)	
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	• Baseline: 122 (13) • At 24 weeks: 119 (15)	2 mg/week	22	• Baseline: 126 (11) • At 24 weeks: 121 (12)	−0.2 (95% CI, −6.5 to 6.1); P > .05 (not significant)
Fox, 2022[82]	52	Placebo	33	7 (10)	2 mg/week	33	4 (10)	−3 (95% CI, −7 to 1); P = .11

Note. Shaded rows indicate studies with pediatric populations.
Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; mmHg: millimeters per mercury; SD: standard deviation.

Table G4. Change in LDL Cholesterol: Exenatide

Study Name Author, Year	Time Point, Weeks	Comparator			Exenatide			Exenatide vs. Comparator, Between-Group Difference, mg/dL (95% CI)
		Type	n	Mean CFB, mg/dL (SD)	Dose	n	Mean CFB, mg/dL (SD)	
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	• Baseline: 95.2 (37.4) • After 24 weeks: 92.1 (25.1) • Center calculated: −3.1	2 mg/week	22	• Baseline: 93.3 (23.2) • After 24 weeks: 85.0 (17.6) • Center calculated: −8.5	−7.3 (95% CI, −14.2 to −0.4); P < .05
Fox, 2022[82]	52	Placebo	33	6.9 (18.4)	2 mg/week	33	14.2 (21.3)	5.8 (95% CI, −2.2 to 13.9); P = .16 (LDL increased with exenatide)

Note. Shaded rows indicate studies with pediatric populations.
Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; LDL: low-density lipoprotein; mg/dL: milligrams per deciliter; SD: standard deviation.

Table G5. Change in HbA1c: Exenatide

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Exenatide			Exenatide vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB: % (SD)	Dose	n	Mean CFB: % (SD)	
Derosa, 2010[84] N/A	T2DM	52	Glibenclamide 5 mg three times/d	57	• Baseline: 8.8 (0.8) • 12 months: 7.1 (0.2) • Center calculated: −1.7	10 µg twice/d	59	• Baseline: 8.7 (0.7) • 12 months: 7.3 (0.3) • Center calculated: −1.4	Center calculated: 0.2 (95% CI, 0.11 to 0.29); P > .05
Fox, 2022[82] N/A	No Diabetes	52	Placebo	33	0.1 (0.2)	2 mg/week	33	0.2 (0.3)	0 (95% CI, −0.1 to 0.1); P = .88

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. Center: Center for Evidence-based Policy; CFB: change from baseline; CI: confidence interval; HbA1c: hemoglobin A1c; SD: standard deviation; µg twice/d: micrograms twice per day.

Table G6. Quality of Life: Exenatide

| Author, Year | Time Point, Weeks | Comparator | | | Exenatide | | | Exenatide vs. Comparator, Between-Group Difference, Total Score (95% CI) |
		Type	n	IWQoL-Kids Total Score, Mean CFB (SD)	Dose	n	IWQoL-Kids Total Score, Mean CFB (SD)	
Fox, 2022[82] N/A	52	Placebo	33	4 (8.8)	2 mg/week	33	−1.7 (19.4)	−4.2 (95% CI, −10.7 to 2.4); *P* = .21

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. CFB: change from baseline; CI: confidence interval; SD: standard deviation.

Table G7. Withdrawals Due to AEs, Any AEs, and AEs Occurring in ≥ 10%: Exenatide

| Author, Year Study Name | Time Point, Weeks | Comparator | | | Exenatide | | | Exenatide vs. Comparator, Between-Group Difference |
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Withdrawals due to AEs								
Derosa, 2010[84] N/A	52	Glibenclamide 5 mg three times/d	65	8 (12.3)	10 μg twice/d	63	4 (6.4)	NR
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	0 (0.0)	2 mg/week	22	1 (4.5)	NR
Any AEs								
Fox, 2022[82] N/A	52	Placebo	33	30 (90.9)	2 mg/week	33	32 (97.0)	NR
Combat-JUDO Weghuber, 2020[83]	24	Placebo	22	83 (total number of AEs)	2 mg/week	22	108 (total number of AEs)	NR
AEs in ≥ 10%								
Fox, 2022[82]	52	Placebo	33	• Nausea: 7 (21.2) • Diarrhea: 6 (18.2) • Constipation: 6 (18.2) • Dyspepsia: 4 (12.1) • Flu-like symptoms: 4 (12.1) • Headache: 14 (42.4) • Injection site reaction: 24 (72.7) • Upper RTI: 13 (39.4)	2 mg/week	33	• Nausea: 13 (39.4) • Vomiting: 8 (24.2) • Diarrhea: 11 (33.3) • Constipation: 6 (18.2) • Dyspepsia: 5 (15.2) • Dizziness: 4 (12.1) • Headache: 19 (57.6) • Injection site reaction: 26 (78.8) • Upper RTI: 7 (21.2)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Exenatide			Exenatide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Combat-JUDO Weghuber, 2020[83]	26	Placebo	22	• Gastrointestinal disorders: 10 (45.5) • General disorders and administration site conditions: 9 (40.9) • Infections and infestations: 20 (90.9) • Injury, poisoning, and procedural complications: 3 (13.6) • Investigations: 5 (22.7) • Musculoskeletal and connective tissue disorders: 6 (27.3) • Nervous system disorders: 13 (59.1) • Respiratory, thoracic, and mediastinal disorders: 8 (36.4)	2 mg/week	22	• Gastrointestinal disorders: 18 (81.8) • General disorders and administration site conditions: 11 (50.0) • Infections and infestations: 18 (81.8) • Injury, poisoning, and procedural complications: 5 (22.7) • Investigations: 5 (22.7) • Musculoskeletal and connective tissue disorders: 5 (22.7) • Nervous system disorders: 16 (72.7) • Reproductive system and breast disorders: 5 (22.7) • Respiratory, thoracic, and mediastinal disorders: 8 (36.4) • Skin and subcutaneous tissue disorders: 5 (22.7)	N/A

Note. Shaded rows indicate studies with pediatric populations.

Abbreviations. NR: not reported; RTI: respiratory tract infection; μg twice/d: micrograms twice per day.

Table G8. Serious Adverse Events: Exenatide

Author, Year Study Name	Time Point, Weeks	Comparator			Exenatide			Exenatide vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Any SAEs								
Fox, 2022[82]	52	Placebo	33	0 (0.0)	2 mg/week	33	1 (3.03)	NR

Note. Shaded rows indicate studies with pediatric populations.

Abbreviation. NR: not reported.

Appendix H. Naltrexone-Bupropion: Full Evidence Tables

Table H1. Weight Change, %: Naltrexone-Bupropion

Author, Year Study Name	Diabetes Status	Time Point, Weeks	Comparator			Naltrexone-bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
COR-I Greenway, 2010[85]	No diabetes	56	Placebo	511	−1.3 (0.3)	16/360 mg/d	471	−5.0 (0.3)	NR; $P < .001$
						32/360 mg/d	471	−6.1 (0.3)	NR; $P < .001$
COR-II Apovian, 2013[86]	No diabetes	56	Placebo	456	−1.2 (0.3)	32/360 mg/d	702	−6.4 (0.3)	NR; $P < .001$
COR-BMOD Wadden, 2011[89]	No diabetes	56	Placebo	193	−5.1 (0.6)	32/360 mg/d	482	−9.3 (0.4)	NR; $P < .001$
COR-Diabetes Hollander, 2013[88]	T2DM	56	Placebo	159	−1.8 (0.4)	32/360 mg/d	265	−5.0 (0.3)	NR; $P < .001$
Halseth, 2017[90]	No diabetes	26	Usual care[a]	82	−0.94 (SD, 12.28)[b]	32/360 mg/d + CLI	71	−9.46 (SD, 12.28)[b]	−8.52 (95% CI, NR); $P < .001$

Notes. [a] Usual care consisted of on-site advice similar to what a patient would receive in a primary care encounter. [b] SD calculated by Center staff.
Abbreviations. CFB: change from baseline; CI: confidence interval; CLI: comprehensive lifestyle intervention; NR: not reported; SD: standard deviation; SE: standard error; T2DM: type 2 diabetes.

Table H2. Weight Change, kg: Naltrexone-Bupropion

Author, Year Study Name	Diabetes Status	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference, kg (95% CI)
			Type	n	Mean CFB, kg (SE)	Dose	n	Mean CFB, kg (SE)	
COR-I Greenway, 2010[85]	No diabetes	56	Placebo	511	−1.4 (0.3)	32/360 mg/d	471	−6.1 (0.3)	NR; *P* < .001
						16/360 mg/d	471	−4.9 (0.3)	NR; *P* < .001
COR-II Apovian, 2013[86]	No diabetes	56	Placebo	456	−1.3 (0.3)	32/360 mg/d	702	−6.2 (0.2)	NR; *P* < .001

Abbreviations. CFB: change from baseline; CI: confidence interval; NR: not reported; SD: standard deviation; SE: standard error.

Table H3. Weight Change ≥ 5% or ≥ 10%: Naltrexone-Bupropion

| Author, Year Study Name | Diabetes Status | Time Point, Weeks | Comparator | | | Naltrexone-Bupropion | | | Naltrexone-Bupropion vs. Comparator, Between-Group Difference, OR (95% CI) |
			Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
≥ 5% weight loss									
COR-I Greenway, 2010[85]	No diabetes	56	Placebo	511	84 (16)	32/360 mg/d	471	226 (48)	NR; *P* < .001
						16/360 mg/d	471	186 (39)	NR; *P* < .001
COR-II Apovian, 2013[86]	No diabetes	56	Placebo	456	78 (17.1)	32/360 mg/d	702	355 (50.5)	NR; *P* < .001
COR-BMOD Wadden, 2011[89]	No diabetes	56	Placebo	193	82 (42.5)	32/360 mg/d	482	320 (66.4)	NR; *P* < .001
COR-Diabetes Hollander, 2013[88]	T2DM	56	Placebo	159	30 (18.9)	32/360 mg/d	265	118 (44.5)	NR; *P* < .001
Halseth, 2017[90]	No diabetes	26	Usual care[a]	82	10 (12.2)	32/360 mg/d + CLI	71	60 (84.5)	44.0 (95% CI, 16.6 to 116.3); *P* < .001
≥ 10% weight loss									
COR-I Greenway, 2010[85]	No diabetes	56	Placebo	511	38 (7)	32/360 mg/d	471	116 (25)	NR; *P* < .001
						16/360 mg/d	471	95 (20)	NR; *P* < .001
COR-II Apovian, 2013[86]	No diabetes	56	Placebo	456	26 (5.7)	32/360 mg/d	702	199 (28.3)	NR; *P* < .001
COR-BMOD Wadden, 2011[89]	No diabetes	56	Placebo	193	39 (20.2)	32/360 mg/d	482	200 (41.5)	NR; *P* < .001
COR-Diabetes Hollander, 2013[88]	T2DM	56	Placebo	159	9 (5.7)	32/360 mg/d	265	49 (18.5)	NR; *P* < .001
Halseth, 2017[90]	No diabetes	26	Usual care[a]	82	3 (3.7)	32/360 mg/d + CLI	71	30 (42.3)	21.4 (95% CI, 6.0 to 76.7); *P* < .001

Note. [a] Usual care consisted of on-site advice similar to what a patient would receive in a primary care encounter.

Abbreviations. CI: confidence interval; CLI: comprehensive lifestyle intervention; NR: not reported; OR: odds ratio; T2DM: type 2 diabetes.

Table H4. Systolic Blood Pressure: Naltrexone-Bupropion

Author, Year Study Name	Diabetes Status	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference
			Type	n	Mean CFB, mmHg (SE)	Dose	n	Mean CFB, mmHg (SE)	
COR-I Greenway, 2010[85]	No diabetes	56	Placebo	511	−1.9 (95% CI, −2.7 to−1.2)	32/360 mg/d	471	−0.1 (95% CI, −0.9 to 0.7)	NR; $P < .001$
						16/360 mg/d	471	0.3 (95% CI, −0.5 to 1.1)	NR; $P < .001$
COR-II Apovian, 2013[86]	No diabetes	56	Placebo	456	−0.5 (0.4)	32/360 mg/d	702	0.6 (0.3)	NR; $P = .04$
COR-Diabetes Hollander, 2013[88]	T2DM	56	Placebo	159	−1.1 (0.9)	32/360 mg/d	265	0.0 (0.7)	NR; $P = .3$
Halseth, 2017[90]	No diabetes	78	NB + CLI at 26 weeks after usual care[a]	28	−2.2 (2.0)	32/360 mg/d + CLI	55	−2.7 (1.4)	NR; P, NR

Note. [a] *Usual care consisted of on-site advice similar to what a patient would receive in a primary care encounter.*

Abbreviations. CFB: change from baseline; CI: confidence interval; CLI: comprehensive lifestyle intervention; mmHg: millimeters of mercury; NB: naltrexone-bupropion; NR: not reported; SE: standard error; T2DM: type 2 diabetes.

Table H5. Change in LDL Cholesterol: Naltrexone-Bupropion

Author, Year Study Name	Diabetes Status	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference
			Type	n	Mean CFB	Dose	n	Mean CFB	
COR-I Greenway, 2010[85]	No diabetes	56	Placebo	511	−0.08 mmol/L (95% CI, −0.15 to−0.02)	32/360 mg/d	471	−0.11 mmol/L (95% CI, −0.17 to−0.05)	NR; P = .48
						16/360 mg/d	471	−0.10 mmol/L (95% CI, −0.16 to−0.03)	NR; P = .81
COR-II Apovian, 2013[86]	No diabetes	56	Placebo	456	−2.1 mg/dL (SE, 1.3)	32/360 mg/d	702	−6.2 mg/dL (SE, 0.9)	NR; P = .008
COR-BMOD Wadden, 2011[89]	No diabetes	56	Placebo	193	10.0% (95% CI, 5.7 to 14.3)	32/360 mg/d	482	7.1% (95% CI, 4.3 to 9.8)	NR; P = .22
COR-Diabetes Hollander, 2013[88]	T2DM	56	Placebo	159	0.0 (SE, 2.4)	32/360 mg/d	265	−1.4 mg/dL (SE, 1.9)	NR; P = .6
Halseth, 2017[90]	No diabetes	26	Usual care[a]	82	−1.9 mg/dl (SE, 2.11)	32/360 mg/d + CLI	71	−2.0 mg/dl (SE, 2.20)	NR; P = .97
						32/360 mg/d	83	0.3 mmol/L (SE, 2.32)	NR

Note. [a] Usual care consisted of on-site advice similar to what a patient would receive in a primary care encounter.
Abbreviations. CFB: change from baseline; CI: confidence interval; CLI: comprehensive lifestyle intervention; mg/dL: milligram per deciliter; mmol/L: millimole per liter; NR: not reported; SE: standard error; T2DM: type 2 diabetes.

Table H6. Change in HbA1c: Naltrexone-Bupropion

Author, Year Study Name	Diabetes Status	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference
			Type	n	Mean CFB, % (SE)	Dose	n	Mean CFB, % (SE)	
COR-Diabetes Hollander, 2013[88]	T2DM	56	Placebo	159	−0.1 (0.1)	32/360 mg/d	265	−0.6 (0.1)	NR; $P < .001$

Abbreviations. CFB: change from baseline; HbA1c: hemoglobin A1c; NR: not reported; SE: standard error; T2DM: type 2 diabetes.

Table H7. Quality of Life: Naltrexone-Bupropion

Author, Year Study Name	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference, OR (95% CI)
		Type	n	Mean CFB IWQoL-Lite-CT total score, points	Dose	n	Mean CFB IWQoL-Lite-CT total score	
IWQoL-Lite								
COR-I Greenway, 2010[85]	56	Placebo	511	8.6 (95% CI, −7.5 to 9.6)	32/360 mg/d	471	12.7 (95% CI,11.6 to 13.8)	NR; *P* < .001
					16/360 mg/d	471	11.7 (95% CI, 10.6 to 12.7)	NR; *P* < .001
COR-II Apovian, 2013[86]	56	Placebo	456	6.4 (SE, 0.6) Physical function, 8.2 (SE, 0.8)	32/360 mg/d	702	10.9 (SE, 0.5) Physical function, 14.1 (SE, 0.6)	NR; *P* < .001
COR-BMOD Wadden, 2011[89]	56	Placebo	193	10.3 (95% CI, 8.6, to 12.0)	32/360 mg/d	482	13.4 (95% CI, 12.3 to 14.5)	NR; *P* < .001
Halseth, 2017[90]	26	Usual care[a]	82	−1.0 points (SD, reported in figure only)	32/360 mg/d + CLI	71	+16.4 points (SD, reported in figure only)	17.4 (95% CI, NR); *P* < .001
				MCID, n (%): 16 (20.0)			MCID, n (%): 48 (67.0)	8.17 (95% CI, NR); *P* < .001

Notes. [a] Usual care consisted of on-site advice similar to what a patient would receive in a primary care encounter. [b] SD calculated by Center staff. Abbreviations. CFB: change from baseline; CI: confidence interval; CLI: comprehensive lifestyle intervention; IWQoL-Lite-CT: impact of weight on quality of life-lite for clinical trials version; MCID: minimal clinically important difference; NR: not reported; SD: standard deviation; SE: standard error; T2DM: type 2 diabetes.

Table H8. Withdrawals Due to AEs, Any AEs, AEs Occurring in ≥ 10%: Naltrexone-Bupropion

Author, Year Study Name	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Withdrawals due to AEs								
COR-I Greenway, 2010[85]	56	Placebo	569	56 (9.8)	32/360 mg/d	573	112 (19.5)	*P* < .05
					16/360 mg/d	569	122 (21.4)	*P* < .05
COR-II Apovian, 2013[86]	56	Placebo	492	68 (13.8)	32/360 mg/d	992	241 (24.3)	*P* < .05
COR-BMOD Wadden, 2011[89]	56	Placebo	200	25 (12.4)	32/360 mg/d	584	150 (25.4)	NR
COR-Diabetes Hollander, 2013[88]	56	Placebo	169	26 (15.3)	32/360 mg/d	333	98 (29.3)	NR
Halseth, 2017[90]	26	Usual care[a]	86	1 (11)	32/360 mg/d + CLI	153	35 (22.9)	NR
	26 to 52			12 (13.5)			0 (0)	
	78			14 (15.7)			37 (24.2)	
Any AE								
COR-I Greenway, 2010[85]	56	Placebo	569	390 (68.5)	32/360 mg/d	573	476 (83.1)	*P* < .05
					16/360 mg/d	569	455 (80.0)	*P* < .05
COR-II Apovian, 2013[86]	56	Placebo	492	370 (75.2)	32/360 mg/d	992	845 (85.2)	NR
COR-Diabetes Hollander, 2013[88]	56	Placebo	169	144 (85.2)	32/360 mg/d	333	301 (90.4)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
AEs occurring in ≥ 10% of participants								
COR-I Greenway, 2010[85]	56	Placebo	569	• UTI: 64 (11.2)	32/360 mg/d	573	• Constipation: 90 (15.7) • Headache: 79 (13.8) • Nausea: 171 (29.8)	*P* < .05 for: • Constipation • Headache • Nausea
					16/360 mg/d	569	• Constipation: 90 (15.8) • Headache: 91 (16.0) • Nausea: 155 (27.2)	
COR-II Apovian, 2013[86]	56	Placebo	492	• UTI: 55 (11.2)	32/360 mg/d	992	• Nausea: 290 (29.2) • Constipation: 189 (19.1) • Headache: 174 (17.5)	*P* < .05 for: • Constipation • Headache • Nausea
COR-BMOD Wadden, 2011[89]	56	Placebo	200	• Nausea: 21 (10.5) • Headache: 35 (17.5) • Constipation: 28 (14.0)	32/360 mg/d	584	• Nausea: 199 (34.1) • Headache: 139 (23.8) • Constipation: 141 (24.1) • Dizziness: 85 (14.6) • Vomiting: 64 (11.0)	*P* < .05 for: • Constipation • Dizziness • Nausea
COR-Diabetes Hollander, 2013[88]	56	Placebo	169	• Congestion: 23 (13.6)	32/360 mg/d	333	• Nausea: 141 (42.3) • Constipation: 59 (17.7) • Diarrhea: 52 (15.6) • Vomiting: 61 (18.3) • Headache: 46 (13.8) • Dizziness: 39 (11.7) • Insomnia: 37 (11.1)	NR

Note. ᵃ Usual care consisted of on-site advice similar to what a patient would receive in a primary care encounter.
Abbreviations. AE: adverse event; CLI: comprehensive lifestyle intervention; NR: not reported; T2DM: type 2 diabetes; UTI: urinary tract infection.

Table H9. Serious Adverse Events: Naltrexone-Bupropion

Author, Year Study Name	Time Point, Weeks	Comparator			Naltrexone-Bupropion			Naltrexone-Bupropion vs. Comparator, Between-Group Difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Any SAE								
COR-II Apovian, 2013[86] COR-II	56	Placebo	492	7 (1.4)	32/360 mg/d	992	21 (2.1)	P > .05
COR-I Greenway, 2010[85]	56	Placebo	569	8 (1.4)	32/360 mg/d	573	9 (1.6)	P > .05
					16/360 mg/d	569		
Halseth, 2017[90]	26	Usual care[a]	89	0 (0)	32/360 mg/d + CLI	153	1 (0.7)	NR
Hollander, 2013[88] COR-Diabetes	56	Placebo	169	8 (4.7)	32/360 mg/d	333	13 (3.9)	NR

Note. [a] Usual care consisted of on-site advice similar to what a patient would receive in a primary care encounter.

Abbreviations. CLI: comprehensive lifestyle intervention; NR: not reported; SAE: serious adverse event; T2DM: type 2 diabetes.

Appendix I. Phentermine-Topiramate: Full Evidence Tables

Table I1. Weight Change, %: Phentermine-Topiramate

Author, Year Study Name	Subgroup Analyses	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	% Mean CFB (95% CI)	Dose	n	% Mean CFB (95% CI)	
CONQUER/ SEQUEL Gadde, 2011[93]	N/A	56	Placebo	994	−1.2 (95% CI, −1.8 to −0.7)	15/92 mg/d	995	−9.8 (95% CI, −10.4 to−9.3)	−8.6 (−9.3 to −8.0); P < .001
						7.5/46 mg/d	498	−7.8 (95% CI, −8.5 to −7.1)	−6.6 (−7.4 to −5.8); P < .001
		108	Placebo	227	−1.8 (NR)	15/92 mg/d	295	−10.5 (NR)	NR; P < .001
						7.5/46 mg/d	153	−9.3 (NR)	
CONQUER/ SEQUEL Gadde, 2011[93]	No prediabetes or metabolic syndrome at baseline (n=813)	56	Placebo	NR	−0.9 (95% CI, −0.1 to −1.7)	15/92 mg/d	NR	−10.2 (95% CI, −9.4 to −11.0)	NR; P < .001
						7.5/46 mg/d		−8.5 (95% CI, −7.4 to −9.7)	
	Prediabetes at baseline (n=1,635)	56	Placebo	NR	−2.3 (95% CI, −1.7 to −2.8)	15/92 mg/d	NR	−10.5 (95% CI, −10.0 to −11.1)	
						7.5/46 mg/d		−8.3 (95% CI, −7.6 to −9.1)	
	Prediabetes or metabolic syndrome at baseline (n = 451)	108	Placebo	159	−2.5 (NR)	15/92 mg/d	201	−12.1 (NR)	
						7.5/46 mg/d	115	−10.9 (NR)	
CONQUER/ SEQUEL Gadde, 2011[93]	T2DM at baseline (n=388)	56	Placebo	NR	−1.9 (95% CI, −0.8 to −3.1)	7.5/46 mg/d	NR	−6.8 (95% CI, −5.1 to −8.6)	NR; P < .001
						15/92 mg/d		−8.8 (95% CI, −7.7 to −9.9)	
		56	Placebo	NR	−1.8 (95% CI, −1.3 to −2.3)	7.5/46 mg/d	NR	−8.7 (95% CI, −8.0 to −9.4)	

Author, Year Study Name	Subgroup Analyses	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	% Mean CFB (95% CI)	Dose	n	% Mean CFB (95% CI)	
	No T2DM at baseline (n=2,060)					15/92 mg/d		−10.7 (95% CI, −10.2 to −11.2)	
CONQUER/ SEQUEL Gadde, 2011[93]	Patients< 65 years (n=2,229)	56	Placebo	NR	−1.7 (95% CI, −1.2 to −2.2)	7.5/46 mg/d	NR	−8.5 (95% CI, −7.8 to −9.2)	NR; *P* < .001
						15/92 mg/d		−10.5 (95% CI, −10. to −11.0)	
	Patients≥ 65 years (n=219)	56	Placebo	NR	−3.2 (95% CI, −1.6 to −4.7)	7.5/46 mg/d	NR	−7.8 (95% CI, −5.7 to −9.9)	
						15/92 mg/d		−9.4 (95% CI, −8.0 to −10.9)	
CONQUER/ SEQUEL Gadde, 2011[93]	Women (n=1,712)	56	Placebo	NR	−1.6 (95% CI, −1.1 to −2.2)	7.5/46 mg/d	NR	−8.8 (95% CI, −8.0 to −9.6)	NR; *P* < .001
						15/92 mg/d		−11.0 (95% CI, −10.4 to −11.6)	
	Men (n=736)	56	Placebo	NR	−2.2 (95% CI, −1.5 to −3.0)	7.5/46 mg/d	NR	−7.5 (95% CI, −6.4 to −8.6)	
						15/92 mg/d		−9.1 (95% CI, −8.4 to −9.9)	
CONQUER/ SEQUEL Gadde, 2011[93]	Black (n=282)	56	Placebo	NR	−0.5 (95% CI, −0.7 to 1.8)	7.5/46 mg/d	NR	−7.3 (95% CI, −5.4 to −9.1)	NR; *P* < .001
						15/92 mg/d		−9.7 (95% CI, −8.5 to −10.9)	
	Non-Black (n=2,166)	56	Placebo	NR	−2.0 (95% CI, −1.5 to 2.5)	7.5/46 mg/d	NR	−8.5 (95% CI, −7.8 to −9.2)	
						15/92 mg/d		−10.5 (95% CI, −10.0 to −11.0)	

Author, Year Study Name	Subgroup Analyses	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	% Mean CFB (95% CI)	Dose	n	% Mean CFB (95% CI)	
EQUIP Allison, 2011[91]	N/A	56	PhenTop, 3.75/23 mg/d	234	−5.10 (95% CI, −4.0 to −6.2)	15/92 mg/d	498	−10.92 (95% CI, −10.2 to −11.7)	NR; $P < .001$
			Placebo	514	−1.55 (95% CI, −0.8 to −2.3)	15/92 mg/d	512	−10.92 (95% CI, −10.2 to −11.7)	
						3.75/23 mg/d	234	−5.10 (95% CI, −4.0 to −6.2)	

Abbreviations. CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; N/A: not applicable; NR: not reported; PhenTop: phentermine-topiramate; T2DM: type 2 diabetes.

Table I2. Weight Change, kg: Phentermine-Topiramate

Author, Year Study Name	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, kg (95% CI)
		Type	n	Mean CFB, kg (95% CI)	Dose	n	Mean CFB, kg (95% CI)	
CONQUER/ SEQUEL Gadde, 2011[93]	56	Placebo	994	−1.4 (95% CI, −2.0 to −0.8)	7.5/46 mg/d	498	−8.1 (95% CI, −8.9, −7.4)	NR; $P < .001$
					15/92 mg/d	995	−10.2 (95% CI, −10.8 to −9.7)	
	108	Placebo	227	−2.1 (NR)	15/92 mg/d	295	−10.9 (NR)	
					7.5/46 mg/d	153	−9.6 (NR)	
OB−403 Kelly, 2022[96]	56	Placebo	56	6.57 (SE, 1.28)	15/92 mg/d	113	−9.23 (SE, 0.86)	−15.80 (95% CI, −18.82 to −12.77)
					7.5/46 mg/d	54	−5.49 (SE, 1.23)	−12.06 (95% CI, −15.55 to −8.58)

Note. Shaded rows indicate studies with a pediatric population.

Abbreviations. CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; NR: not reported: SE: standard error.

Table I3. Change in Body Mass Index: Phentermine-Topiramate

Author, Year Study Name	Timepoint, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, (95% CI)
		Type	n	Mean CFB	Dose	n	Mean CFB	
Change in BMI, kg/m^2 (SE)								
OB−403 Kelly, 2022[96]	56	Placebo	56	1.20 (0.46)	15/92 mg/d	113	−4.15 (0.31)	−5.35 kg/m^2 (95% CI, −6.44 to −4.27)
					7.5/46 mg/d	54	−2.53 (0.44)	−3.73 kg/m^2 (95% CI, −4.97 to −2.50)
Change in BMI, % (SE)								
OB−403 Kelly, 2022[96]	56	Placebo	56	3.34(1.44)	15/92 mg/d	113	−7.11 (1.0)	−10.44% (95% CI, −13.89 to −6.99); *P* < .001
					7.5/46 mg/d	54	−4.78 (1.30)	−8.11% (95% CI, −11.92 to −4.31); *P* < .001
		PhenTop, 7.5/46 mg/d	54	−4.78 (1.30)	15/92 mg/d	113	−7.11 (1.01)	−2.33% (95% CI, −5.27 to 0.62); *P* = .12
Change in BMI ≥ 5%, n of n (%)								
OB−403 Kelly, 2022[96]	56	Placebo	56	3 of 56 (5.4%)	15/92 mg/d	113	53 of 113 (46.9%)	NR
					7.5/46 mg/d	54	21 of 54 (38.9%)	
Change in BMI ≥ 10%, n of n (%)								
OB−403 Kelly, 2022[96]	56	Placebo	56	0 (0%)	15/92 mg/d	113	32 of 113 (28.3%)	NR
					7.5/46 mg/d	54	7 of 54 (13.0%)	

Note. Shaded rows indicate studies with a pediatric population.

Abbreviations. BMI: body mass index; CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; NR: not reported: SE: standard error

Table I4. Weight Change ≥ 5% or ≥ 10%: Phentermine-Topiramate

Author, Year Study Name	Subgroup Analyses	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, OR (95% CI)
			Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Weight change ≥ 5%									
CONQUER/ SEQUEL Gadde, 2011[93]	N/A	56	Placebo	994	204 (20.8)	15/92 mg/d	995	687 (70)	6.3 (95% CI, 4.9 to 8.0); *P* < .001
						7.5/46 mg/d	498	303 (62.1)	9.0 (95% CI, 7.3 to 11.1); *P* < .001
		108	Placebo	227	68 (30.0)	15/92 mg/d	295	234 (79.3)	NR; *P* < .001
						7.5/46 mg/d	153	115 (75.2)	
CONQUER/ SEQUEL Gadde, 2011[93]	With dyslipidemia at baseline (n=1,341)	56	Placebo	526	121 (23.0)	15/92 mg/d	526	372 (70.7)	NR; *P* < .001
						7.5/46 mg/d	271	171 (63.1)	
	With hypertension at baseline (n = 1305	56	Placebo	516	112 (21.7)	15/92 mg/d	514	360 (70.0)	
						7.5/46 mg/d	256	159 (62.1)	
EQUIP Allison, 2011[91]	N/A	56	PhenTop, 3.75/23 mg/d	234	105 (44.9)	15/92 mg/d	498	332 (66.7)	NR; *P* < .001
			Placebo	498	86 (17.3)	15/92 mg/d	498	332 (66.7)	NR; *P* < .001
						3.75/23 mg/d	234	105 (44.9)	NR; *P* < .001
Weight change ≥ 10%									
CONQUER/ SEQUEL Gadde, 2011[93]	N/A	56	Placebo	979	72 (7.4)	15/92 mg/d	981	467 (47.6)	11.7 (95% CI, 8.9 to 15.4); *P* < .001
						7.5/46 mg/d	488	182 (37.3)	7.6 (95% CI, 5.6 to 10.2); *P* < .001
		108	Placebo	227	26 (11.5)	15/92 mg/d	295	159 (53.9)	NR; *P* < .001
						7.5/46 mg/d	153	77 (50.3)	

Author, Year Study Name	Subgroup Analyses	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, OR (95% CI)
			Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
EQUIP Allison, 2011[91]	N/A	56	PhenTop, 3.75/23 mg/d	234	44 (18.8)	15/92 mg/d	498	235 (47.2)	NR; *P* < .001
			Placebo	498	37 (7.4)	15/92 mg/d	498	235 (47.2)	NR; *P* < .001
						3.75/23 mg/d	234	44 (18.8)	NR; *P* < .001
Patients with dyslipidemia at baseline									
CONQUER/ SEQUEL Gadde, 2011[93]	With dyslipidemia at baseline (n=1,341)	56	Placebo	526	45 (8.6)	15/92 mg/d	526	252 (47.9)	NR; *P* < .001
						7.5/46 mg/d	271	99 (36.5)	
	With hypertension at baseline (n = 1,305)	56	Placebo	516	43 (8.3)	15/92 mg/d	514	236 (45.9)	
						7.5/46 mg/d	256	97 (37.9)	

Abbreviations. CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; N/A: not applicable; NR: not reported; OR: odds ratio; PhenTop: phentermine-topiramate.

Table I5. Change in Systolic Blood Pressure: Phentermine-Topiramate

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, mmHg (95% CI)
			Type	n	Mean CFB, mmHg (95% CI)	Dose	n	Mean CFB, mmHg (95% CI)	
CONQUER/ SEQUEL Gadde, 2011[93]	~15.5% with T2DM	56	Placebo	994	−2.4 (95% CI, −3.3 to −1.5)	7.5/46 mg/d	498	−4.7 (95% CI, −5.9 to −3.5)	NR; $P < .001$
						15/92 mg/d	995	−5.6 (95% CI, −6.5 to −4.6)	
CONQUER/ SEQUEL Gadde, 2011[93]	~21.5% with T2DM	108	Placebo	227	−3.2 (95% CI, reported in chart only)	15/92 mg/d	295	−4.3 (95% CI, reported in chart only)	NR; $P > .05$
						7.5/46 mg/d	154	−4.7 (95% CI, reported in chart only)	
CONQUER/ SEQUEL Gadde, 2011[93]	Prediabetes or metabolic syndrome at baseline	108	Placebo	159	−3.9 (SE, 0.98)	15/92 mg/d	201	−5.1 (SE, 0.91)	NR; $P > .05$
						7.5/46 mg/d	115	−5.0 (SE, 1.14)	NR; $P > .05$
EQUIP Allison, 2011[91]	No diabetes	56	PhenTop, 3.75/23 mg/d	234	−1.8 (95% CI, −3.4 to −0.3)	15/92 mg/d	512	−2.9 (95% CI, −4.0 to −1.8)	NR; $P = .22$
			Placebo	514	0.9 (95% CI, −0.2 to 2.1)	15/92 mg/d	512	−2.9 (95% CI, −4.0 to −1.8)	NR; $P < .001$
						3.75/23 mg/d	234	−1.8 (95% CI, −3.4 to −0.3)	NR; $P = .002$
OB−403 Kelly, 2022[96]	No diabetes	56	Placebo	56	2.80 (SE, 1.62)	15/92 mg/d	113	1.0 (SE, 1.04)	−1.80 (95% CI, −5.58 to 1.97)
						7.5/46 mg/d	54	−0.97 (SE, 1.50)	−3.76 (95% CI, −8.09 to 0.56)

Note. Shaded rows indicate studies with a pediatric population.

Abbreviations. CFB: change from baseline; CI: confidence interval; mg/d: milligrams per day; mmHg: millimeters of mercury; NR: not reported: SE: standard error; T2DM: type 2 diabetes.

Table I6. Change in LDL Cholesterol: Phentermine-Topiramate

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group Difference, % (95% CI)
			Type	n	Mean CFB, % (95% CI)	Dose	n	Mean CFB, % (95% CI)	
CONQUER/ SEQUEL Gadde, 2011[93]	~15.5% with T2DM	56	Placebo	994	−4.1 (95% CI, −5.8 to −2.4)	7.5/46 mg/d	498	−3.7 (95% CI, −6.0 to −1.5)	NR; *P* = .74
						15/92 mg/d	995	−6.9 (95% CI, −8.6 to −5.2)	NR; *P* = .007
	~21.5% with T2DM	108	Placebo	227	−10.8 (95% CI, −13.7 to −7.9)	15/92 mg/d	295	−5.8 (95% CI, −8.4 to −3.2)	NR; *P* = .01 (in favor of PBO; more individuals who received intervention had a decrease in lipid-lowering medications than did those who received placebo)
						7.5/46 mg/d	153	−4.6 (95% CI, −8.2 to −1.1)	
EQUIP Allison, 2011[91]	No Diabetes	56	PhenTop, 3.75/23 mg/d	230	−7.7 (95% CI, −10.3 to −5.2)	15/92 mg/d	512	−8.4 (95% CI, −10.2 to −6.5)	NR; *P* = .66
			Placebo	514	−5.5 (95% CI, −7.4 to −3.7)	15/92 mg/d	512	−8.4 (95% CI, −10.2 to −6.5)	NR; *P* = .02
						3.75/23 mg/d	230	−7.7 (95% CI, −10.3 to −5.2)	NR; *P* = .13

Abbreviations. CFB: change from baseline; CI: confidence interval; LDL: low-density lipoprotein; mg/d: milligrams per day; NR: not reported; PBO: placebo; PhenTop: phentermine-topiramate.

Table I7. Change in HbA1c: Phentermine-Topiramate

Author, Year Study Name	Baseline Diabetes Status	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group difference, % (95% CI)
			Type	n	Mean CFB, % (95% CI)	Dose	n	Mean CFB, % (95% CI)	
CONQUER/ SEQUEL Gadde, 2011[93]	~15.5% with T2DM	56	Placebo	994	0.1 (95% CI, 0 to 0.1)	15/92 mg/d	995	−0.1 (95% CI, −0.1 to 0)	NR; *P* < .001
						7.5/46 mg/d	498	0.0 (95% CI, −0.1 to 0)	
	~21.5% with T2DM	108	Placebo	227	0.2 (95% CI, 0.1 to 0.2)	15/92 mg/d	295	0.0 (95% CI, −0.07 to 0.07)	NR; *P* = .003
						7.5/46 mg/d	153	0.01 (95% CI, −0.08 to 0.1)	NR; *P* = .004
	Prediabetes or metabolic syndrome at baseline	108	Placebo	159	0.07 (SE, 0.02)	15/92 mg/d	201	−0.09 (SE, 0.02)	NR; *P* < .001
						7.5/46 mg/d	115	−0.03 (SE, 0.03)	NR; *P* = .004

Abbreviations. CFB: change from baseline; CI: confidence interval; HbA1c: hemoglobin A1c; mg/d: milligrams per day; NR: not reported; SE: standard error.

Table I8. Withdrawals Due to AEs, Any AEs, and AEs Occurring in ≥ 10%: Phentermine-Topiramate

Author, Year Study Name	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Withdrawals due to AEs								
CONQUER/ SEQUEL Gadde, 2011[93]	56	Placebo	994	89 (9.0)	15/92 mg/d	995	192 (19.0)	NR
					7.5/46 mg/d	498	58 (12.0)	
	56 to 108	Placebo	227	7 (3.1)	15/92 mg/d	295	13 (4.4)	
					7.5/46 mg/d	153	7 (4.5)	
EQUIP Allison, 2011[91]	56	Placebo	514	43 (8.4)	15/92 mg/d	512	82 (16.0)	NR
					3.75/23 mg/d	240	27 (11.3)	
OB–403 Kelly, 2022[96]	56	Placebo	56	3 (5.4)	15/92 mg/d	113	3 (2.7)	NR
					7.5/46 mg/d	54	1 (1.9)	
Any AE								
EQUIP Allison, 2011[91]	56	Placebo	513	374 (72.9)	15/92 mg/d	511	432 (84.5)	NR
					3.75/23 mg/d	240	192 (80.0)	
OB–403 Kelly, 2022[96]	56	Placebo	56	29 (51.8)	15/92 mg/d	113	59 (52.2)	NR
					7.5/46 mg/d	54	20 (37.0)	
AEs occurring in ≥ 10%								
CONQUER/ SEQUEL Gadde, 2011[93]	56	Placebo	993	• Upper RTI: 128 (13)	15/92 mg/d	994	• Dry mouth: 207 (21) • Paresthesia: 204 (21) • Constipation: 173 (17) • Upper RTI: 133 (13) • Nasopharyngitis (cold-like symptoms): 98 (10) • Dysgeusia (altered taste): 103 (10) • Insomnia: 102 (10)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
							• Headache: 101 (10) • Dizziness: 99 (10)	
					7.5/46 mg/d	498	• Dry mouth: 67 (13) • Paresthesia: 68 (14) • Constipation: 75 (15) • Upper RTI: 61 (12) • Nasopharyngitis (cold-like symptoms): 53 (11)	
	56 to 108	Placebo	227	• Upper RTI: 42 (18.5) • Congestion: 26 (11.5)	15/92 mg/d	295	• Upper RTI: 45 (15.3)	
					7.5/46 mg/d	153	• Upper RTI: 26 (17.0)	
EQUIP Allison, 2011[91]	56	Placebo	513	• Paresthesia: 10 (1.9) • Dry mouth: 19 (3.7) • Constipation: 35 (6.8) • Upper RTI: 56 (10.9) • Headache: 52 (10.1) • Nasopharyngitis: 37 (7.2)	15/92 mg/d	511	• Paresthesia: 96 (18.8) • Dry mouth: 87 (17.0) • Constipation: 72 (14.1) • Upper RTI • 63 (12.3) • Headache: 61 (11.9)	• Paresthesia: $P < .001$ • Dry mouth: $P < .001$ • Constipation: $P < .001$ • Upper RTI: $P = .46$ • Headache: $P = .37$
					3.75/23 mg/d	240	• Upper RTI: 38 (15.8) • Headache: 25 (10.4) • Nasopharyngitis: 30 (12.5)	• Upper RTI: $P = .059$ • Headache: $P = .89$ • Nasopharyngitis: $P = .02$
OB−403 Kelly, 2022[96]	56	Placebo	56	• Broad categories • Infections and infestations (e.g., Covid−19,	15/92 mg/d	113	• Broad categories • Infections and infestations (e.g., Covid−19, influenza): 25 (22.1)	NR

Author, Year Study Name	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
				influenza): 15 (26.8) • Nervous system disorders (e.g., headaches): 7 (12.5) • Gastrointestinal disorders: 8 (14.3) • Respiratory, thoracic and mediastinal disorders (e.g., nasal congestion): 7 (12.5) • General disorders and administration site conditions: 13 (11.5)			• Nervous system disorders (e.g., headaches): 16 (14.2) • Gastrointestinal disorders: 12 (10.6) • Respiratory, thoracic and mediastinal disorders (e.g., nasal congestion): 13 (11.5) • General disorders and administration site conditions: 13 (11.5)	
					7.5/46 mg/d	54	• Broad categories • Infections and infestations (e.g., Covid−19, influenza): 9 (16.7) • Gastrointestinal disorders: (13.0)	

Note. Shaded rows indicate studies with a pediatric population.

Abbreviations. AE: adverse event; mg/d: milligrams per day; NR: not reported; RTI: respiratory tract infection.

Table I9. Serious Adverse Events and Deaths: Phentermine-Topiramate

Author, Year Study Name	Time Point, Weeks	Comparator			Phentermine-Topiramate			Phentermine-Topiramate vs. Comparator, Between-Group difference
		Type	n	Proportion, n (%)	Dose	n	Proportion, n (%)	
Any SAE								
CONQUER/ SEQUEL Gadde, 2011[93]	56	Placebo	993	40 (4.0)	15/92 mg/d	994	50 (5.0)	NR ("rates were similar")
					7.5/46 mg/d	498	15 (3.0)	
	56 to 108	Placebo	227	9 (4.0)	15/92 mg/d	295	12 (4.1)	NR
					7.5/46 mg/d	153	4 (2.6)	
EQUIP Allison, 2011[91]	56	Placebo	513	13 (2.5)	15/92 mg/d	511	13 (2.5)	NR
					3.75/23 mg/d	240	6 (2.5)	
OB−403 Kelly, 2022[96]	56	Placebo	56	0 (0)	15/92 mg/d	113	2 (1.8)	NR
					7.5/46 mg/d	54	0 (0)	
Deaths								
CONQUER/ SEQUEL Gadde, 2011[93]	56	Placebo	993	1 (< 1.0)	15/92 mg/d	994	0 (0)	NR
					7.5/46 mg/d	498	0 (0)	

Note. Shaded rows indicate studies with a pediatric population.

Abbreviations. mg/d: milligrams per day; NR: not reported; SAE: serious adverse event.

Appendix J. Setmelanotide: Full Evidence Tables

Table J1. Weight Change, %: Setmelanotide

Author, Year	Population	Time Point, Weeks	Setmelanotide, 3 mg/day		Comparator			Between-group Difference, % (95% CI)
			n	Mean CFB, % (SD)	Type	n	Mean CFB, % (SD)	
Clement, 2020[100] Single-arm	POMC variant, successful with weight loss at 12 weeks	52	9	−25.6% (9.9; 90% CI, −28.8 to −22.0); *P* < .001	N/A			N/A
	LEPR variant, successful with weight loss at 12 weeks	52	7	−12.5% (8.9; 90% CI, −16.1 to −8.8); *P* < .001	N/A			N/A
Haqq, 2022[97] RCT	BBS or AS	14	16	−2.4 (4.8)	Placebo, ≥ 12 years	17	−0.3 (2.3)	−2.1 (−4.6 to 0.4); *P* = .05
	BBS only, ≥ 12 years	14	18	−3.7 (4.2)	Placebo	18	−0.2 (2.1)	−3.4 (−5.7 to −1.2); *P* = .002
Haqq, 2022[97] Single-arm extension	BBS only, ≥ 12 years	52	28	−6.5 (7.0); *P* < .001	N/A			N/A
	BBS or AS, ≥ 12 years	52	31	−5.2 (7.9); *P* < .001	N/A			N/A
	BBS only ≥ 18 years	52	15	−7.6 (−7.1); *P* < .001	N/A			N/A
Haws, 2020[101] Single-arm	BBS	12	8	−5.5 (90% CI, −9.3 to −1.6); *P* = .02	N/A			N/A
		24	8	−11.3 (90% CI, −15.5 to −7.0); *P* < .001	N/A			N/A
		52	7	−16.3 (90% CI, −19.9 to −12.8); *P* < .001	N/A			N/A

Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; CFB: change from baseline; CI: confidence interval; N/A: not applicable; LEPR: leptin receptor; POMC: proopiomelanocortin; SD: standard deviation.

Table J2. Weight Change, kg: Setmelanotide

Author, Year	Population	Time Point, Weeks	n	Mean CFB, kg (SD)
Haqq, 2022[97] Single-arm extension	≥ 12 years	52	31	−5.9 (9.3); *P* < .001
	BBS only, ≥ 12 years	52	28	−7.4 (8.2); *P* < .001
	BBS only ≥ 18 years	52	15	−9.4 (9.4); *P* < .001

Abbreviations. BBS: Bardet-Biedl syndrome; CFB: change from baseline; SD: standard deviation.

Table J3. Weight Loss ≥ 10%: Setmelanotide

Author, Year	Population	Time Point, Weeks	n	Proportion, n (%)
Clement, 2020[100] Single-arm	POMC variant	52	10	8 (80)
	LEPR variant	52	9	4 (45)
Haqq, 2022[97] Single-arm extension	BBS or AS, ≥ 12 years	52	31	10 (32.3; 95% CI, 16.7 to 51.4); *P* < .001

Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; CFB: change from baseline; CI: confidence interval; LEPR: leptin receptor; POMC: proopiomelanocortin.

Table J4. Change in Body Mass Index: Setmelanotide

Author, Year	Population	Time Point, Weeks	n	Mean CFB
BMI, kg/m^2				
Clement, 2020[100] Single-arm	POMC variant, ≥ 18 years	52	4	−9.3 kg/m^2 (SD, 6.9; 90% CI −17.4 to −1.2); *P* = .07
	LEPR variant, ≥ 18 years	52	7	−5.2 kg/m^2 (3.9; 90% CI −8.1 to −2.3); *P* = .013
Haqq, 2022[97] Single-arm extension	BBS only < 18 years	52	16	−3.4 kg/m^2 (SD, 2.1); *P*, NR
BMI, %				
Clement, 2020[100] Single-arm	POMC variant, successful with weight loss at 12 weeks	52	9	−27.8% (SD, 9.9; 90% CI −31.7 to −23.7); *P* < .001;
	LEPR variant, successful with weight loss at 12 weeks	52	6	−13.1% (SD, 9.4; 90% CI −16.9 to −9.6); *P* < .001
Haws, 2020[101] Single-arm	BBS	12	8	−5.5% (SD, 5.6); *P* = .01
		24	8	−11.1% (SD, 6.3); *P* < .001
		52	7	−16.2% (SD, 5.3); *P* < .001
BMI z score				
Haqq, 2022[97] Single-arm extension	BBS only, < 18 years	52	16	-0.8 SDs, (SD, 0.5); *P* < .05

Abbreviations. BBS: Bardet-Biedl syndrome; BMI: body mass index; CFB: change from baseline; CI: confidence interval; LEPR: leptin receptor; N/A: not applicable; POMC: proopiomelanocortin; SD: standard deviation.

Table J5. Change in Systolic Blood Pressure: Setmelanotide

Author, Year	Baseline Diabetes Status	Population	Time Point, Weeks	n	Mean CFB, % mmHg
Clement, 2020[100] Single-arm	No diabetes	POMC variant	52	10	−1.4% (SD, 5.1; 90% CI, −4.3 to 1.6); *P* = .42
		LEPR variant	52	9	−3.8% (SD, 9.9; 90% CI, −9.9 to 2.4); *P* = .29
Haws, 2020[101] Single-arm	NR	BBS	12	8	8.9% (90% CI, −0.2 to 17.9); *P* > .05
			52	7	8.9% (90% CI, −1.0 to 18.8); *P* > .05

Abbreviations. BBS: Bardet-Biedl syndrome; CFB: change from baseline; CI: confidence interval; mmHg: millimeter of mercury; LEPR: leptin receptor; N/A: not applicable; POMC: proopiomelanocortin; SD: standard deviation.

Table J6. Change in LDL Cholesterol: Setmelanotide

Author, Year	Baseline Diabetes Status	Population	Time Point, Weeks	n	Mean CFB
Clement, 2020[100] Single-arm	No diabetes	POMC variant	52	10	−7.6% mg/dL (SD, 23.1; 90% CI, −21.1 to 5.8); *P* = .32
		LEPR variant	52	9	−10.0% mg/dL (SD, 12.1; 90% CI, −17.5 to −2.5); *P* = .04
Haqq, 2022[97] Single-arm extension	Diabetes not exclusion criteria; proportion NR	BBS or AS, all ages	52	38	−0.2 mmol/L (SD, 0.4); *P*, NR
		BBS only, all ages	52	31	−0.2 mmol/L (SD, 0.4); *P*, NR
Haws, 2020[101] Single-arm	NR	BBS	12	9	−10.1% (90% CI, −20.8 to 0.7); *P*, NR
			24	8	−9.0% (90% CI, −24.6 to 6.6); *P*, NR
			52	7	−1.9% (90% CI, −17.6 to 13.8); *P*, NR

Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; CFB: change from baseline; CI: confidence interval; LEPR: leptin receptor; LDL: low-density lipoprotein; mg/dL: milligrams per deciliter; mmol/L: millimole per liter; NR: not reported; POMC: proopiomelanocortin.

Table J7. Change in HbA1c: Setmelanotide

Author, Year	Baseline Diabetes Status	Population	Time Point, Weeks	n	Mean CFB, % (SD; 90% CI)
Clement, 2020[100]	No diabetes	POMC variant	52	10	−4.0 (10.5; 90% CI, −10.1 to 2.1); *P* = .26
		LEPR variant	52	9	−4.9% (7.8; 90% CI, −12.3 to 2.6); *P* = .24

Abbreviations. CFB: change from baseline; CI: confidence interval; HbA1c: hemoglobin A1c; LEPR: leptin receptor; POMC: proopiomelanocortin; SD: standard deviation.

Table J8. Quality of Life: Setmelanotide

Author, Year	Population	Time Point, Weeks	n	Mean CFB
IWQoL-Lite: total score [a]				
Clement, 2020[100] Single-arm	≥ 18 years with POMC or LEPR variant	52	7	Total score: 24.2 (SD, 12.1); *P*, NR
	≥ 18 years with POMC or LEPR variant	52	7	Physical function score: 18 (SD, 13.6); *P*, NR
Haqq, 2022[97] Single-arm extension	BBS only, ≥ 18 years	52	11	Total score: 12.0 (SD, 10.3); *P*, NR
	BBS only, ≥ 18 years	52	11	Physical function score: 15.3 (SD, 11.6); *P*, NR
PedsQL[a]				
Clement, 2020[100] Single-arm	POMC variant, age 8 to 12 years	52	2	Total score: 15.8 (SD, 17.7)
	POMC variant, age 13 to 17 years	52	4	Total score: 5.8 (SD, 18.3)
Haqq, 2022[97] Single-arm extension	BBS only, < 18 years	52	9	Total score: 11.2 (SD, 14.3); *P*, NR
	BBS only, < 18 years	52	9	Physical function score: 14.0 (SD, 27.7); *P*, NR

Note. [a] Larger values (higher scores) indicated higher levels of quality of life.

Abbreviations. BBS: Bardet-Biedl syndrome; CFB: change from baseline; IWQoL-Lite: impact of weight on quality of life; LEPR: leptin receptor; NR: not reported; PedsQL: pediatric quality of life inventory; POMC: proopiomelanocortin; RCT: randomized controlled trial.

Table J9. Withdrawals Due to AEs, Any AEs, and AEs Occurring in ≥ 10%: Setmelanotide

Author, Year	Population	Time Point, Weeks	Setmelanotide, 3 mg/day		Comparator		
			n	Proportion, n (%)	Type	n	Proportion, n (%)
Withdrawals due to AEs							
Clement, 2020[100] Single-arm	POMC variant	52	10	0 (0)	N/A		
	LEPR variant	52	11	1 (11.1)[a]	N/A		
Haqq, 2022[97] RCT	BBS or AS	14	19	1 (5.3)	Placebo	19	3 (15.8)
Haqq, 2022[97] Single-arm extension	BBS or AS	52	37	4 (11.8)	N/A		
Haws, 2020[101] Single-arm	BBS	52	10	0 (0)	N/A		
Any AE							
Clement, 2020[100] Single-arm	POMC variant	52	10	10 (100)	N/A		
	LEPR variant	52	11	11 (100)			
Haqq, 2022[97] RCT	BBS or AS	14	19	18 (94.7)	Placebo	19	18 (94.7)
Haqq, 2022[97] Single-arm extension	BBS or AS	52	38	38 (100)	N/A		
Haws, 2020[101] Single-arm	BBS	52	10	10 (100)[b]	N/A		
AEs occurring in ≥ 10							
Clement, 2020[100] Single-arm	POMC variant	52	10	• Injection site reaction: 10 (100) • Skin and subcutaneous disorders related to hyperpigmentation: 10 (100) • Skin hyperpigmentation: 10 (100) • Nausea: 5 (50) • Vomiting: 3 (30)	N/A		
	LEPR variant	52	11	• Injection site reaction: 11 (100)			

Author, Year	Population	Time Point, Weeks	Setmelanotide, 3 mg/day		Comparator		
			n	Proportion, n (%)	Type	n	Proportion, n (%)
				• Skin and subcutaneous disorders related to hyperpigmentation: 5 (45) • Skin hyperpigmentation: 4 (36) • Pigmentation disorder: 4 (36) • Skin discoloration: 2 (18) • Nausea: 4 (36)			
Haqq, 2022[97] RCT	BBS or AS	14	19	• Injection site erythema: 9 (47.4) • Injection site pruritus: 6 (31.6) • Injection site bruising: 3 (15.8) • Injection site pain: 3 (15.8) • Skin hyperpigmentation: 11 (57.9) • Nausea: 4 (21.1) • Injection site induration: 5 (26.3) • HDL decrease: 4 (21.1) • Vomiting: 4 (21.1)	Placebo	19	• Injection site erythema: 7 (36.8) • Injection site pruritus: 5 (26.3) • Injection site bruising: 6 (31.6) • Injection site pain: 6 (31.6) • Nausea: 5 (26.3) • Injection site induration: 2 (10.5) • Headache: 4 (21.1)
Haws, 2020[101] Single-arm	BBS	52	10	• Injection site reaction: 10 (100) • Hyperpigmentation: 8 (80) • Nausea: 3 (30) • Vomiting: 2 (20)	N/A		

Notes. [a] One participant discontinued the trial because of grade 1 hypereosinophilia, which was considered to be possibly related to setmelanotide treatment and resolved following discontinuation. [b] All considered drug related.

Abbreviations. AE: adverse event; AS: Alström syndrome; BBS: Bardet-Biedl syndrome; LEPR: leptin receptor; N/A: not applicable; NR: not reported; POMC: proopiomelanocortin; RCT: randomized controlled trial.

Table J10. Serious Adverse Events and Deaths: Setmelanotide

Author, Year	Population	Time Point, Weeks	Setmelanotide, 3 mg/day		Comparator			Between-group difference
			n	Proportion, n (%)	Type	n	Proportion, n (%)	
Any SAE								
Clement, 2020[100] Single-arm	POMC variant	52 weeks	10	4 (40)	N/A			N/A
	LEPR variant		11	3 (27)				
Haqq, 2022[97] RCT	BBS or AS	14	19	0 (0)	Placebo	19	2 (10.5)	NR
Haqq, 2022[97] Single-arm extension	BBS or AS	52	38	2 (5)	N/A			N/A
Haws, 2020[101] Single-arm	BBS	52	10	1 (10)	N/A			N/A
Deaths								
Haqq, 2022[97] RCT	BBS or AS	14	19	0 (0)	Placebo	19	0 (0)	NR
Haqq, 2022[97] Single-arm extension	BBS or AS	52	38	0 (0)	N/A			N/A

Abbreviations. AS: Alström syndrome; BBS: Bardet-Biedl syndrome; LEPR: leptin receptor; N/A: not applicable; NR: not reported; POMC: proopiomelanocortin; RCT: randomized controlled trial; SAE: serious adverse event.

Appendix K. Economic Studies

Table K1. Study Characteristics and Evidence Tables for Economic Studies

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings

Atlas et al., 2022[171]
 	
US
	Aim:
	Conduct cost-effectiveness analysis of four pharmaceutical interventions added to usual care compared to usual care alone, which included standard diet and activity and lifestyle recommendations.
	
	Design:
	Cost-effectiveness analysis using a Markov state transition model.
	
	Interventions compared:
	• Semaglutide (2.4 mg, weekly)
	• Liraglutide (3 mg, daily)
	• Phentermine-topiramate (7.5-15 mg/46-92 mg, daily)
	• Naltrexone-bupropion (32 mg/360 mg, daily)
		Population:
		Adults without pre-existing T2DM and either a BMI ≥ 30 or ≥ 27 with at least one weight-related comorbidity.
		
		Analytic assumptions:
		• US payer perspective
		• Lifetime time horizon
		• Costs in US dollars, reference year not specified
		• Discount rate of 3% per year
		• Patients are assumed to continue to receive the intervention throughout the model time horizon with discontinuation included in the first year of treatment
		• The interventions are assumed to be added to usual care, which included standard diet and activity and lifestyle recommendations
		• Treatment effectiveness estimates are from all clinical trials separately evaluating effectiveness of each intervention identified in a rigorous systematic review with clear inclusion and exclusion criteria
		• Harms and adverse events are included in the models
		• Health gains were derived from increased utility associated with enhanced daily functioning, decreased risk of developing diabetes or cardiovascular disease, and reduced complications and comorbidities
			Base-case results:
			• Total discounted lifetime costs (drug and non-drug) assuming lifetime treatment:
			    ○ Semaglutide: $392,100
			    ○ Liraglutide: $377,000
			    ○ Phentermine-topiramate: $182,600
			    ○ Naltrexone-bupropion: $207,300
			    ○ Lifestyle modification only: $179,200
			• QALYs:
			    ○ Semaglutide: 17.85
			    ○ Liraglutide: 17.36
			    ○ Phentermine-topiramate: 17.40
			    ○ Naltrexone-bupropion: 17.18
			    ○ Lifestyle modification only: 16.95
			• CERs (cost per QALY gained relative to usual care or lifestyle modification only):
			    ○ Semaglutide: $238,000
			    ○ Liraglutide: $485,000
			    ○ Phentermine-topiramate: $8,000
			    ○ Naltrexone-bupropion: $124,000
			
			Scenario analyses:
			• Conducting the analysis from a societal perspective reduced incremental CERs relative to usual care:
			    ○ Semaglutide: $216,600
			    ○ Liraglutide: $460,900
			    ○ Phentermine-topiramate: less costly, more effective
			    ○ Naltrexone-bupropion: $106,000

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings

		• Cost associated with comorbidities were included in the models
		• Cost of treatment included drug costs only. Annual costs (net of rebates and discounts):
		   ○ Semaglutide: $13,618
		   ○ Liraglutide: $11,760
		   ○ Phentermine-topiramate: $1,465
		   ○ Naltrexone-bupropion: $2,094
			• Annualized price ranges required to achieve $50,000 to $200,000 per QALY thresholds were:
			   ○ Semaglutide: $5,275 to $11,933
			   ○ Liraglutide: $2,714 to $5,830
			   ○ Phentermine-topiramate: $2,440 to $5,892
			   ○ Naltrexone-bupropion: $1,241 to $2,980
			
			Sensitivity analyses:
			• One-way sensitivity analyses evaluated sensitivity to disutility per BMI change, baseline HbA1c, cost of diabetes management, baseline BMI, weight-lowering effect of treatment and change in HbA1c with treatment. Semaglutide and liraglutide was most sensitive to disutility per BMI change, while, for phentermine-topiramate, the cost of diabetes was most impactful. Varying the effectiveness of each treatment and the baseline HbA1c had a considerable influence across all four treatment options
			• Probabilistic sensitivity analyses:
			   ○ Semaglutide was cost-effective 8.7% of the time at a WTP of $200,000 per QALY, and was never cost-effective at $50,000 or $100,000 per QALY thresholds
			   ○ Liraglutide was never cost-effective at any threshold level
			   ○ Phentermine-topiramate was cost-effective 94.9%, 92.5%, 87%, and 67.4% of the time at $200,000, $150,000, $100,000, and $50,000 per QALY WTP thresholds, respectively
			   ○ Naltrexone-bupropion was cost-effective 59%, 38.4%, 12.4%, and 1.1% of the time at $200,000, $150,000, $100,000, and $50,000 per QALY thresholds, respectively

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings
Azuri et al., 2023[172] US	Aim: Calculate cost needed to achieve 1% body weight loss using tirzepatide vs. semaglutide. Design: Simulated scenario analysis, specific model choice was not indicated. Interventions compared: • Tirzepatide (15 mg, weekly) • Semaglutide (2.4 mg, weekly)	Population: People with T2DM Analytic assumptions: • US payer perspective • Time horizon: 68 weeks for semaglutide, 72 weeks for tirzepatide, as well as 1 year for both • Costs in 2022 US dollars • Discount rate of 3% per year • Treatment effectiveness estimates are from 2 separate clinical trials (STEP-1 trial for semaglutide and SURMOUNT-1 trial for tirzepatide) • Linear decline in body weight during the treatment period • Discontinuation of treatment, harms and adverse events or the costs associated with comorbidities were not included in the models • Cost of treatment included drug costs only. Annual costs: ○ Semaglutide: $17,495 ○ Tirzepatide: $12,658	• Total cost needed to treat per 1% of body weight reduction with tirzepatide (in 72-week time horizon) was $955 compared with $1,845 with semaglutide (in 72-week time horizon) • Total cost needed to treat per 1% of body weight reduction over 52 weeks was $683 for tirzepatide and $1,351 for semaglutide
Finkelstein et al., 2019[173] US	Aim: Conduct incremental cost-effectiveness analysis of all commercially available, evidence-based non-surgical weight loss interventions for people with excess weight. Design: Cost-effectiveness analysis using a simulation-based	Population: Adults with BMI ≥ 30. Analytic assumptions: • US payer perspective • 4-year time horizon • Costs in US dollars, reference year not specified • Discount rate of 3.5% per year • Patients are assumed to continue to receive the intervention in the first 12	Base-case results: • Cost per kg lost at 12 months relative to no treatment: ○ Weight Watcher Meetings: $134 ○ Jenny Craig: $444 ○ Intragastric balloon system: $1,467 ○ Orlistat (180 mg): $251 ○ Orlistat (360 mg): $2,028 ○ Phentermine-topiramate: $327 ○ Naltrexone-bupropion: $541 ○ Liraglutide: $2,102

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings

	model. Specific model choice was not indicated.
	
	Interventions compared:
	• Weight Watchers Online
	• Weight Watchers Meetings
	• Jenny Craig
	• Intragastric balloon system (Orbera)
	• Orlistat (Alli, 180 mg, weekly)
	• Orlistat (Xenical, 360 mg, weekly)
	• Phentermine-topiramate (7.5 mg/46 mg, daily)
	• Naltrexone-bupropion (32 mg/360 mg, daily)
	• Liraglutide (3 mg, daily)
	• Lorcaserin (20 mg, daily)
		months. The weight loss benefits of intervention assumed to last 3 years post-intervention with QoL benefits at 12 months assumed to decay linearly to zero from the beginning of year 2 to the end of year 4
		• Attrition rates from the studies are included in the models at mid-year for each year
		• Treatment effectiveness estimates are from separate clinical trials for each intervention. Effectiveness estimates from a total of 21 studies identified in a rigorous systematic review with clear inclusion and exclusion criteria were combined
		• Harms and adverse events are not included in the models
		• QoL gains associated with weight loss were based on previously published estimates of the relationship between weight loss and QoL change that controls for gender, age, baseline BMI, and baseline QALY
		• Cost associated with comorbidities were not included in models
		• Cost of treatment included program fees and food costs for commercial programs, medication costs and physician costs for pharmaceutical products, and for intragastric balloon, the balloon costs as well as insertion and removal costs
		• Total costs (subscription or drug costs and other costs) for the first 12 months were:
		  o Weight Watcher Meetings: $424
		  o Jenny Craig: $3,301
			o Lorcaserin: $823
			• Cost per QALY gained at 4 years relative to no treatment:
			  o Weight Watcher Meetings: $30,071
			  o Jenny Craig: $102,516
			  o Intragastric balloon system: $333,333
			  o Orlistat (180 mg): $56,442
			  o Orlistat (360 mg): $476,593
			  o Phentermine-topiramate: $75,167
			  o Naltrexone-bupropion: $122,451
			  o Liraglutide: $479,177
			  o Lorcaserin: $185,874
			
			Scenario and sensitivity analyses:
			• Price reductions required to achieve $50,000 per QALY WTP thresholds varied between $60 (for Orlistat, 180 mg) and over $10,000 (for liraglutide)
			• When the duration of benefits changed from linear decay over 3 years to linear decay over 1 year all CERs nearly doubled with only Weight Watchers Meetings remaining close to the cost-effectiveness threshold
			• At lower WTP thresholds for cost-effectiveness (< $80,000), Weight Watchers Meetings was the most cost-effective option for more than 90% of the time. As WTP threshold increases, interventions with higher effectiveness were more likely to be cost-effective. At the $100,000 and $150,00 WTP thresholds, phentermine-topiramate was cost-effective for about 25% and 70% of the time, respectively, while the other pharmaceutical interventions were cost-effective less than 2% of the time.

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings
		o Intragastric balloon system: $6,500 o Orlistat (180 mg): $615 o Orlistat (360 mg): $6,164 o Phentermine-topiramate: $2,194 o Naltrexone-bupropion: $2,498 o Liraglutide: $11,644 o Lorcaserin: $2,658	
Hu et al., 2022[175] US	Aim: Assess cost-effectiveness of 4 GLP-1RAs for weight loss in adult patients with obesity. Design: Cost-effectiveness analysis using a decision tree model. Interventions compared: • Liraglutide (1.8 mg, daily) • Semaglutide (1.0 mg, weekly) • Dulaglutide (1.5 mg, weekly) • Exenatide (10 µg, twice daily)	Population: Adults with obesity. Analytic assumptions: • US payer perspective • 6-month time horizon • Costs in 2019 US dollars • Discount rate of 3% per year • Patients are assumed to continue to receive the intervention for the 6-month duration • Treatment effectiveness estimates are from 4 separate clinical trials, one for each treatment. No justification was offered for the choice of dose or trials • Discontinuation of treatment, harms and adverse events or the costs associated with comorbidities were not included in the models • Weight loss gains were converted into QALY gains based on QoL constants used in previous studies assuming a unit of BMI loss leads to a gain of 0.0056 QALYs • Cost of treatment included drug costs, cost of 2 doctor visits and cost of injection needles • Monthly drug costs: o Liraglutide (1.8 mg, daily): $922	• None of the interventions were cost-effective compared to no treatment. • Exenatide had the smallest CER at $982,032, which is above conventional WTP thresholds. • Relative to exenatide, the incremental CER was $135,467 for semaglutide (1.0 mg, weekly) and $733,243 for Dulaglutide (1.5 mg, weekly).

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings
		o Semaglutide (1.0 mg, weekly): $828 o Dulaglutide (1.5 mg, weekly): $814 o Exenatide (10 µg, twice daily): $730	
Kim et al., 2022[117] US	Aim: Assess cost-effectiveness of semaglutide 2.4 mg for weight management. Design: Cost-effectiveness analysis using a Markov state transition model Interventions compared: • Semaglutide (2.4 mg, weekly) • Diet and exercise • Liraglutide (3 mg, daily) • Phentermine-topiramate • Naltrexone-bupropion	Population: Adults with BMI ≥ 30, or BMI between 27 and 29.9 and at least 1 weight-related comorbidity Analytic assumptions: • US payer perspective • 30-year time horizon • Costs in 2021 US dollars • Discount rate of 3% per year • Patients are assumed to continue to receive the intervention for 2 years with discontinuation due to non-response within those 2 years included in the models • Patients are assumed to receive treatment in conjunction with diet and exercise, which continues the entire duration of the time horizon • Weight loss benefits are assumed to diminish at a higher rebound rate than natural weight gain until patients' BMI return to baseline levels • Treatment effectiveness estimates are from respective Phase 3 clinical trials for each treatment • Treatment-related adverse events are included in the model • Comorbidities and acute events considered in the models (both in terms of QoL gains and costs) include diabetes,	Base-case results: • Total discounted lifetime costs (drug and non-drug) assuming 2-year treatment: o Semaglutide: $130,040 o Liraglutide: $126,786 o Phentermine-topiramate: $109,078 o Naltrexone-bupropion: $109,977 o Diet and exercise only: $107,902 o No treatment: $104,954 • QALYs: o Semaglutide: 13.49 o Liraglutide: 13.35 o Phentermine-topiramate: 13.35 o Naltrexone-bupropion: 13.34 o Diet and exercise only: 13.31 o No treatment: 12.57 • Semaglutide was estimated to be cost-effective relative to diet and exercise only with an incremental CER (cost per QALY gained) of $122,549 • Semaglutide was also estimated to be cost-effective relative to no treatment and other pharmaceutical interventions with incremental CERs ranging from $27,113 (relative to no treatment) to $144,296 (relative to phentermine-topiramate) Scenario and sensitivity analyses: • Scenario analyses exploring alternative treatment discontinuation assumptions, maximum treatment durations, bariatric surgery

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings
		cardiovascular disease, sleep apnea, knee replacement, bariatric surgery and cancer • Obesity monitoring costs are considered for all drug treatments and for diet and exercise, but not for the no treatment scenario	consideration, time horizons, discount rates, treatment discontinuation rates, baseline utilities by BMI, and natural weight-gain rates resulted in incremental CERs for semaglutide ranging from $30,540 to $253,206 compared to diet and exercise only. • The model was most sensitive to maximum treatment duration and time horizon, followed by regimen after treatment discontinuation, weight-rebound rate, and drug efficacy on BMI. • Subgroup analysis by patient obesity class revealed that semaglutide was particularly cost-effective compared with diet and exercise only, no treatment and other drugs in patients with obesity class III (incremental CERs ranging from $8,094 for liraglutide 3 mg to $85,024 for phentermine-topiramate). • Incremental CERs for semaglutide was higher in the subgroup of patients with T2DM (ranging from $87,211 for liraglutide to $225,171 for phentermine-topiramate). • At a WTP threshold of $150,000 per QALY, semaglutide was cost-effective 82% of the time relative to diet and exercise, 98% of the time relative to liraglutide, 64% of the time relative to phentermine-topiramate, 74% of the time relative to naltrexone-bupropion, and 100% of the time relative to no treatment.
Lee et al., 2020[176] US	Aim: Compare cost-effectiveness of 6 pharmacotherapies and intensive lifestyle intervention in patients with mild obesity. Design:	Population: People with BMI 30-35. Analytic assumptions: • US payer perspective • 1-, 3-, and 5-year time horizon • Costs in 2019 US dollars	Base-case results: • In all time horizons, phentermine had the lowest CERs ($46,258, $20,157, and $17,880 in 1-, 3-, and 5-year horizons respectively) • While the weight loss in the first year was the greatest on phentermine, this weight loss was not sustained with patients returning to baseline

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings

	Cost-effectiveness analysis using a microsimulation model.
	
	Interventions compared:
	• Intensive lifestyle intervention
	• Phentermine/topiramate (7.5mg/46 mg, daily)
	• Liraglutide (3.0 mg, daily)
	• Semaglutide (0.4 mg, daily)
	• Orlistat (120 mg, three times daily)
	• Lorcaserin (10 mg, twice daily)
	• Phentermine (37.5 mg, daily)
		• Discount rate of 3% per year
		• Patients are assumed to continue to receive the intervention for the duration of the time horizon modeled with discontinuation included in the first year of treatment
		• Treatment effectiveness estimates are from separate clinical trials for each intervention. For intervention with more than one published clinical trial, the findings of the trial with the longest duration are used. All clinical trials for the pharmaceutical interventions also included lifestyle modification counseling
		• Harms and adverse events or the costs associated with comorbidities were not included in the models
		• Weight loss gains were converted into QALY gains based on QoL constants used in previous studies assuming a unit of BMI loss leads to a gain of 0.0056 QALYs
		• Cost of pharmaceutical interventions included drug costs and costs of 2 doctor visits
		• Total costs (drug and non-drug) in the first year are
		   o Intensive lifestyle intervention: $675
		   o Phentermine-topiramate (7.5mg/46 mg, daily): $1,424
		   o Liraglutide (3.0 mg, daily): $13,533
		   o Semaglutide (0.4 mg, daily): $6,972
		   o Orlistat (120 mg, three times daily): $1,108
		   o Lorcaserin (10 mg, twice daily): $2,065
			weight by year 5. Patients on semaglutide, on the other hand, maintained significant weight loss throughout the 5-year time horizon making semaglutide the most effective strategy in the longer term. However, semaglutide was not cost-effective with incremental CERs higher than $500,000 per QALY even in the longest time horizon
			• When phentermine was excluding from the analysis, intensive lifestyle intervention was the most cost-effective strategy with CERs of $82,733, $41,265, and $39,219 in 1-, 3-, and 5-year horizons respectively
			• Semaglutide remained cost-ineffective even with phentermine excluded from the analysis
			• When the quality of constant was increased to 0.017 QALYs gained per BMI unit lost, semaglutide approached cost-effectiveness in 3- and 5-year time horizons with an incremental CER of $127,062 and $106,873, respectively.

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings
		○ Phentermine (37.5 mg, daily): $636	
Gomez Lumbreras et al., 2023[174] US	Aim: Compare cost-effectiveness of 5 weight management drugs. Design: Cost-effectiveness analysis using a Markov state transition model. Interventions compared: • Tirzepatide • Semaglutide (2.4 mg, weekly) • Phentermine-topiramate • Naltrexone-bupropion • Liraglutide (3.0 mg, daily)	Population: Adults with obesity and no comorbidities. Analytic assumptions: • US payer perspective • 40-year time horizon • Costs in 2021 US dollars • Discount rate of 3% per year • Patients are assumed to continue to receive the intervention throughout the model time horizon with discontinuation included in the model in all years • Discontinuing patients are assumed to maintain their weight the first year followed by a yearly BMI increase • Treatment effectiveness estimates are from each drug's respective clinical trials with a duration of at least 20 weeks • Costs and utilities were adjusted for severe adverse events with an average side effect duration of 2 months • Health gains were derived from increased utility associated with decreased risk of developing diabetes and cardiovascular events • Cost associated with comorbidities were included in the model • Cost of treatment included drug costs only. WACs were discounted by 30% to account for manufacturer rebates and discounts	Base-case results: • Total discounted lifetime costs (drug and non-drug) assuming lifetime treatment: ○ Phentermine-topiramate: $118,900 ○ Naltrexone-bupropion: $126,957 ○ Tirzepatide: $234,084 ○ Liraglutide: $252,146 ○ Semaglutide: $308,767 • QALYs: ○ Phentermine-topiramate: 29.226 ○ Naltrexone-bupropion: 29.223 ○ Tirzepatide: 29.550 ○ Liraglutide: 29.229 ○ Semaglutide: 29.233 • The no-treatment QALYs were not reported and cost-effectiveness of the interventions relative to no treatment were not evaluated. Only the cost-effectiveness relative to the least costly intervention, phentermine-topiramate was evaluated • Compared to phentermine-topiramate, naltrexone-bupropion was dominated (less effective, costlier) and semaglutide and liraglutide were slightly more effective but came at a much higher cost Scenario and sensitivity analyses: • The results were most sensitive to the disutility of obesity followed by the drug prices and to a lesser extent cost of obesity and obesity-related complications • Phentermine-topiramate was the optimal choice across WTP threshold values up to $400,000

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings
Nuijten et al., 2018[177] US	**Aim:** Calculate cost savings associated with a medically supervised weight loss program, OPTIFAST, relative to no treatment, 2 weight management drugs and bariatric surgery, and evaluate cost-effectiveness of OPTIFAST relative to no treatment. **Design:** Cost-effectiveness analysis using a decision tree model. **Interventions compared:** • OPTIFAST • Liraglutide (3 mg, daily) • Naltrexone-bupropion • Bariatric surgery	**Population:** People with BMI ≥ 30, cost savings calculated separately for people with class I or II obesity, class III obesity, and class I or II obesity and T2DM **Analytic assumptions:** • US payer perspective • 3-year time horizon • Costs in 2016 US dollars • Discount rate of 5% per year • Patients in OPTIFAST arm are assumed to receive the complete program consisting of 12 weeks diet with total meal replacement at 5 servings a day followed by two subsequent phases of transition to a food-based diet for 12 weeks at 2-3 servings and 24 weeks at 1 serving a day • Patients receiving liraglutide or naltrexone-bupropion are assumed to continue the intervention for the duration of the time horizon with discontinuation due to non-response included in the models • Treatment effectiveness estimates are from each intervention's respective clinical trials • Costs associated with harms and adverse events are included in the model • Cost associated with a comprehensive list of obesity- and T2DM-related comorbidities were included in the model • Cost of pharmaceutical interventions included drug costs and costs of 2 doctor visits	**Base-case results:** • OPTIFAST reduces costs of obesity complications by $1,951 compared to no intervention, leading to $2,549 additional cost for the payer for people with class I or II obesity • The increase in quality of life associated with OPTIFAST relative to no treatment is estimated to be 0.394 QALYs resulting in an incremental CER of $6,475 per QALY gained • Total 3-year costs of interventions (drug and non-drug) for people with class I or II obesity: ○ No intervention: $9,382 ○ OPTIFAST: $11,931 ○ Naltrexone-bupropion: $12,589 ○ Liraglutide: $21,216 • Total 3-year costs of interventions (drug and non-drug) for people with class III obesity: ○ No intervention: $16,095 ○ OPTIFAST: $18,087 ○ Naltrexone-bupropion: $19,057 ○ Liraglutide: $27,643 ○ Bariatric Surgery: $40,738 • Total 3-year costs of interventions (drug and non-drug) for people with class I or II obesity and T2DM: ○ No intervention: $52,882 ○ OPTIFAST: $34,807 ○ Naltrexone-bupropion: $38,712 ○ Liraglutide: $47,370 ○ Bariatric Surgery: $55,600 Scenario analyses involving longer time horizons: • 5-year costs of interventions (drug and non-drug) for people with class I or II obesity:

Citation Country	Design Intervention Comparator(s)	Population Analytic Assumptions	Main Findings
		• Cost of bariatric surgery includes the surgery costs and physician visits following the surgery, 3 visits in the first year and 1 visit every year thereafter	- No intervention: $20,323 - OPTIFAST: $21,059 - Naltrexone-bupropion: $22,315 - Liraglutide: $31,016 • 10-year costs of interventions (drug and non-drug) for people with class I-II obesity: - No intervention: $62,227 - OPTIFAST: $58,247 - Naltrexone-bupropion: $58,812 - Liraglutide: $70,372

Abbreviations. BMI: body mass index; CER: cost-effectiveness ratio; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA1c: hemoglobin A1c; QALY: quality-adjusted life year; QoL: quality of life; T2DM: type 2 diabetes; WAC: weighted average coupon; WTP: willingness-to-pay.

Appendix L. Ongoing Studies

Table L1. Ongoing Studies

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
Head-to-head studies				
EMPOWER-T2D[137] NCT04531176 US	• N = 69 • BMI ≥ 30 + T2DM • ≥ 18 years	• 12 months + 12 months • Liraglutide, 3 mg/d • Naltrexone-bupropion (dose, NR) • Orlistat (dose, NR) • Phentermine-topiramate (dose, NR) • Weight management program • Usual care	• Blood pressure • Cost of care • HbA1c • LDL • QoL • Weight	August 2022
NCT05579249[130] US	• N = 500 • BMI ≥ 30 • ≥ 18 years	• 52 weeks • Liraglutide, 3 mg/d • Naltrexone/Bupropion (dose, NR) • Orlistat (dose, NR) • Phentermine/Topiramate (dose, NR) • Semaglutide, 2.4 mg/d	• QoL • Weight	November 2024
SURMOUNT-5[134] NCT05822830 US, Puerto Rico	• N = 700 • BMI ≥ 27 + ≥ 1 weight-related comorbidity, or ≥ 30 • ≥ 18 years	• 72 weeks • Semaglutide, 2.4 mg/d • Tirzepatide (dose, NR)	• BMI • Weight	December 2024
Dulaglutide				
No ongoing studies identified				
Exenatide				
No ongoing studies identified				
Liraglutide				
ACTRN12617001613392[138]	• N = 48	• 12 months	• AEs	February 2021

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
Australia	• BMI, NR • Post-bariatric surgery without sufficient weight loss • 20 to 65 years	• Liraglutide, 3 mg/d • Placebo	• HbA1c • LDL • Medication use • QoL • Weight	
NCT03048578[140] US Completed; results on CT.gov; no publications	• N = 132 • BMI ≥ 27 + ≥ 1 weight-related comorbidity, or ≥ 30 • Post-bariatric weight gain > 10% • ≥ 18 years	• 12 months • Liraglutide, 3 mg/d • Placebo	• Weight	March 2021
STRIVE[139,167] NCT03036800 Ireland, United Kingdom Published protocol 2020; cited	• N = 392 • BMI ≥ 35 • Prediabetes, T2DM, hypertension, or obstructive sleep apnea • ≥ 18 years	• 52 weeks + 52 weeks • Liraglutide, 3 mg/d • Usual care	• Adherence • AEs • Blood pressure • BMI • Cost-effectiveness • HbA1c • LDL • Medication use • QoL • Weight	June 2022
NCT05285397[142] Egypt	• N = 60 • BMI > 35 • Post-bariatric surgery or requiring secondary bariatric surgery due to weight regain • Any	• 6 months • Liraglutide, 3 mg/d • Usual care	• Blood pressure • BMI • Body weight • HbA1c • LDL • Resolution of T2DM • Weight	September 2022
NCT03115424[118] US	• N = 75 • Authorized for bariatric surgery • 20 to 65 years	• 33 months • Liraglutide, 3 mg/d • Placebo	• Blood pressure • LDL • Weight	July 2023

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
SCALE KIDS[141] NCT04775082 US, Belgium, Israel, Portugal, Russia, Switzerland	• N = 78 • BMI ≥ 95th percentile • 6 to 12 years	• 56 weeks + 26 weeks • Liraglutide, 3 mg/d • Placebo	• AEs • Blood pressure • BMI • HbA1c • Weight	July 2023
RESETTLE[120] EudraCT: 2019-002274-31 Denmark	• N = 150 • BMI > 30 • 18 to 25 years	• 52 weeks • Liraglutide, 3 mg/d • Placebo	• BMI • Weight	December 2025
Naltrexone-bupropion				
NCT03047005[152] US Completed; results on CT.gov; no publications.	• N = 68 • Obesity + binge-eating disorder • ≥ 18 years	• 4 months + 6 months • Naltrexone-bupropion, 32/360 mg/d • Placebo	• Binge-Eating Frequency • BMI	December 2021
NCT03063606[153] US	• N = 38 • Obesity + binge-eating disorder • ≥ 18 years	• 4 months + 6 months • Naltrexone-bupropion (dose, NR) • Cognitive-behavioral therapy	• Binge-Eating Frequency • BMI	December 2021
NCT03539900[154] US	• N = 200 • BMI ≥ 25 + binge-eating disorder • ≥ 18 years	• 3 months + 12 months • Naltrexone-bupropion, 32/360 mg/d • Placebo	• Binge-Eating Frequency • BMI	April 2022
COR-WM[157] NCT04589130 Canada	• N = 214 • BMI ≥ 27 + ≥ 1 weight-related comorbidity • ≥ 18 years	• 52 weeks • Naltrexone-bupropion, 32/360 mg/d • Placebo	• Adherence • AEs • HbA1c • LDL • Maintenance • QoL • SAEs • Weight	November 2022
COR-WR[156] NCT04587843 Canada	• N = 200	• 52 weeks • Naltrexone-bupropion, 32/360 mg/d	• Adherence • AEs • Blood pressure	May 2023

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
	• BMI ≥ 27 + ≥ 1 weight-related comorbidity, or ≥ 30 • Post-bariatric surgery • ≥ 18 years	• Placebo	• BMI • HbA1c • LDL • Medication use • QoL • SAEs • Weight	
NCT03946111[155] US	• N = 40 • BMI ≥ 27 + binge- eating disorder • 18 to 64 years	• 12 weeks + 12 months • Naltrexone-bupropion (dose, NR) • Placebo	• Binge-Eating Frequency • BMI • Depressive Symptoms	July 2024
NCT04902625[159] Netherlands	• N = 116 • BMI ≥ 35 prior to bariatric surgery + weight regain ≥ 5% • ≥ 18 years	• 22 weeks + 6 months • Naltrexone-bupropion, 32/360 mg/d • Lifestyle intervention	• AEs • Persistence • Weight	March 2025
NCT04605081[158] US	• N = 100 • BMI, NR • 10 months post- bariatric surgery • ≥ 18 years	• 12 weeks + 12 months • Naltrexone-bupropion (dose, NR) • Placebo	• BMI • Depressive Symptoms • Relapse	May 2026
NCT05157698[160] US	• N = 160 • BMI ≥ 27 + ≥ 1 weight-related comorbidity, or ≥ 30 and < 50 • Post-bariatric surgery • 18 to 64 years	• 6 months + 12 months • Naltrexone-bupropion (dose, NR) • Behavioral Weight Loss • Placebo	• BMI • LDL • HbA1c	January 2027
Phentermine-topiramate				
NCT04408586[161] US	• N = 80 • BMI ≥ 30 • ≥ 18 years	• 12 months • Phentermine-topiramate, 7.5/46 mg/d • Placebo	• QoL • Weight	June 2022

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
Completed; results submitted to CT.gov June 15, 2023; no publications		• Online support system		
NCT05378503[162] South Korea	• N = 301 • BMI ≥ 25 • 19 to 70 years	• 56 weeks • Phentermine-topiramate, 7.5/46 or 11.25/69 mg/d • Placebo	• Blood pressure • BMI • HbA1c • LDL • Weight	November 2023
Semaglutide				
STEP 10[126] NCT05040971 Canada, Denmark, Finland, Spain, United Kingdom	• N = 201 • BMI ≥ 30 • Prediabetes • ≥ 18 years	• 52 weeks • Semaglutide, 2.4 mg/d • Placebo	• Blood pressure • HbA1c • LDL • Weight	January 2023
OASIS 1[144] NCT05035095 US, Canada, Denmark, Finland, France, Germany, Japan, Poland, Russia Completed; no publications	• N = 667 • BMI ≥ 27 + ≥ 1 weight-related comorbidity, or ≥ 30 • ≥ 18 years	• 68 weeks • Semaglutide, 50 mg/d • Placebo	• AEs • Blood pressure • BMI • HbA1c • LDL • QoL • SAEs • Weight	March 2023
NCT05302596[131] US	• N = 16 • BMI ≥ 30 • ≥ 65 years	• 16 weeks • Semaglutide, 1 mg/week • Standard of care	• Weight	March 2023
STEP-HFpEF[143,168] NCT04788511 US, Argentina, Australia, Canada, Czechia, Denmark, Germany, Hungary, Israel, Netherlands, Poland, Spain, United Kingdom	• N = 516 • BMI ≥ 30 • HFpEF • ≥ 18 years	• 52 weeks + 5 weeks • Semaglutide, 2.4 mg/d • Placebo	• Blood pressure • CV events requiring hospitalization or urgent heart failure visit • Mortality • Weight	April 2023

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
Completed; no results publications; protocol and baseline characteristics published May 2023; cited				
SELECT[119,169 170] NCT03574597 US, Algeria, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Croatia, Denmark, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Portugal, Russian, Serbia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom Protocol published 2020; baseline characteristics published 2023; all cited	• N = 17,500 • BMI ≥ 27 • CV disease • ≥ 45 years	• Up to 59 months • Semaglutide, 2.4 mg/d • Placebo	• Blood pressure • CV events • HbA1c • LDL • Mortality • Weight	June 2023
NCT05064735[127] US, Canada, Colombia, Denmark, France, Norway, Russia, Saudi Arabia, South Africa, Spain, Sweden	• N = 407 • BMI ≥ 30 • Knee osteoarthritis • Any	• 68 weeks • Semaglutide, 2.4 mg/d • Placebo	• Knee pain • QoL • Weight	July 2023
OASIS 2[145] NCT05132088 Japan, South Korea	• N = 198 • BMI ≥ 27+ ≥ 2 weight-related comorbidity, or ≥ 30 + ≥ 1 weight-related comorbidity • ≥ 18 years	• 68 weeks • Semaglutide, 50 mg/d • Placebo	• AEs • Blood pressure • BMI • HbA1c • LDL • QoL • SAEs	July 2023

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
			• Weight	
NCT04998136[125] South Korea, Thailand	• N = 150 • BMI ≥ 25 • Both parents of Asian descent • Any	• 44 weeks • Semaglutide, 2.4 mg/d • Placebo	• Blood pressure • LDL • Weight	November 2023
SWEET[123] NCT04873050 US	• N = 102 • BMI ≥ 25 + history of gestational diabetes • 18 to 45 years	• 6 months • Semaglutide, 1 mg/week • Placebo	• HbA1c • Weight	February 2024
BARI-STEP[128] NCT05073835 United Kingdom	• N = 70 • Post-bariatric surgery with poor weight loss • 18 to 65 years	• 68 weeks • Semaglutide, 2.4 mg/d • Placebo	• Blood pressure • HbA1c • Medication use (e.g., antihypertensives) • QoL • Weight	March 2024
OASIS 4[146] NCT05564117 US, Canada, Germany, Poland	• N = 281 • BMI ≥ 27 + ≥ 1 weight-related comorbidity, or ≥ 30 • ≥ 18 years	• 64 weeks + 7 weeks • Semaglutide, 25 mg/d • Placebo	• AEs • Blood pressure • BMI • HbA1c • LDL • QoL • SAEs • Weight	March 2024
STEP UP[132] NCT05646706 US, Bulgaria, Canada, Czechia, Germany, Greece, Hungary, Norway, Poland, Portugal, Slovakia, South Africa	• N = 1,407 • BMI ≥ 30 • ≥ 18 years	• 72 weeks • Semaglutide, 7.2 mg/week • Placebo	• AEs • BMI • HbA1c • LDL • Medication use (e.g., antihypertensives) • SAEs • Weight	October 2024
NCT05649137[136]	• N = 513	• 72 weeks	• AEs	October 2024

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
US, Bulgaria, Canada, Hungary, Poland, Portugal, Slovakia, South Africa	• BMI ≥ 30 + T2DM • ≥ 18 years	• Semaglutide, 7.2 mg/week • Placebo	• BMI • HbA1c • LDL • SAEs • Weight	
[a]SEMASEARCH[149] NCT05897398 France	• N = 1,000 • BMI ≥ 40 + ≥ 1 weight-related comorbidity • ≥ 18 years	• 12 months • Semaglutide, 2.4 mg/d	• Weight	September 2025
STEP Young[147] NCT05726227 US, Austria, Belgium, Germany, Israel, Mexico, Portugal, Sweden, United Kingdom	• N = 210 • BMI ≥ 95th percentile or ≥ 85th percentile + weight-related comorbidity (e.g., T2DM) • 6 to 18 years	• Up to 2.5 years • Semaglutide, 2.4 mg/d • Placebo	• Blood pressure • BMI • HbA1c • LDL • Weight	November 2025
[a]SELECT-LIFE[124] NCT04972721 US, Algeria, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Croatia, Denmark, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Portugal, Russian, Serbia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom	• N = 12,450 • Participated in SELECT • ≥ 45 years	• Up to 10 years • Semaglutide	• CV events • Mortality • QoL • Weight	April 2032
[a]NCT05872022[148] NR	• N = 728 • Overweight or obese + ≥ 1 weight-	• Up to 12 months post-birth • Semaglutide, 2.4 mg/d	• Pregnancy-related outcomes (e.g.,	October 2032

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
	related comorbidity and exposed to 0 or ≥ 1 dose of semaglutide, during recent or current pregnancy • 15 to 45 years		malformations, preterm delivery)	
Setmelanotide				
[a]NCT04966741[163] US, Australia, Spain, United Kingdom	• N = 12 • BMI ≥ 97th percentile + Bardet-Biedl syndrome, *POMC*, *PCSK1*, or *LEPR* • 2 to 5 years	• 52 weeks • Setmelanotide, 10 mg/ml	• BMI • Weight	September 2023
[a]NCT03651765[164] US, Canada, France, Germany, Greece, Netherlands, Spain, United Kingdom	• N = 300 • Obesity Associated *LEPR* • ≥ 2 years	• Up to 5 years • Setmelanotide (dose, NR)	• AEs • Tolerability	December 2024
EMANATE[165,166] NCT05093634 US, Canada, France, Germany, Greece, Israel, Netherlands, Puerto Rico, Spain, United Kingdom Protocol published 2022; cited	• N = 400 • BMI ≥ 30 or 95th percentile + *POMC*, *PCSK1*, *NCOA1*, *SH2B1* • 6 to 65 years	• 52 weeks • Setmelanotide (dose, NR) • Placebo	• BMI • Weight	December 2024
Tirzepatide				
SURMOUNT-2[135,151] NCT04657003	• N = 938 • BMI ≥ 27 + T2DM • ≥ 18 years	• 72 weeks • Tirzepatide (dose, NR) • Placebo	• Blood pressure • BMI • HbA1c • LDL	March 2023

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
US, Argentina, Brazil, India, Japan, Puerto Rico, Russia, Taiwan Completed; no results posted or publications. Protocol paper for SURMOUNT 1-4 , including baseline chars, published December 2022; cited			• QoL • Weight	
SURMOUNT-3[121,151] NCT04657016 US, Argentina, Brazil, Puerto Rico Completed; no results posted or publications. Protocol paper for SURMOUNT 1-4 , including baseline chars, published December 2022; cited	• N = 806 • BMI ≥ 27 + ≥ 1 weight-related comorbidity or ≥ 30 • ≥ 18 years	• 72 weeks • Tirzepatide (dose, NR) • Placebo	• Blood Pressure • BMI • HbA1c • LDL • QoL • Weight	April 2023
SURMOUNT-4[122,151] NCT04660643 US, Argentina, Brazil, Taiwan Completed; no results posted or publications. Protocol paper for SURMOUNT 1-4 , including baseline chars, published December 2022; cited	• N = 783 • BMI ≥ 27 + ≥ 1 weight-related comorbidity or ≥ 30 • ≥ 18 years	• 88 weeks • Tirzepatide (dose, NR) • Placebo	• Blood Pressure • BMI • HbA1c • LDL • QoL • Weight	April 2023
SURMOUNT-J[129] NCT04844918 Japan	• N = 261 • BMI ≥ 27 + ≥ 2 weight-related comorbidity or ≥ 35	• 72 weeks • Tirzepatide (dose, NR) • Placebo	• Blood Pressure • HbA1c • LDL • QoL	June 2023

Study Name Trial Number Location(s)	N Enrolled Condition(s) Age	Study Duration + Follow-up Interventions	Outcome Measures	Primary Completion Date
	+ ≥ 1 weight-related comorbidity • ≥ 20 years		• Weight	
SUMMIT[150] NCT04847557 US, Argentina, Brazil, China, India, Israel, Mexico, Puerto Rico, Russia, Taiwan	• N = 700 • BMI ≥ 30 + heart failure with preserved ejection fraction • ≥ 40 years	• 52 weeks + 1.5 years • Tirzepatide (dose, NR) • Placebo	• CV events • Mortality • Weight	June 2024
NCT05556512[133] US, Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czechia, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Netherlands, Poland, Puerto Rico, Romania, Slovakia, South Korea, Spain, Taiwan, Turkey, United Kingdom	• N = 15,000 • BMI ≥ 27 + CV disease or ≥ 2 risk factors • ≥ 40 years	• Up to 5 years • Tirzepatide (dose, NR) • Placebo	• Blood Pressure • CV events • HbA1c • Mortality • QoL	October 2027

Notes. Shaded rows indicate studies that include pediatric populations. [a] This is a nonrandomized study.

Abbreviations. AE: adverse event; BED: binge-eating disorder; BMI: body mass index; CV: cardiovascular; HbA1c: hemoglobin A1c; HFpEF; heart failure with preserved ejection fraction; LDL: low-density lipoprotein; LEPR: leptin receptor; PCKS1: prohormone convertase 1/3; POMC: proopiomelanocortin; Nal/bup: naltrexone/bupropion; NR: not reported; Phen/top: phentermine/topiramate; QoL: quality of life; SAE: serious adverse event; T2DM: type 2 diabetes.

Appendix M. Bibliography of Included Studies

Clinical Evidence by Treatment (Alphabetical Order)

Exenatide

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Liraglutide

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Appendix N. Bibliography of Excluded Studies With Reasons

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Bergenstal, R. M., Wysham, C., Macconell, L., Malloy, J., Walsh, B., Yan, P., Wilhelm, K., Malone, J., Porter, L. E., Group, Duration- Study. **Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial.** *Lancet.* 2010. 376:431-9 10.1016/S0140-6736(10)60590-9	Aim
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