Tirzepatide for Type 2 Diabetes

Draft Evidence Report

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Prepared for

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

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2021/11/Key-Stakeholder-List.pdf

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List of Acronyms and Abbreviations Used in this Report

AACE	American Association of Clinical Endocrinologists
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	American College of Endocrinology
ADA	American Diabetes Association
AE	Adverse event
ASCVD	Atherosclerotic cardiovascular disease
BL	Baseline
BMI	Body Mass Index
bpm	Beats per minute
BT	Background therapy
CEPAC	Comparative Effectiveness Public Advisory Council
CGM	Continuous glucose monitor
CHF	Congestive heart failure
CI	Confidence interval
cm	Centimeter
CKD	Chronic kidney disease
CR	Credible range
CV	Cardiovascular
CVD	Cardiovascular disease
CVO	Cardiovascular outcomes
CVOT	Cardiovascular outcomes trial
DBP	Diastolic blood pressure
D/C	Discontinuation
dL	Deciliter
DPP-4	Dipeptidyl peptidase-4
DTSQc	Diabetes Treatment Satisfaction Questionnaire change version
DUA	Dulaglutide
Dx	Diagnosis
EASD	European Association of the Study of Diabetes
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
evLY	Equal value of life years
evLYG	Equal value of life years gained
EMPA	Empagliflozin
ER	Emergency room
ESRD	End-stage renal disease
ETD	Estimated treatment difference
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
GLP-1 RA	GLP-1 receptor agonist
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HUI-3	Health Utilities Index Mark 3
ICER	Institute for Clinical and Economic Review

IGlar	Insulin glargine
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
ITT	Intention to treat
kg	Kilogram
LDL	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
LYG	Life years gained
m	Meter
MACE	Major adverse cardiovascular event
MACE-3	3-point MACE
MACE-4	4-point MACE
MAR	Missing at random
MET	Metformin
mg	Milligram
MI	Myocardial infarction
mITT	Modified intent to treat
mL	Milliliter
MM	Mixed-effects model
mmol	Millimole
mmHg	Millimeter of mercury
MMRM	Mixed-effects model repeated measures
mol	Mole
MTD	Maximum tolerated dose
n	Number of subjects with events
N	Number of subjects in full analysis set
NA	Not applicable
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NR	Not reported
NMA	Network meta-analysis
NON	Noninferiority
OM2	Outcomes Model 2
OR	Odds ratio
OSEM	Oral semaglutide
OW	Once weekly
PBO	Placebo
PICOTS	Population, Intervention, Comparator, and Study Design
PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
QALY	Quality-adjusted life year
QW	Once weekly
RA	Receptor agonist
RCT	Randomized controlled trial
REF	Reference
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Semaglutide (injectable)
SF-36	Short Form Health Survey
SGLT-2	Sodium-dependent glucose co-transporter-2
SITA	Sitagliptin
SU	Sulfonylurea

TEAE	Treatment emergent adverse event
T2DM	Type 2 diabetes mellitus
Tx	Treatment
TZD	Thiazolidinedione
TZP	Tirzepatide
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
USD	United States dollar
USPSTF	United States Preventive Services Task Force
VAS	Visual analogue scale
WAC	Wholesale acquisition cost

Executive Summary

Type 2 diabetes mellitus (T2DM), characterized by the progressive loss of adequate insulin secretion from the pancreas and peripheral insulin resistance, affects more than 34 million Americans. Minorities bear a disproportionate burden of disease, with a higher prevalence in the American Indian/Alaska Native, Hispanic, Black, and Asian communities.[1] Chronic exposure to high blood glucose levels may damage both small (microvascular) and large (macrovascular) blood vessels, resulting in life-altering complications.[2] Blindness, end-stage renal disease, cardiovascular disease, amputation, and death are among the most severe consequences of T2DM. Consequently, the annual costs associated with T2DM exceeded $300 billion in 2017.[3] Additionally, there can be financial toxicity to individuals due to high treatment costs.[4]

Patients described the struggle of managing their disease, including struggles with glycemic control, losing weight, and the expense of medications. Many patients also have comorbidities such as kidney and heart disease, adding to their burden of daily management. Early and comprehensive education about diabetes self-management, along with access to and affordability of medications, were identified as critical factors in the success of managing T2DM over a patient's lifetime.

A measurable short-run goal of treatment is glycemic control, with a goal glycated hemoglobin (HbA1c) of < 7.0% in most patients.[5] Beyond lifestyle modifications, many patients require medications to achieve glycemic goals. Metformin is recommended as first-line therapy based on its efficacy and favorable safety profile.[6] Options for add-on therapy if metformin is not sufficient to reach glycemic targets include both oral and injectable options. Some newer agents such as sodium glucose transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA) have favorable cardiovascular and renal outcomes data; these agents are preferred in patients with or at high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure, or established chronic kidney disease, independent of baseline HbA1c, glycemic target, or baseline metformin use.[7]

With current treatment options, nearly half of T2DM patients may not be at an adequate level of glycemic control.[1] Tirzepatide (Eli Lilly), a novel, once-weekly injectable dual glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 RA combination drug, has been developed to treat patients with T2DM. The manufacturer (Eli Lilly) announced the submission of a biologics license application with priority review to the FDA for T2DM on October 27, 2021, with a decision expected in mid-2022.

We compared the clinical and cost-effectiveness of tirzepatide added on to background therapy compared with background therapy alone, or injectable semaglutide (Ozempic®, Novo Nordisk) or empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly) added on to background therapy. Treatment with tirzepatide 15 mg resulted in a greater decrease in HbA1c and weight compared

with background therapy after 26 weeks of treatment (estimated treatment difference of -2.5% and -10.9 kg, respectively; p<.0001 for both comparisons).[8] The most common adverse events of tirzepatide therapy were gastrointestinal symptoms such as diarrhea, nausea or vomiting; severe hypoglycemia was rare.

Tirzepatide was compared head-to-head with injectable semaglutide in a Phase 3 randomized controlled trial.[9] Compared with semaglutide, tirzepatide showed greater reduction in HbA1c and weight as well as in triglycerides and blood pressure. However, the tirzepatide group had a greater incidence of gastrointestinal side effects, injection-site reactions, severe adverse events, and discontinuation compared with semaglutide.

There were no head-to-head trials comparing tirzepatide and empagliflozin, so we compared these drugs indirectly through a network meta-analysis (NMA). The NMA results demonstrated that compared to empagliflozin, tirzepatide had a greater decrease in HbA1c and weight loss, though there was more uncertainty in these estimates given the indirect comparison. The point estimate decreases in HbA1c, and weight loss fell in between the point estimates observed when comparing tirzepatide to injectable semaglutide and comparing tirzepatide to background therapy alone. We did not have data to compare adverse events between tirzepatide and empagliflozin.

Both semaglutide and empagliflozin have demonstrated improvement in composite cardiovascular outcomes based on their respective cardiovascular outcomes trials and have FDA indications for prevention of cardiovascular events.[10,11] Empagliflozin has also been shown to improve outcomes in patients with chronic kidney disease.[12] The cardiovascular outcomes trial for tirzepatide is ongoing and less mature; however, a meta-analysis of cardiovascular events for safety across the SURPASS trials showed no increase in cardiovascular events and a trend towards cardiovascular benefit.

Although tirzepatide shows an impressive impact on glucose-lowering and weight loss, given the established cardiovascular benefits of semaglutide and empagliflozin, establishing whether tirzepatide has cardiovascular benefit is imperative to reducing uncertainty in its comparative effectiveness. Additionally, GIP inhibition is a new mechanism and its long-term safety and impact on cardiovascular outcomes is unknown. Finally, the lack of head-to-head comparison between tirzepatide and empagliflozin makes it more difficult to fully assess whether tirzepatide provides superior net health benefit to empagliflozin.

Thus, compared to background therapy alone, we judge the net health benefits of tirzepatide to be incremental or better (B+). For tirzepatide compared with semaglutide, although tirzepatide had greater impact on glycemic control and weight, the lack of a cardiovascular outcomes trial for tirzepatide causes us to judge tirzepatide to have comparable or incremental net health benefits (C+). For tirzepatide compared with empagliflozin, the fact that we had only indirect comparisons, added to the lack of definitive cardiovascular or renal outcomes data for tirzepatide, cause us to judge tirzepatide to have comparable or better net health benefits (C++).

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Tirzepatide	Background therapy	B+
Tirzepatide	Injectable Semaglutide	C+
Tirzepatide	Empagliflozin	C++

We developed an individual, patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2DM among US adults using the United Kingdom Prospective Diabetes Study Outcomes Model 2 (UKPDS-OM2)[13] equations. Patients, with data from multiple National Health and Nutrition Examination Survey (NHANES) surveys, were simulated through the modeling steps for each comparator versus tirzepatide. The base case analysis took a health care sector perspective and thus focused on direct medical care costs only. Costs and outcomes were discounted at 3% per year.[14] Because no long-term cardiovascular outcomes trial data exist for tirzepatide, health benefits were informed by intermediate outcomes and were unadjusted. Modeled cardiovascular and renal outcomes for therapies with existing long-term trials were adjusted to trial data using hazard ratios.

We found that tirzepatide produced a slightly lower point estimate for quality-adjusted life-years (QALYs) compared to injectable semaglutide, but higher versus empagliflozin and background therapy alone. Credible ranges for lifetime discounted QALYs did not overlap for tirzepatide versus background therapy alone but did overlap comparing tirzepatide to both injectable semaglutide and empagliflozin. Using a placeholder price equal to injectable semaglutide, the incremental cost per QALY gained for tirzepatide compared to empagliflozin and background therapy were under $100,000 (tirzepatide point estimate was less costly and less effective compared to semaglutide). Compared to background therapy alone, tirzepatide's cost per evLY gained was under the $50,000 threshold. Uncertainty analyses suggested a wide range of plausible cost-effectiveness estimates for tirzepatide.

Table ES2. Incremental Cost-Effectiveness Ratios for the Base Case – Mean (95% CR)

Treatment	Comparator	Cost per QALY Gained		Cost per Life Year Gained		Cost per evLY Gained	
		Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range
Tirzepatide*	Background Therapy	$38,000	(-$33,000 to $91,000)	$41,000	(-$94,000 to $150,000)	$23,000	(-$23,000 to $60,000)
Tirzepatide*	Injectable Semaglutide	Less Costly and Less Effective	(-$1,469,000 to $1,541,000)	Less Costly and Less Effective	(-$346,000 to $377,000)	NA†	NA†
Tirzepatide*	Empagliflozin	$96,000	(-$408,000 to $594,000)	$472,000	(-$1,069,000 to $1,071,000)	NA†	NA†

*Using a placeholder price equal to the annualized net price of injectable semaglutide

†evLY Gained were only calculated versus background therapy alone in the microsimulation, precluding incremental comparisons between therapies

This model should be interpreted with its limitations in mind. Neither cost nor long-term outcome data for tirzepatide are available at this time, but once available, will reduce the uncertainty in model findings. Additionally, there are noted limitations to the UKPDS-OM2 risk equations used for this analysis, including that they were developed based on a patient cohort from the United Kingdom in decades past. Our choice to use UKPDS-OM2 risk equations was made based on lack of feasible alternatives at the time, and hazard ratios for outcomes were used in an attempt to ensure the model estimates align with clinical evidence where possible. Additionally, because the price of tirzepatide is still unknown, a placeholder price was used in calculations and should not be interpreted as factual.

1. Background

More than 34 million Americans, or around 13% of the US population, have diabetes mellitus.[1] T2DM, which is characterized by progressive loss of adequate insulin secretion from the pancreas and peripheral resistance to insulin, accounts for 90-95% of those cases. The hallmark of diabetes is an abnormal elevation in blood glucose, or hyperglycemia. Chronic hyperglycemia puts patients at risk for damage to both small (microvascular) and large (macrovascular) blood vessels, resulting in damage to the eyes, nerves, and kidneys, as well as cardiovascular events and limb ischemia.[2] Obesity is a major risk factor for developing T2DM with more than 60% of people with diabetes having a body mass index (BMI) in the obese or extreme obesity range.[1,15] Other risk factors include older age, family history, a history of gestational diabetes, high blood pressure, a sedentary lifestyle, and a low level of HDL.[16]

Minorities bear a disproportionate burden of T2DM. Among adults, the prevalence of diagnosed T2DM is highest in American Indian/Alaska Natives (approximately 14%); for Asian Indian, non-Hispanic Black and Hispanic populations, prevalence estimates are around 12% for each group.[1] These populations are also at greater risk of developing diabetes, with the incidence in Black and Hispanic populations 1.7-1.8 times greater than in White populations.[1,17]. For example, Blacks and Hispanics had lower rates of receipt for HbA1c testing than Whites and were less likely to receive annual cholesterol testing and retinal examination, which may be correlated with higher rates of complications in these populations.[18]

Complications of diabetes can be severe and life-altering. Diabetes is the leading cause of new blindness, end-stage renal disease, and limb amputations, and it is the seventh leading cause of death in the US.[1] In 2016, diabetes was associated with 16 million emergency department visits, 7.8 million hospitalizations, and 1.7 million hospitalizations for cardiovascular disease.[1] Total direct and indirect costs for diabetes exceeded $327 billion in 2017, with 72% of the total considered direct costs (e.g., health care services or technologies).[3] Furthermore, patients with diabetes are more likely to suffer financial hardship from medical bills and its consequences, including cost-related medication nonadherence, delayed or skipped medical care, high financial distress, and food insecurity.[4]

Management of T2DM is focused on both shorter-term goals such as controlling hyperglycemia and managing comorbidities, and longer-term goals such as preventing complications of disease. Treatment goals are based in part on measurements of HbA1c, a measure of average blood sugar over three months. Since tight control of blood sugar has been shown to decrease microvascular and macrovascular complications, clinical practice guidelines recommend a HbA1c target of 7.0% or less in most patients, with less stringent control accepted in patients with a higher risk of hypoglycemia, more severe comorbidities, and shorter life expectancy.[5] Achieving near-

normal glycemic control with intensive therapy may have additional benefits in terms of slowing onset or progression of neuropathy, retinopathy, and nephropathy.[19] However, such tight control of glucose may come at the expense of more hypoglycemia.

The cornerstones of therapy for T2DM includes lifestyle modifications such as diet, exercise, and weight loss, and management of cardiovascular risk factors such as high cholesterol and high blood pressure.[20,21] Self-management is a critical component of managing diabetes, and individually tailored, culturally appropriate diabetes self-management education can improve outcomes and reduce costs.[22,23] For example, medical nutrition therapy delivered by a registered dietician or diabetic educator is associated with a 0.3-2% decrease in HbA1c in patients with T2DM.[21] For some patients, intensive lifestyle changes may be enough to control blood sugars and prevent progression. However, many patients will require pharmacologic therapy during their disease course to achieve adequate glycemic control.

Metformin is recommended as initial pharmacotherapy for patients with T2DM due to its efficacy and favorable safety profile, and should be continued as long as it is tolerated and not contraindicated. It is associated with modest weight loss, does not have a significant risk of hypoglycemia, and may improve cardiovascular outcomes, though there are no direct cardiovascular outcomes trials.[24] Combination therapy with additional agents can be considered if patients do not meet their HbA1c goal on metformin and lifestyle changes. Older oral medications such as sulfonylureas (SU) and thiazolidinediones (TZD) are inexpensive but have significant side effects such as hypoglycemia (with SU) and heart failure (with TZDs). Newer agents include oral agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors and SGLT-2 inhibitors, and oral and injectable GLP-1 RA. These newer agents are effective at lowering blood glucose without a substantial risk of hypoglycemia, and SGLT-2 inhibitors and GLP-1 RAs are also associated with weight loss. Gastrointestinal side effects are particularly common with GLP-1 RAs and use of SGLT-2 inhibitors are associated with genitourinary infections and ketoacidosis.[25-28]

Since 2008, when the Food and Drug Administration (FDA) issued recommendations for the evaluation of cardiovascular risk for new antihyperglycemic therapies, multiple cardiovascular outcome trials (CVOTs) have been conducted, adding greater certainty in the assessment of the relative risks and benefits of each therapy.[29] Thus, for patients with or at high risk of ASCVD, heart failure, or established chronic kidney disease (CKD) recommended second-line therapy includes either a GLP-1 RA or SGLT-2 inhibitor with proven cardiovascular or renal benefit, independent of HbA1c target or baseline metformin use.[7] For patients without those comorbidities, choice of drug is dependent on comorbidities, cost, side effects, and patient preferences. More details on each drug class can be found in the Supplement A2.

Although many options for therapy for T2DM exist, nearly half of patients may not be at an adequate level of glycemic control.[1] Tirzepatide (Eli Lilly), a novel, once-weekly injectable dual GIP

and GLP-1 RA combination drug, has been developed to treat patients with T2DM. Trials are also ongoing to assess tirzepatide for the treatment of obesity and cardiovascular disease. The manufacturer (Eli Lilly) announced the submission of a biologics license application with priority review to the FDA for T2DM on October 27, 2021, with a decision expected in mid-2022.

Table 1.1. Interventions of Interest

Intervention Brand Name (Generic Name)	Mechanism of Action	Delivery Route	Prescribing Information
Tirzepatide	Dual GIP inhibitor/GLP-1 receptor agonist	Subcutaneous injection	5-15 mg once weekly

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

2. Patient and Caregiver Perspectives

This draft evidence report was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review.

Patients and patient groups discussed that T2DM has a substantial impact on daily life, including trying to manage diet and blood glucose readings, affording testing supplies and medications, and managing complications of the disease. Patients described the frustrations of trying to follow prescribed diets, particularly when the dietary recommendations conflict (e.g., patients with diabetes are recommended to limit carbohydrates while patients with CKD are recommended to avoid a high protein diet). Glycemic control, particularly HbA1c levels, is one of the most important actionable and short-run outcomes to patients, and patients value potentially getting to near normal glycemic levels.[30] Improvements in glucose tracking with new technologies such as continuous glucose monitors (CGM) are empowering to patients to help manage their daily life. Weight loss is another critical struggle described by patients, and patients would welcome medications that would produce significant weight loss. Patients also spoke about feelings of guilt and self-blame for their diabetes, describing the stigma they feel about the perception of diabetes as a "lifestyle" disease that they should be able to control with their actions, even though the causes of diabetes are complex and genetics can play an important role.

Affordability of diabetes medications and access to CGMs were cited as major barriers to the successful management of T2DM. Medication costs for patients with diabetes can be substantial, even for those who are insured. For example, co-pays and co-insurance for insulin and newer medications like GLP-1 RAs can be very high, particularly for patients with high deductible health plans, even if they successfully navigate a time-consuming prior authorization process. For patients with lower socioeconomic status, the inability to pay can lead to skipping medication doses and cancelling medical appointments. Additionally, patients often have multiple comorbidities such as cardiac or renal disease, which can further increase the financial burden of medications. Patients may turn to foundations or prescription assistance programs from manufacturers to help with medication costs; however, patients with Medicare are usually not eligible for manufacturer prescription assistance programs so such programs have limited reach. Finally, although patients described new technologies such as CGMs as "game changers" in terms of helping them manage their disease, obtaining insurance coverage for CGMs can be very challenging.

Patients discussed that another unmet need is more detailed and comprehensive education about disease management and trajectory, particularly in the time period around diagnosis. In addition, linguistically and culturally sensitive education delivered within the community appears to be a key to improving patient engagement and self-management of the disease. This is particularly important because the burden of diabetes is substantial in minority populations, with Native

Americans/Alaska Natives, Blacks, Hispanics, and Asians having a higher rate of disease compared with White Americans. Thus, patient groups mentioned that a greater focus on efforts to decrease disparities in prevention and treatment of diabetes and accurate modeling of the health effects of diabetes are critical to improving health equity.

Clinicians were enthusiastic about the prospect of therapies that both improved glycemic control and resulted in substantial weight loss. However, they emphasized the importance of cardiovascular outcomes on their assessments of efficacy and were eagerly awaiting the results of the CVOT for tirzepatide. Cost of therapy for patients was an additional issue of great importance to both clinicians and patients and was cited as a major factor in the choice of therapy.

Manufacturers and payers highlighted additional non-glycemic outcomes that may be important to consider when assessing the value of therapy, including improvements in cardiovascular and renal outcomes, satisfaction with the delivery device, and the ability of the therapy to address comorbidities related to obesity that may be impacted by weight loss (e.g., obstructive sleep apnea, nonalcoholic fatty liver disease, etc.).

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence of tirzepatide for T2DM are detailed in Supplement D1.

Scope of Review

We reviewed the clinical effectiveness of tirzepatide added on to background therapy (metformin +/- sulfonylureas or thiazolidinediones) versus background therapy alone, or injectable semaglutide or empagliflozin added on to background therapy in adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We sought evidence on patient-important outcomes such as change in HbA1c levels, weight, waist circumference, lipid levels, blood pressure, health-related quality of life measures, and adverse events. Additionally, we reviewed available information on each treatment's effect on micro- and macrovascular outcomes including retinopathy, nephropathy, and neuropathy, all-cause mortality, cardiovascular (CV) mortality, myocardial infarction (MI), stroke, and heart failure requiring hospitalization.

We also looked for data on subpopulations of interest, including T2DM patients with (1) established ASCVD, (2) congestive heart failure, (3) moderate-to-severe renal impairment, (4) requiring a second and/or third antihyperglycemic agent, (5) who are overweight or obese, and (6) identified by race, ethnicity, or socioeconomic status.

The full scope of the review is detailed in Supplement D1.

Evidence Base

The SURPASS clinical trial program contains five Phase 3 global registration studies comparing tirzepatide against placebo (background diet and exercise alone), injectable semaglutide, insulin degludec, insulin glargine, and placebo (background insulin glargine ± metformin).[31] SURPASS-2 and SURPASS-4 were selected as studies of interest due to a relevant comparator arm or population and are outlined below. We also reviewed two Phase 2 trials to assess the efficacy of tirzepatide added on to background therapy compared with background therapy alone.

Tirzepatide versus Background Therapy

Our search identified two randomized controlled trials (RCT) of tirzepatide that provide evidence on the efficacy and safety of tirzepatide plus background therapy (diet and exercise alone or stable metformin treatment) versus background therapy alone. These include a Phase 2b study comparing once-weekly injectable tirzepatide (1, 5, 10, or 15 mg) versus once-weekly injectable dulaglutide (1.5 mg) and placebo (Frias 2018)[8], and a follow-up Phase 2 study evaluating the tolerability of three tirzepatide dose-escalation regimens (12 mg or two versions of a 15 mg arm) versus placebo (Frias 2020).[32] Participants in both trials were largely on stable metformin doses for background therapy. Baseline characteristics of the two trials are outlined in Table 3.1. The two Phase 2 trials were qualitatively assessed for evidence on the efficacy and safety of tirzepatide as an add-on to background therapy.

Table 3.1 Selected Baseline Characteristics of Two Phase 2 Tirzepatide Trials

	Frias 2018 Phase 2				Frias 2020 Phase 2		
Study Arms	PBO	TZP 5 mg	TZP 10 mg	TZP 15 mg	PBO	TZP 15 mg-1*	TZP 15 mg-2*
Background Therapy	MET				MET		
Study Duration, weeks	26 weeks				12 weeks		
Mean Age, years	56.6	57.9	56.5	56	56	55.5	56.6
Sex, Male, %	57	62	59	42	46.2	57.1	82.1
HbA1c, %	8	8.2	8.2	8.1	8.2	8.5	8.4
Weight, kg	91.5	92.8	92.7	89.1	89.6	88.7	89.8
BMI, kg/m^2	32.4	32.9	32.6	32.2	32.5	32	31.1
Race, White, %	80	84	74	81	NR	NR	NR
Metformin, %	92.2	89.1	86.3	96.2	88.5	89.3	82.1

kg: kilogram, m: meter, MET: metformin, mg: milligram, NR: not reported, PBO: placebo, TZP: tirzepatide
*In the Frias 2020 trial, there were two versions of a 15 mg arm. See Supplement D3 for further details.

Additionally, we conducted a network meta-analysis that provided an indirect comparison of tirzepatide added to background therapy versus background therapy alone using five Phase 3 trials. The NMA is described in further detail in the evidence base for the tirzepatide vs empagliflozin scenario and in Supplement D2.

Tirzepatide versus Semaglutide

SURPASS-2 is a Phase 3 head-to-head open-label trial evaluating the clinical efficacy and safety of tirzepatide (5, 10, or 15 mg) versus injectable semaglutide (1 mg) over a 40-week period in patients with T2DM inadequately controlled with baseline metformin therapy. Baseline characteristics can be found in Table 3.2, and additional details of the study design can be found in Supplemental Table D4.2.

Tirzepatide versus Empagliflozin

There are no head-to-head trials comparing the clinical efficacy and safety of tirzepatide versus empagliflozin. Thus, to be able to draw an indirect comparison between the two treatments, we conducted a NMA on the available intermediate outcomes of changes in HbA1c, weight, low-density lipoprotein (LDL) cholesterol, and systolic blood pressure (SBP). These outcomes were presented as between-treatment mean differences of change from baseline at 40 weeks. We included five Phase 3 trials and five drugs into the network: tirzepatide (SURPASS-2), injectable semaglutide (SURPASS-2, SUSTAIN-2), oral semaglutide (PIONEER-2, PIONEER-3), empagliflozin (PIONEER-2), and sitagliptin (SUSTAIN-2, PIONEER-3, HARMONY-3). The study design and baseline characteristics of the five trials are outlined in Table 3.2.

Table 3.2 Selected Study Design and Baseline Characteristics of the Randomized Controlled Trials in the Network Meta Analysis Evaluating Tirzepatide, Semaglutide, Empagliflozin, and Background Therapy

	SURPASS-2		**SUSTAIN-2**		**PIONEER-2**		**PIONEER-3**		**HARMONY-3**	
Study Arms	TZP 15 mg	SEM 1 mg	SEM 1 mg	SITA 100 mg	OSEM 14 mg	EMPA 25 mg	OSEM 14 mg	SITA 100 mg	PBO	SITA 100 mg
N	470	469	409	407	411	410	465	467	101	302
Background Therapy	MET		MET ± TZD (4.5%)		MET		MET ± SU (47.1%)		MET	
Study Duration	40 weeks		56 weeks		52 weeks		78 weeks		104 weeks	
Mean Age, years	55.9	56.9	56	54.6	57	58	57	58	56.1	54.3
Sex, Male, %	45.5	48	50	51	50.1	51	53.1	51.0	49.5	46
HbA1c, %	8.3	8.3	8	8.2	8.1	8.1	8.3	8.3	8.2	8.1
Weight, kg	93.8	93.7	89.2	89.3	91.9	91.3	91.2	90.9	91.6	90.3
BMI, kg/m^2	34.5	34.2	32.5	32.5	32.9	32.8	32.3	32.5	32.8	32.5
Race, White, %	71.1	71.6	68	69	86.4	86.1	68.2	71.3	63.4	74.5
Metformin, %	100	100	100	100	100	100	100	100	100	100

EMPA: empagliflozin, kg: kilogram, m: meter, MET: metformin, N: number of subjects in full analysis set, OSEM: oral semaglutide, PBO: placebo/background therapy, SEM: injectable semaglutide, SITA: sitagliptin, SU: sulfonylurea, TZD: Thiazolidinediones, TZP: tirzepatide

Cardiovascular Outcomes Trials

Tirzepatide

The SURPASS-CVOT is evaluating the non-inferiority and superiority of once weekly tirzepatide versus dulaglutide (1.5mg) in participants with T2DM and increased cardiovascular risk.[33] The trial has an estimated completion date of October 17, 2024; interim data was unavailable at the time of this report.[33]

In lieu of SURPASS-CVOT data, we sought data on baseline characteristics, efficacy, and adverse event parameters of SURPASS-4, a Phase 3 trial that evaluated three doses of tirzepatide (5, 10, 15 mg) against insulin glargine in adults with T2DM on 1-3 oral antihyperglycemic medications and increased cardiovascular risk.[34] Cardiovascular events were recorded as safety events. Additional details of the trial are available in Supplemental Table D4.2.

Due to the unavailability of long-term CVOT data and lack of placebo arm in the above tirzepatide trials, we were unable to include any microvascular (neuropathy, nephropathy, and retinopathy) or macrovascular outcomes (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina or heart failure) in our NMA.

Injectable Semaglutide

SUSTAIN-6 was a CVOT that assessed the efficacy and safety of semaglutide (0.5 or 1 mg) versus placebo as an add-on therapy to background therapy (73.2% on metformin, 58% on insulin, 42.8% on sulfonylurea) in patients with T2DM and established ASCVD, CKD, or both.[10] A total of 3297 patients with a mean age of 64.6 years and baseline HbA1c of 8.7% were observed for a median period of 2.1 years.[10] The pooled semaglutide group was analyzed for non-inferiority and superiority versus the placebo group for the primary composite outcome of MACE-3 (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke).[10] Additional details of the trial are available in Supplemental Table D4.2.

Empagliflozin

EMPA-REG OUTCOME was a CVOT that assessed the efficacy and safety of empagliflozin (10 or 25 mg) as an add-on to background therapy (74% on metformin, 48% on insulin, 43% on sulfonylurea) compared with placebo in patients with T2DM and established cardiovascular disease.[11,35] In this trial, 7020 patients with a mean age of 63.1 years and a baseline HbA1c of 8.1% were treated and observed for a median period of 2.6 and 3.1 years, respectively.[11] The pooled empagliflozin group was analyzed for non-inferiority and superiority versus the placebo group for the primary composite outcome of MACE-3 (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and the key secondary composite outcome of MACE-3 or hospitalization for unstable angina.[11] Additional details of the trial are available in Supplemental Table D4.2.

Subgroup Analysis of Patient-Important Outcomes

Our population of interest for this review are adults with T2DM with inadequate glycemic control despite current treatment with background therapy. In addition to our primary analysis, we sought to evaluate all available patient-important outcomes in the context of the following six patient subgroups:

1. Established ASCVD, e.g., a history of acute coronary syndrome (ACS), MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease.[36]

Currently, there is no available evidence to evaluate the clinical efficacy or safety of tirzepatide for this subgroup. The SURPASS-4 trial included participants with an increased risk of ASCVD as well as participants with established ASCVD; cardiovascular events were recorded as safety events. [34] When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

2. Established congestive heart failure (New York Heart Association class II or III)

Currently, there is no available evidence to evaluate the clinical efficacy and safety of tirzepatide for this subgroup. When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

3. Established moderate-to-severe renal impairment (CKD Stage 3 or higher (eGFR <60 mL/min per 1.73 m^2))

Academic-in-confidence data on change in HbA1c (%) from baseline at week 40 between the subgroups of eGFR <60 and ≥60 mL/min per 1.73 m^2 for the SURPASS-2 trial was provided by the manufacturer.[37] When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

4. Tirzepatide as a second- or third-line antihyperglycemic agent

We did not find any data assessing the efficacy or safety of tirzepatide specific to these two subpopulations. When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

5. Overweight (BMI 25.0-29.9 kg/m^2) or obese (≥30.0 kg/m^2)

Academic-in-confidence data on change in HbA1c (%) from baseline at week 40 between the subgroups of BMI <30 kg/m^2, ≥30 to <35 kg/m^2, and ≥35 kg/m^2 was provided by the manufacturer for the SURPASS-2 trial.[37] When available, we qualitatively assessed any subgroup analyses done in these populations the semaglutide and empagliflozin CVOTs.

6. Race and ethnicity or socioeconomic status

Academic-in-confidence data on change in HbA1c (%) from baseline at week 40 between the subgroups of Hispanic/Latino and Not Hispanic/Latino was provided by the manufacturer for the SURPASS-2 trial.[37] When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

3.2. Results

A subset of trials within our review report treatment effects using two estimands. The treatment-regimen, also called treatment policy, estimand evaluates the treatment effect for all randomized patients regardless of premature trial product discontinuation or use of rescue medication.[9,38] The efficacy, or trial product, estimand evaluates the treatment effect of all randomized patients who had completed the study without the use of rescue medication. The treatment-regimen estimand and the efficacy estimand provide different perspectives on a drug's efficacy; we feel that the treatment-regimen/treatment policy estimand is more relevant to the patient and clinician experience as it considers the common challenges of medication adherence and need for rescue medication in the diabetes treatment realm.

When possible, we prioritized the reporting of values from the treatment-regimen estimand for several reasons: to ensure consistency with our 2019 ICER Type 2 Diabetes report, the estimand's reflection of the intention-to-treat principle, and its preference by regulatory agencies such as the FDA.[39] If the treatment-regimen estimand was not available, we reported efficacy estimands and have noted as such via in-text and evidence table references.

We conducted an NMA comparing tirzepatide added to background therapy to background therapy alone, and injectable semaglutide or empagliflozin added to background therapy. Oral semaglutide and sitagliptin were used as linkages in the NMA and therefore were not emphasized in this report. Additionally, due to limited data reported in publications and/or provided by manufacturers, there were only four available outcomes for which we could provide inputs into the NMA: change from baseline in HbA1c, body weight, LDL, and SBP at week 40. (Supplemental Tables D2.2-2.3)

Clinical Benefits

Tirzepatide versus Background Therapy

The efficacy of tirzepatide compared with background therapy was evaluated through two Phase 2 trials (Frias 2018 and Frias 2020) and the NMA. Tirzepatide consistently showed a dose-dependent decrease in HbA1c of -1.6% to -2.4% compared with background therapy (efficacy estimand). Results from the NMA were consistent with these trials, with a mean treatment difference in HbA1c from placebo of -1.7%. Furthermore, in the Frias 2018 trial, all three tirzepatide doses had a greater proportion of participants who achieved a HbA1c target of <7.0% (69.1-77.4%) compared to placebo (11.8%) (p<.0001 for all three comparisons), and 30.2% of participants in the tirzepatide 15 mg arm achieved HbA1c levels of <5.7%, an indication of normal glycemic control. (Supplement Table D4.4)

In terms of weight, tirzepatide also showed a dose-dependent decrease in weight (Supplement Table D4.4), with the greatest weight loss seen in the tirzepatide 15 mg group (-11.3 kg from

baseline in the Frias 2018 trial and -11.5 kg difference from placebo in the NMA). Additionally, in the Frias 2018 trial, more than one-third of patients in the 10 mg and 15 mg groups achieved body weight reduction of ≥10% and almost one-quarter of participants in the 15 mg arm achieved ≥15% reduction. Impact on waist circumference was mixed between the two trials. (Supplement Table D4.4)

The impact of tirzepatide on other outcomes was mixed. Tirzepatide had a significant 7.46 mmHg decrease in systolic blood pressure compared with placebo in the NMA (fixed effects model) but not the Phase 2 trials. Similarly, tirzepatide had significant decrease in LDL of -4.34 mg/dL from baseline in the NMA (fixed effects model) that was not seen in the Phase 2 trials. Tirzepatide also decreased mean total cholesterol and triglycerides concentrations ($p<.05$ for all interactions) in the Frias 2018 trial (Supplement Table D4.4).

Tirzepatide versus Semaglutide

The primary outcome of the SURPASS-2 trial was the mean change in HbA1c from baseline to 40 weeks between three arms of tirzepatide (5 mg, 10 mg, or 15mg) and injectable semaglutide (1 mg). Tirzepatide reduced HbA1c levels by 2%, 2.2%, and 2.3% in the 5 mg, 10 mg, and 15 mg dose groups, respectively, compared with 1.86% with semaglutide. The estimated treatment differences for all groups compared with semaglutide were statistically significant: tirzepatide 5 mg -0.15% (95% CI -0.28 to -0.03); tirzepatide 10 mg -0.39% (-0.51 to -0.26); tirzepatide 15 mg -0.45% (-0.57 to -0.32).

Additionally, the two larger tirzepatide doses (10 mg, 15 mg) also had a greater proportion of participants who achieved a HbA1c target of <7.0% (86%) compared to semaglutide (79%) ($p<.05$ for both dose groups). Nearly half of participants in the tirzepatide 10 mg and 15 mg arms achieved near-normal glucose levels (HbA1c <5.7%), compared with 19% in the semaglutide arm, $p<.001$).

Treatment with tirzepatide produced a dose-dependent change in mean body weight (kg) from baseline compared with semaglutide. At week 40, participants experienced a weight loss of 7.6 kg (5 mg), 9.3 kg (10 mg), and 11.2 kg (15 mg) compared with 5.7 kg in the semaglutide group ($p<.0001$ for all 3 comparisons). The percentage of participants achieving body weight reduction of ≥10% was 24% (semaglutide), 34% (5 mg), 47% (10 mg), and 57% (15 mg), and 36% of participants in the 15 mg arm achieved a ≥15% reduction in body weight. Finally, at week 40, there was a greater reduction in mean waist circumference (cm) in all three dosage arms of tirzepatide compared with semaglutide (Supplement Table D4.5).

The 15 mg tirzepatide arm had a greater reduction in systolic and diastolic blood pressure from baseline (−6.5 mmHg and −2.9 mmHg, respectively) as compared with 1 mg semaglutide (−3.6 mmHg and −1.0 mmHg, respectively). Treatment with tirzepatide also resulted in a greater reduction in mean HDL and triglycerides concentrations versus semaglutide across the three dosage

arms (efficacy estimand) (Supplement Table D4.5). Changes in mean total cholesterol and LDL concentrations were not statistically significant among the four treatment groups (efficacy estimand).

Treatment with 15 mg of tirzepatide resulted in better overall quality of life than semaglutide across several quality-of-life measures, including the Diabetes Treatment Satisfaction Questionnaire change version (DTSQc), EQ-5D-5L (index score), EQ-5D-5L visual analogue scale (VAS), Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) (psychosocial, physical, and physical functioning score).[37] (data on file)

Tirzepatide versus Empagliflozin

As there are no head-to-head trials comparing tirzepatide to empagliflozin, all results for this comparison are derived from the NMA. Compared with empagliflozin, tirzepatide decreased HbA1c by 1.1% (statistically significant change using fixed effects model) (Supplemental Table D2.4). A similar advantage is seen in the comparison of weight loss, with an estimated mean difference of -7.2kg between tirzepatide and empagliflozin (statistically significant change using both fixed and random effects models) (Supplemental Table D2.4).

Tirzepatide appears to decrease systolic blood pressure by 2.6 mmHg compared with empagliflozin (statistically significant change using fixed effects model) (Supplemental Table D2.4). For the outcome of LDL, tirzepatide appears to lower LDL by 7.5 mg/dL compared with empagliflozin (statistically significant change using both fixed and random effects models) (efficacy estimand)(Supplemental Table D2.4).

Cardiovascular Outcomes

Tirzepatide

Although the CVOT for tirzepatide is ongoing, the manufacturer performed a CV safety meta-analysis within SURPASS-4 and across the five SURPASS trials on the adjudicated composite outcome (MACE-4) of death from cardiovascular or undetermined causes, myocardial infarction, stroke, and hospitalization for unstable angina. In SURPASS-4, there was no evidence of an increase in the occurrence of MACE-4 and there was an overall trend towards benefit (HR: 0.74;95% CI: 0.51 to 1.08; p=NR).[34] Additionally, the tirzepatide 15 mg group showed a decrease in MACE-4 (HR 0.50; 95% CI 0.26-0.95) over a median of 85 weeks of follow-up.[34] Likewise, pooled data from the SURPASS program showed that tirzepatide had a trend towards benefit in the occurrence of MACE-4 as compared to pooled comparators (HR: 0.81; 97.85% CI: 0.52 to 1.26; p=NR).[40]

Injectable Semaglutide

The primary outcome of the SUSTAIN-6 CVOT was the first occurrence of MACE-3 (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The pooled doses of semaglutide (0.5 mg and 1 mg) were noninferior and superior to placebo in reducing the occurrence of MACE-3 (HR: 0.74; 95% CI: 0.58 to 0.95; p<0.001 for noninferiority; p=0.02 for superiority). When expanding the primary composite outcome to also include the occurrences of revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure, semaglutide was noninferior to placebo (HR: 0.74; 95% CI: 0.62 to 0.89; p=.002). The reduction of risk in both composite outcomes was largely driven by semaglutide's ability to reduce the occurrence of nonfatal stroke versus placebo (HR: 0.61; 0.38 to 0.99; p<.04); the differences in risk reduction between semaglutide and placebo were not significant for the remaining components of the composite outcomes: cardiovascular or all-cause death, nonfatal MI, hospitalization for unstable angina or heart failure (Supplemental Table D4.10).

SUSTAIN-6 included several pre-specified subgroup analyses of interest for the primary outcome of MACE-3: established cardiovascular disease, established chronic heart failure, established moderate-to-severe renal impairment, baseline BMI, race, and ethnicity. None of the subgroups had a significant treatment interaction between semaglutide and placebo (Supplemental Table D4.11).

There was mixed evidence on semaglutide's impact on microvascular outcomes. When compared to placebo, semaglutide reduced the risk of new or worsening nephropathy (HR, 0.64; 95% CI: 0.46 to 0.88; p=.005) but was associated with an increased the risk of diabetic retinopathy complications (HR: 1.76; 95% CI: 1.11 to 2.78; p=.02), although it is not clear whether semaglutide's effect on retinopathy differs between patients with and without baseline retinopathy.[41] The incidence of diabetic neuropathy was not reported in SUSTAIN-6.

Data from the SUSTAIN-6 CVOT led to semaglutide's approved indication of reducing the risk of cardiovascular death, nonfatal MI, or nonfatal stroke in adults with T2DM and established cardiovascular disease.[42]

Empagliflozin

The primary outcome of the EMPA-REG OUTCOME CVOT was the first occurrence of MACE-3. The pooled doses of empagliflozin (10 mg and 25 mg) were noninferior and superior to placebo in reducing the occurrence of MACE-3 (HR: 0.86; 95% CI: 0.74 to 0.99; p<0.001 for noninferiority; p=0.04 for superiority). When expanding the primary composite outcome to also include hospitalization for unstable angina, empagliflozin was noninferior but not superior to placebo (HR: 0.89; 95% CI: 0.78 to 1.01; p<0.001 for noninferiority; p=0.08 for superiority).

The reduction of risk in both composite outcomes was largely driven by empagliflozin's ability to reduce the occurrence of cardiovascular death by 38% (HR: 0.62; 0.49 to 0.77; p<.001); the differences in risk reduction between empagliflozin and placebo were not significant for the remaining components of the composite outcomes (Supplemental Table D4.10). Patients in the empagliflozin group also had lower risk than placebo from hospitalization for heart failure and death from any cause (Supplemental Table D4.10).

EMPA-REG OUTCOME included several pre-specified subgroup analyses of interest for the outcomes of MACE-3 and cardiovascular death: established moderate-to-severe renal impairment, baseline BMI, race, and ethnicity (CV death only). For MACE-3, none of the subgroups had a significant treatment interaction between empagliflozin and placebo (Supplemental Table D4.11).

There was mixed evidence on empagliflozin's impact on microvascular outcomes. There was a statistically significant difference between the empagliflozin and placebo group on the reduced risk of new or worsening nephropathy (HR, 0.61; 95% CI: 0.53 to 0.70; p<.001) but not the risk of diabetic retinopathy complications (HR: 0.69; 95% CI: 0.43 to 1.12; p=.134). The incidence of diabetic neuropathy was not reported in EMPA-REG OUTCOME.

Data from the EMPA-REG OUTCOME CVOT led to empagliflozin's approval for the indication of reducing the risk of cardiovascular death in adults with T2DM and established cardiovascular disease.[43]

Participants treated with empagliflozin in the EMPA-REG OUTCOME CVOT group experienced significantly lower rates of both acute renal failure (p<.01) and acute kidney injury (p<.05) than placebo, suggesting a renal protective effect. These promising results have led to further study of empagliflozin's effect on kidney disease progression or CV death in adults with established chronic kidney disease both with and without diabetes (EMPA-KIDNEY), scheduled to conclude in 2022.[44]

Table 3.3. CVOT Key Trial Results

Cardiovascular Outcomes		SUSTAIN-6		EMPA-REG OUTCOME	
		SEM 1 mg	PBO 1 mg	PBO	EMPA (10/25 mg)
Composite Outcome	n (%)	108 (6.6)	146 (8.9)	282 (12.1)	490 (10.5)
	HR (95%CI)	0.74 (0.58 to 0.95)		0.86 (0.74 to 0.99)	
	p-value, NON	<0.001	REF	<.001	REF
	p-value, SUP	0.02	REF	0.04	REF
Expanded Composite Outcome	n (%)	199 (12.1)	264 (16.0)	333 (14.3)	599 (12.8)
	HR (95%CI)	0.74 (0.62 to 0.89)		0.89 (0.78 to 1.01)	
	p-value, NON	0.002	REF	<.001	REF
	p-value, SUP	NA	NA	0.08	REF

CI: confidence interval, EMPA: empagliflozin, HR: hazard ratio, N: number, NA: not applicable, NON: noninferiority, PBO: placebo, REF: reference, SEM: injectable semaglutide, SUP: superiority

Harms

Tirzepatide versus Background Therapy

The most frequent adverse events in the Frias 2018 and 2020 trials for tirzepatide compared with background therapy were gastrointestinal-related. Participants in the tirzepatide 15 mg arm experienced nausea (40%), diarrhea (32%), or vomiting (26%) at greater proportion than placebo (Supplemental Table D4.6). The discontinuation rate in the 15 mg arm was substantial in the Frias 2018 study (24.5% vs. 3.9% placebo).

Other adverse events in the two trials included hypoglycemia (plasma glucose of ≤70 mg/dL) (10-18%), decreased appetite (18-28%), headache (9-21%), abdominal pain (5-18%), dizziness (9-11%), and injection site reaction (6-8%). There were no reported episodes of severe hypoglycemia across the two trials.

Tirzepatide versus Semaglutide

The safety profile of tirzepatide in the 40 week SURPASS-2 trial was consistent with Phase 2 results; the most frequent adverse events were gastrointestinal-related (Table D4.6). A greater proportion of participants in the tirzepatide 15 mg arm had a serious adverse event than in the semaglutide arm (5.7% vs 2.8%). Adverse events resulted in the discontinuation of the trial in 8.5% (15 mg tirzepatide) and 4.1% (1 mg semaglutide) of participants.

Injection-site reactions (4.5% vs 0.2%) and hypoglycemia (1.7% vs 0.4%) were more frequent in the tirzepatide 15 mg arm compared with semaglutide. Both drugs had similar rates of adjudicated pancreatitis, hypersensitivity, and cholelithiasis (Supplemental Table D4.6). There were no cases of diabetic retinopathy among the 15 mg tirzepatide or 1 mg semaglutide arms, with two cases (0.4%) in the 10 mg tirzepatide arm.

Tirzepatide versus Empagliflozin

There were no available direct or indirect comparisons of safety outcomes between tirzepatide and empagliflozin.

Subgroup Analyses and Heterogeneity

Established ASCVD

Currently, there is no available evidence to evaluate the clinical efficacy and safety of tirzepatide for this subgroup. The SUSTAIN CVOT trial is ongoing and expected to be completed in 2024.

Established CHF

Currently, there is no available evidence to evaluate the clinical efficacy and safety of tirzepatide for this subgroup.

Established moderate-to-severe renal impairment

In the 40 week SURPASS-2 trial, participants receiving tirzepatide 15 mg achieved a greater reduction in HbA1c from baseline than semaglutide, irrespective of renal impairment (eGFR <60, ≥60 mL/min per 1.73 m^2).[37](data on file) Participants with established moderate-to-severe renal impairment (eGFR <60 mL/min per 1.73 m^2) experienced a smaller reduction in HbA1c from baseline in both trial arms.[37] (data on file)

Obesity

In the 40 week SURPASS-2 trial, participants receiving tirzepatide 15 mg achieved a greater reduction in HbA1c from baseline than semaglutide, irrespective of obesity status (BMI categories <30 kg/m^2, ≥30 to <35 kg/m^2, ≥35 kg/m^2).[37](data on file)

Race and ethnicity or socioeconomic status

In the 40 week SURPASS-2 trial, Hispanic/Latino participants experienced a greater reduction in HbA1c from baseline in all trial arms compared with non-Hispanic/Latino participants, with the pattern of relative HbA1c decline between groups consistent with the overall trial results (i.e., greater reduction in HbA1c in the tirzepatide arms compared with semaglutide) [37] (data on file)

Heterogeneity

Table 3.2 outlines the baseline characteristics across the five trials used in our NMA. There were no notable differences between studies in the distribution of baseline characteristics of age, sex, race, ethnicity, HbA1c, weight, BMI, and background use of metformin. We were unable to assess baseline history of microvascular or macrovascular events. Participants in the SUSTAIN-2 and PIONEER-3 trials received additional background therapy via thiazolidinediones and sulfonylurea, respectively.

Uncertainty and Controversies

For the newer antihyperglycemic drugs, particularly GLP-1 RAs and SGLT-2 inhibitors, the glucose-lowering effect of the drug is only one facet of its overall clinical value. The importance of other outcomes such as weight loss, prevention of cardiovascular events, and renal protection have gained prominence, as reflected both by separate indications for such benefits and in clinical practice guidelines favoring GLP-1 RAs and SGLT-2 inhibitors for certain groups of patients with T2DM.[45] Thus, the value assessment of new T2DM therapies includes examining data beyond glucose lowering and glycemic control.

Tirzepatide shows an impressive impact on glucose-lowering and glycemic control, with an average HbA1c lowering of around 2% compared with background therapy, 0.4% in direct comparison to semaglutide and 1.1% in indirect comparison to empagliflozin. Additionally, a substantial number of patients taking 15 mg of tirzepatide achieved near-normal glycemic levels, which is both important to patients and may have benefits in terms of slowing progression of disease.[19] Tirzepatide is also associated with more weight loss than its comparators. Given that the majority of patients with T2DM are overweight or obese and that nearly half of patients with T2DM are inadequately controlled on current therapy, these results are promising. However, gastrointestinal side effects were frequent with tirzepatide and this may affect real-world acceptance and adherence of the drug. Furthermore, GLP-1 RAs may be associated with an increased risk of pancreatitis, acute kidney injury, and thyroid cancer, and GIP inhibition is a new mechanism of action so long-term side effects of this type of drug are unknown.[46] Since there are already multiple approved options for treatment of T2DM, the unknown harms of tirzepatide may influence treatment decision-making by clinicians and patients.

Additionally, tirzepatide lacks definitive data on improvement in cardiovascular and renal outcomes that its comparators have demonstrated. Although tirzepatide had an impact on surrogate cardiovascular outcomes such as blood pressure and lipids in comparison to semaglutide and empagliflozin and there is a trend towards cardiovascular benefit overall in SURPASS-4 (which was powered only to examine cardiovascular safety), the formal CVOT is ongoing. Additionally, although GLP-1 receptor agonism is part of the mechanism for tirzepatide, the drug has an additional mechanism of GIP inhibition, which may have some direct effects in the myocardium. There are

mixed data from pre-clinical, clinical, and epidemiological studies on whether GIP inhibition is helpful or harmful with regard to protection from cardiovascular events.[47-50] Finally, cardiovascular benefit is not uniform across the GLP-1 RA class.[51] Therefore, we hesitate to fully extrapolate the cardiovascular benefits of GLP-1 RAs like semaglutide to tirzepatide, and eagerly await the results from tirzepatide's CVOT.

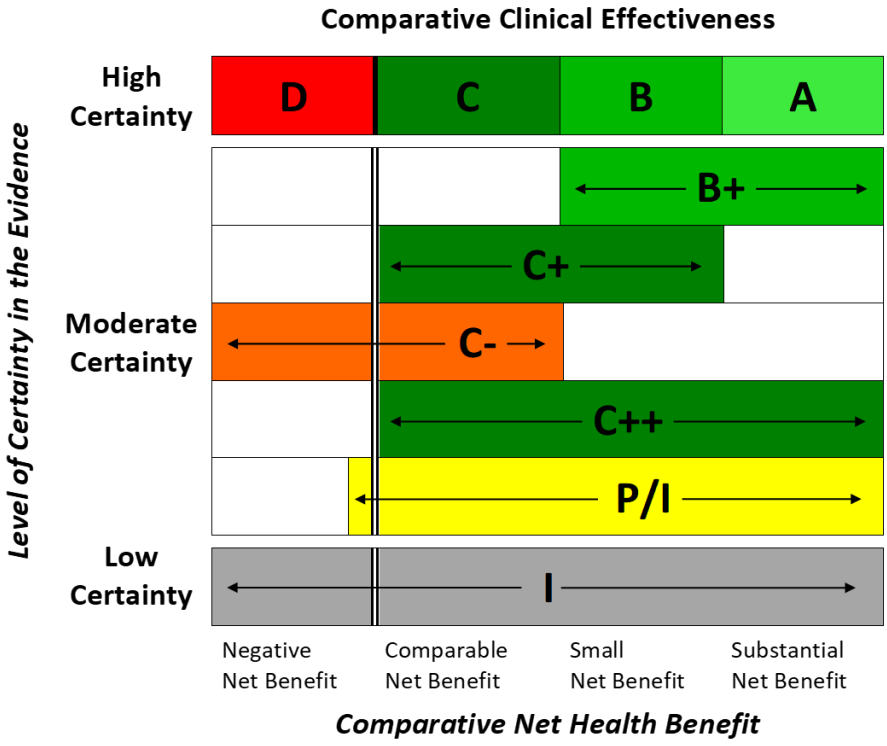
The lack of head-to-head comparison between tirzepatide and empagliflozin made our assessment of the net benefit of tirzepatide more challenging. Since tirzepatide and empagliflozin have completely different mechanisms of action, without a direct comparison, it is difficult to judge whether tirzepatide may represent a substantial improvement over empagliflozin, particularly in patients with established or at high risk of ASCVD, CKD, or heart failure; three common co-morbid conditions. Furthermore, we have only moderate certainty about the results from the indirect comparison through the NMA, as tirzepatide and empagliflozin are compared through trials of three other drugs.

Finally, T2DM is a disease that disproportionately affects minority populations. However, trials of antihyperglycemic drugs including tirzepatide do not reflect the demographics of the disease in the US. The lack of inclusion of minority populations in the clinical trials poses a serious issue in terms of evaluating whether new treatments may increase or decrease health inequities. Furthermore, as access to newer, potentially more expensive drugs tends to be limited at least during initial launch, missing potential differences in population subgroups may prevent populations who may derive greater benefit from the drug from being able to access it. More diverse representation in clinical trials can also provide more precise data to help match drugs with the patients who have the most favorable benefit/side effect profile, which may in turn improve adherence and clinical outcomes of treatment.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided in the Supplement (Section D).

Figure 3.1. ICER Evidence Rating Matrix



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

In this review, we set out to compare the clinical efficacy and safety of tirzepatide to background therapy, injectable semaglutide and empagliflozin.

For the comparison between tirzepatide and background therapy, we evaluated data from two Phase 2 trials on change in glucose levels, weight, lipid profiles, and blood pressure, as well as indirect comparisons on glycemic control, weight loss, LDL, and SBP via results from a five trial

NMA. Compared to background therapy, tirzepatide treatment provided consistent, substantial, and clinically meaningful reductions in HbA1c and weight across the two trials; results for systolic blood pressure and LDL are more modest. The NMA results support the superiority of tirzepatide over background therapy, with statistically significant treatment differences in body weight and SBP in both the fixed and random effects models. The impact of tirzepatide on cardiovascular outcomes has yet to be determined; however, SURPASS-4 provides a glimpse into the positive direction of tirzepatide's cardiovascular safety and potential benefit (in comparison with insulin). Finally, although there was a relatively high discontinuation rate due to gastrointestinal side effects seen in the Phase 2 trial, dose titration appears to mitigate these effects, and severe adverse events are rare. Therefore, we have high certainty that tirzepatide provides a substantial net benefit compared with background therapy for glycemic control and weight loss. We judge tirzepatide to be incremental or better ("B+") for this comparison.

For the comparison between tirzepatide and injectable semaglutide, we relied on head-to-head evidence from a Phase 3 trial (SURPASS-2) to evaluate change from baseline in the intermediate outcomes of glucose levels, weight, lipid profiles, blood pressure, and quality-of-life. Tirzepatide demonstrated a small estimated net benefit in reducing HbA1c and substantial net benefit in weight loss when compared to semaglutide. The drugs appear to be comparable in terms of effects on lipid profile and blood pressure. However, while semaglutide has been demonstrated to improve cardiovascular outcomes and has an indication for this purpose, these data are currently lacking for tirzepatide. We hesitate to fully extrapolate the favorable cardiovascular outcomes data for GLP-1 RAs to tirzepatide, as cardiovascular benefit is not uniform across the GLP-1 RA class, and because of the dual GLP-1/GIP mechanism of action. In consideration of tirzepatide's superiority over semaglutide in outcomes of glycemic control and weight loss, similar safety profiles but current lack of cardiovascular outcome data and the uncertainty about the impact of the GIP moiety, we judge tirzepatide to be comparable or incremental ("C+") for this comparison.

For the comparison between tirzepatide and empagliflozin, tirzepatide provided a substantial net benefit versus empagliflozin via changes in HbA1c, weight, LDL, and SBP. However, with no direct head-to-head trials, we were limited to making an indirect comparison via NMA and thus there is more uncertainty in the precision of these estimates. Additionally, empagliflozin has established cardiovascular and renal benefits in adults with T2DM; data on such outcomes is less certain for tirzepatide, though early signals for the cardiovascular benefit of the drug are promising. Given the benefits seen for intermediate outcomes such as HbA1c and weight and the current lack of definitive cardiovascular and renal outcomes for tirzepatide, we judge that tirzepatide is comparable or better (C++) for this comparison.

Table 3.4. Evidence Ratings

Treatment	Comparator	Evidence Rating
Tirzepatide	Background Therapy	B+
Tirzepatide	Injectable Semaglutide	C+
Tirzepatide	Empagliflozin	C++

4. Long-Term Cost Effectiveness

4.1. Methods Overview

We used a patient-level microsimulation relying on the UKPDS-OM2,[13] which was an adaptation of a published microsimulation[52] and an update of the 2019 ICER report on diabetes therapies.[39,53] Our model analysis plan indicated use of the BRAVO risk engine,[54] however feasibility testing after the publication of the model analysis plan suggested that the information available on BRAVO within the public domain was insufficient to fully implement that engine in a microsimulation model.[54] We therefore reverted to the use of the same risk engine as described in the 2019 ICER report evaluating oral semaglutide.[39,53]

Consistent with the Comparative Clinical Effectiveness assessment, the intervention of interest was tirzepatide plus background therapy versus (1) background therapy alone, (2) injectable semaglutide, and (3) empagliflozin.

The model was informed by clinical trials, the ICER NMA of relevant clinical trials, quality-of-life literature, and validation versus other prior economic models.[53,55,56] The base case analysis took a health care sector perspective and thus focused on direct medical care costs only. Costs and outcomes were discounted at 3% per year.[14] Because no long-term cardiovascular outcomes trial data exist for the primary intervention under examination in this review, tirzepatide, health benefits for all modeled therapies were informed by intermediate outcomes: HbA1c, body weight, LDL, and SBP, that are predictors in the UKPDS-OM2 risk engine.[13] For therapies with existing long-term CVO trials, modeled CVO event risks, predicted by the UKPDS-OM2 equations, were further multiplied by trial-based hazard ratios and their respective confidence intervals.

The model (Figure 4.1) is an individual patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2DM among US adults with the disease. Two modeling steps were used: (1) event microsimulation and (2) calculation of mean results from the pool of simulated patients' lifetime outcomes. Patients, with data from multiple NHANES surveys, were separately simulated through the modeling steps for tirzepatide and each comparator (each added to current ongoing background antihyperglycemic therapy), plus background therapy alone. The two model steps are explained below:

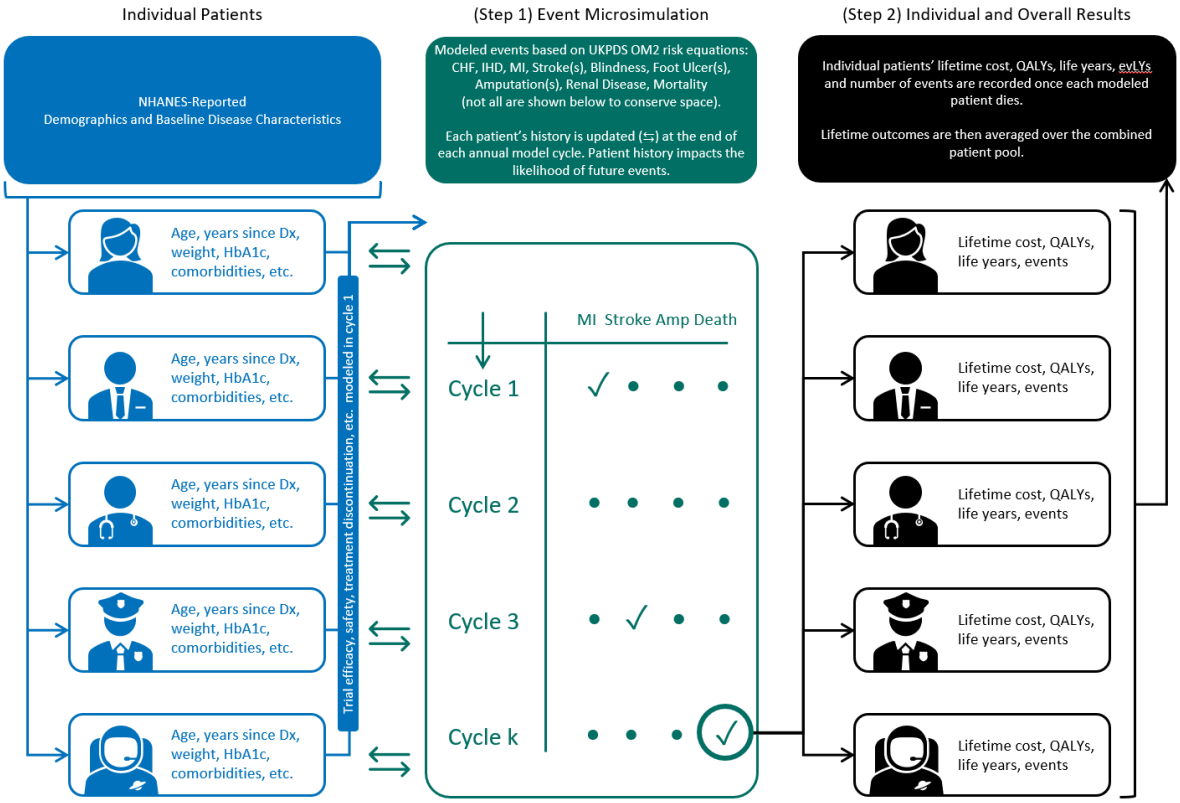
(1) Event microsimulation. Each NHANES patient was sequentially run through the event microsimulation. Each model cycle was one year in duration. The UKPDS-OM2 risk equations were used to calculate the incidence of any clinical event(s) and/or mortality in each year until the simulated patient died. Effects of each included therapy, such as change in HbA1c after the first cycle, were included depending on data availability from the NMA. All event and/or mortality associated costs and health state utility weights were applied concurrently. The

UKPDS-OM2 risk equations accounted for patient history upon entering the model as well as new clinical events that occurred during the microsimulation; for example, a patient who experienced a first MI in a given year of the microsimulation then had the history of MI covariate turned on in each subsequent year.

(2) Calculation of mean results. After each simulated patient died, the model recorded the patient's lifetime cost, quality-adjusted life years (QALYs), equal-value of life years (evLYs), life years, and clinical events. Each outcome was then averaged over the entire pool of patients to derive overall model results.

Further details on the economic modeling methods used are available in Supplement E.

Figure 4.1. Model Structure



4.2. Key Model Assumptions and Inputs

Below is a list of key model choices:

- Long-term survival and the incidence of diabetes-related clinical events were modeled by applying the UKPDS-OM2 risk equations to a US patient population in an event microsimulation, adjusting the risk equation outputs using available long-term outcome data.[13] These equations were created from a population of T2DM patients in the United Kingdom and may not reflect US T2DM patient demographics, including differences in race and differences in risk of T2DM-related events.
- Cardiovascular and nephropathy event rates for injectable semaglutide and empagliflozin were adjusted using data (HRs) from their respective cardiovascular outcomes trials.[10,11] Tirzepatide was not adjusted in the base case, reflecting its currently immature CV and renal outcomes and its lack of in-class comparators to use as proxies, but was adjusted in a scenario analysis. In the scenario, tirzepatide HR adjustment followed the same approach as used for injectable semaglutide, given overlap in GLP-1 RA mechanism of action, but used larger estimates of uncertainty.
- Quality of life was modeled within QALYs using projected patient survival weighted by additive disutilities for each diabetes-related complication experienced in each model cycle.
- The model included all treatment costs associated with each individual drug regimen, including drug acquisition costs, downstream treatments such as insulin, and supportive care costs (e.g., clinician visits and self-monitoring), as well as costs associated with diabetes-related complications experienced in each model cycle.
- All model outcomes were calculated over a lifetime time horizon.[14]
- Life-years, QALYs, equal value life-years (evLYs), and health care cost outcomes were discounted at 3% per year.[14]

Our model included several assumptions stated below.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Modeled risk equation adjustment for CV and renal outcomes for active comparators with CVOT data is maintained while patients remain on treatment.	Active treatment comparators (injectable semaglutide and empagliflozin) have data from CVOTs. We considered adjusting the output of the risk equations based on how the model outcomes compare to those trial outcomes, either in the base case analysis or as a scenario analysis.
Modeled risk equation adjustment for CV and renal outcomes for tirzepatide is maintained while patients remain on treatment.	Long-term effectiveness of tirzepatide is currently unknown. We evaluated the impact of not applying any adjustment relative effect to tirzepatide for changes in CV and renal outcomes in the base case. To assess this assumption, we ran a scenario where tirzepatide had the same relative effect in changes in long-term CV and renal outcome effectiveness as semaglutide (due to the shared GLP-1 RA activity), but with 20% inflated confidence intervals to reflect uncertainty.
Ongoing background therapy was assumed the same for all comparators, and all patients in all model arms who discontinue treatment (including those on background therapy alone) transition to insulin.	The goal is to evaluate direct comparisons among the treatments of interest and not multiple possible treatment sequences.
Patients discontinued their add-on treatment at a rate of 9.1% in the second model cycle. The discontinuation rate was derived from the EMPA-REG-EXTEND trial, the only trial to present discontinuation data contingent on a successful initial treatment period. Subsequent treatment discontinuation occurred when the patient's HbA1c reached 8.5% or above during any model cycle after the first.	Equivalent discontinuation was assumed for active treatments after the initial model cycle as this measure was not included in the NMA and we had insufficient evidence to suggest differential long-term discontinuation across all therapies. We evaluated the 8.5% HbA1c discontinuation threshold in scenario analyses.

The patient population for this analysis was derived from the National Health and Nutrition Examination Survey (NHANES), conducted by the United States Centers for Disease Control and Prevention. Survey participants from years 2013-2014, 2015-2016, and 2017-2018 were included if they had self-reported diabetes, HbA1c levels greater than 7%, and were already taking metformin (with or without sulfonylureas), but not another type of add-on diabetes therapy. This resulted in 387 unique patients, whose characteristics are described in Table 4.2.

Table 4.2. Base-Case Model Cohort Characteristics

Description	Mean (SD) or Percentage (N)
Patient Characteristics	
Age at Time of survey	60.4 (11.53)
% Female	42.9% (166)
Duration of disease	9.9 (7.91)
Race	26.6% (103)
White, %	22.7% (88)
Black or African American, %	14.5% (56)
Asian, %	11.4% (44)
Hispanic, %	24.8% (96)
Other	21.2% (82)
Weight (kg)	88.8 (24.94)
BMI (kg/m^2)	31.9 (7.55)
HbA1c (%)	8.4 (1.54)
LDL (mmol/L)	2.7 (0.93)
SBP (mmHg)	132.5 (18.88)
% Current smokers	36.7% (142)
% on Metformin	100.0% (387)
% on Sulfonylurea	42.9% (166)
Disease History	
Myocardial infarction	5.9% (23)
Stroke	4.4% (17)
Heart failure	4.1% (16)
Ischemic heart disease	7.8% (30)
Angina	4.1% (16)
Renal disease	15.8% (61)

HbA1c: hemoglobin A1c, LDL: low-density lipids, SBP: systolic blood pressure, SD: standard deviation

Clinical inputs regarding the efficacy of tirzepatide, injectable semaglutide, and empagliflozin as compared to background therapy alone on intermediate outcomes such as changes in HbA1c, lipid levels, blood pressure, and body weight were derived from the NMA described in Chapter 3. Each model cycle utilized updated patient-level input parameters based on the predictions of the UKPDS-OM2 risk equations and patient history. To supplement UKPDS-OM2 output, time-varying values of HbA1c and weight were calculated using additional published equations.[57]

Health state utilities and mortality risk equations are detailed in Supplement E2.

Calculated net drug prices were applied to each patient while they remained on treatment. For each comparator, we obtained net pricing estimates from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price.[58] We estimated net prices by comparing the most recent four-quarter averages (i.e., third quarter of 2020 through second quarter of 2021) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (accessed September 2021) to arrive at an estimated net price per unit. Tirzepatide was given a placeholder price equal to semaglutide, the only suitable proxy drug in the injectable GLP drug class, until its price is publicly available. Drug cost inputs can be found in Table 4.3.

Table 4.3. Drug Cost Inputs

Drug	WAC per 30-Pill Bottle/Pen	Net Price Per 30-Pill Bottle/Pen	Discount From WAC	Net Price per Year‡
Tirzepatide*	(4 weekly doses)	(4 weekly doses)		Placeholder $4,643.50
Semaglutide (Ozempic®) 4 mg/3 mL pen†	$851.60 (4 weekly doses)	$355.97 (4 weekly doses)	58.20%	$4,643.50
Empagliflozin (Jardiance®) 30-tablet bottle§	$548.54	$107.51	80.40%	$1,402.43
Metformin#	$0.83	-	-	$10.04
Sulfonylureas¤	$5.05	-	-	$61.48

WAC: wholesale acquisition cost
*As a placeholder, we used the net price of Ozempic® (semaglutide), which is a once weekly injectable GLP-1; WAC pricing and discounts reflect the number of pen doses and quantity of pens necessary for Ozempic® use.
†The 4 mg/3 mL Ozempic® pen includes four 1 mg doses; assumes 1 mg weekly dose.
‡1 year = 365.25 days or 52 weeks
§Assumes 25 mg daily dose of Jardiance® (empagliflozin). Source: Red Book.
#Assumes 1000 mg daily dose of metformin. Source: Red Book.
¤Assumes 20 mg daily dose of glipizide. Source: Red Book.

The average clinical costs of experiencing a diabetes-related event within a cycle, as well as the average annual clinical costs of subsequent years after a health event, were adapted from the literature.[52,59,60] Patients were able to experience events concurrently within the model. Costs were inflated to 2021 USD. Additional details on the economic model can be found in Supplement E.

4.3. Results

Base-Case Results

Due to the characteristics of the microsimulation, the model's base-case results are presented as the mean and 95% credible range estimates from probabilistic sensitivity analyses, by jointly varying all model parameters and UKPDS-OM2 risk engine equation coefficients over 3,000 simulations per patient, then calculating 95% credible range estimates for each model outcome based on the distributions of those simulations. The base-case results are presented in Table 4.4, with incremental comparisons of tirzepatide to the three comparators presented in Table 4.5.

Table 4.4. Results for the Base Case for Tirzepatide and Comparators: Injectable Semaglutide, Empagliflozin, and Background Therapy – Mean (95% Credible Range)*

	Add-On Drug Cost		Total Cost (including background therapy and insulin)		QALYs		Life-years		evLYs‡	
Treatment	Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range
Tirzepatide†	$30,000	($29,000 to $32,000)	$284,000	($255,000 to $315,000)	4.69	(4.48 to 4.90)	8.87	(8.44 to 9.31)	4.97	(4.63 to 5.33)
Injectable Semaglutide	$29,000	($28,000 to $31,000)	$289,000	($260,000 to $318,000)	4.76	(4.55 to 4.95)	9.22	(8.77 to 9.64)	5.17	(4.82 to 5.51)
Empagliflozin	$7,000	($6,800 to $7,700)	$264,000	($238,000 to $293,000)	4.49	(4.29 to 4.67)	8.83	(8.42 to 9.22)	4.78	(4.44 to 5.10)
Background therapy	$0	NA	$263,000	($235,000 to $291,000)	4.14	(3.95 to 4.32)	8.35	(7.93 to 8.77)	4.14	(3.95 to 4.32)

*All costs and outcomes discounted at 3% annually

†Using a Placeholder Price equal to the net price of semaglutide

‡All evLY estimates were calculated against background therapy alone within the microsimulation with background therapy evLYs equal to QALYs.

Of the known drug costs, injectable semaglutide had the highest lifetime drug costs at $30,000 (a placeholder cost was used for tirzepatide). For total lifetime costs, including background treatment costs and costs of cardiovascular and renal complications, injectable semaglutide had the highest costs at approximately $289,000, followed by tirzepatide ($284,000), empagliflozin ($264,000), and background therapy ($263,000). Injectable semaglutide was estimated to produce the highest QALYs of all considered therapies, however the QALY 95% credible ranges for active comparators overlapped. Treatment with tirzepatide and semaglutide produced higher QALYs than background therapy alone. As compared to background therapy alone, semaglutide produced the highest evLYs, followed by tirzepatide and empagliflozin.

Table 4.5. Incremental Cost-Effectiveness Ratios for the Base Case – Mean (95% CR)†

Treatment	Comparator	Cost per QALY Gained		Cost per Life Year Gained		Cost per evLY Gained‡	
		Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range
Tirzepatide*	Background therapy	$38,000	(-$33,000 to $91,000)	$41,000	(-$94,000 to $150,000)	$23,000	(-$23,000 to $60,000)
Tirzepatide*	Injectable Semaglutide	Less Costly and Less Effective	(-$1,469,000 to $1,541,000)	Less Costly and Less Effective	(-$346,000 to $377,000)	NA	NA
Tirzepatide*	Empagliflozin	$96,000	(-$408,000 to $594,000)	$472,000	(-$1,069,000 to $1,071,000)	NA	NA

*Using a Placeholder Price equal to the net price of semaglutide

†Ratios and credible ranges displayed in table are the mean values across all microsimulations rather than derivations of output in table 4.4

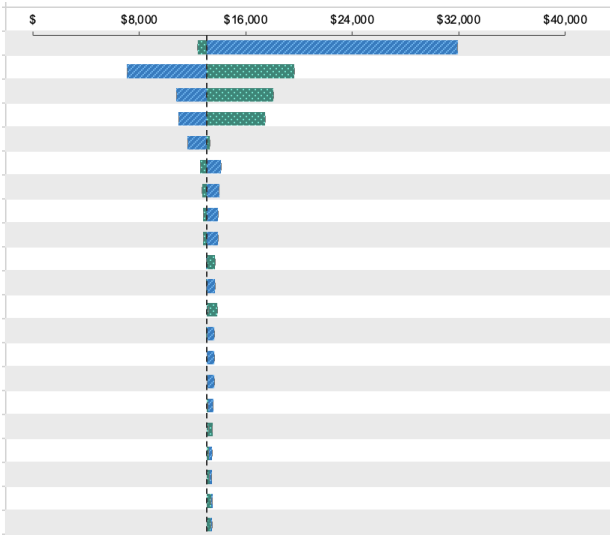
‡All evLY Gained estimates were calculated against background therapy alone, precluding incremental comparisons between therapies

The incremental cost-effectiveness measures reported in Table 4.5 are based on a placeholder price equal to the net value of injectable semaglutide and should be interpreted with caution.

Sensitivity Analyses

One-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes were performed. Details about the sensitivity analysis methods can be found in Supplement E4. Compared to background therapy alone, the inputs that were associated with the largest variation in incremental costs were the tirzepatide event hazard ratios, tirzepatide's annual price, and the HbA1c discontinuation threshold (Figure 4.2). The tornado diagram for incremental costs was truncated to include inputs with at least a $100 difference between the high and low value. Compared to background therapy alone, the inputs that were associated with the largest variation in incremental QALYs were the tirzepatide event hazard ratios, the baseline T2DM patient utility value, and other disutilities (Figure 4.3). The tornado diagram for incremental QALYs was truncated to include inputs with at least a 0.01 QALY difference between the high and low value.

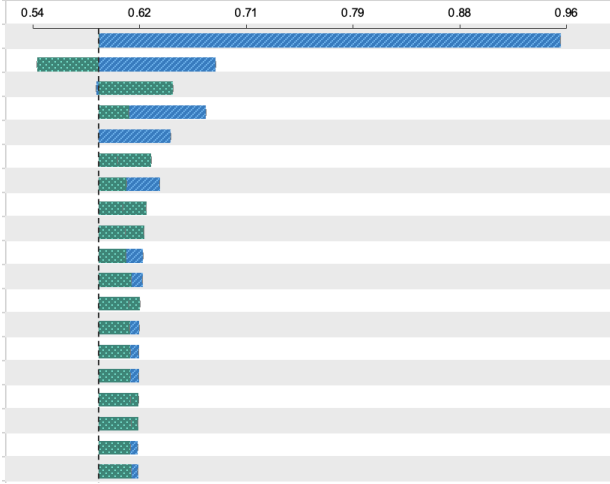
Figure 4.2. Incremental Costs Tornado Diagram (Tirzepatide versus Background Therapy Alone)*



Parameter	Low Result	High Result	Spread
Tirzepatide MACE HR vs. Background Tx	$31,931	$12,387	$19,544
Tirzepatide Annual Cost	$7,069	$19,651	$12,582
HbA1c Discontinuation Threshold	$10,768	$18,080	$7,312
Tirzepatide CHF HR vs. Background Tx	$10,953	$17,449	$6,495
Tirzepatide Nephr. HR vs. Background Tx	$11,609	$13,318	$1,710
Premix Insulin Cost/Unit	$14,142	$12,577	$1,565
Basal Insulin Cost/Unit	$14,014	$12,706	$1,308
Requiring Hospitalization Cost	$13,922	$12,798	$1,124
Blindness History Cost	$13,915	$12,805	$1,110
Outpatient visit Costs: noninsulin	$13,017	$13,702	$684
Myocardial infarction Cost	$13,690	$13,029	$661
Tirzepatide Weight Change	$13,215	$13,870	$655
Congestive heart failure Cost	$13,650	$13,069	$581
Outpatient visit Costs: insulin	$13,648	$13,071	$577
Congestive heart failure History Cost	$13,631	$13,089	$542
Stroke Cost	$13,546	$13,174	$372
Renal Disease History Cost	$13,213	$13,507	$294
Bolus Insulin Cost/Unit	$13,489	$13,231	$258
Myocardial infarction History Cost	$13,434	$13,285	$149
Tirzepatide HbA1c Change	$13,500	$13,387	$113
Background Tx Initial Discontinuation	$13,463	$13,360	$103

*Using a placeholder price for tirzepatide

Figure 4.3. Incremental QALYs Tornado Diagram (Tirzepatide versus Background Therapy Alone)



Parameter	Low Result	High Result	Spread
Tirzepatide MACE HR vs. Background Tx	0.96	0.59	0.36
Tirzepatide CHF HR vs. Background Tx	0.68	0.54	0.14
Baseline T2DM Utility	0.59	0.65	0.06
Tirzepatide Nephr. HR vs. Background Tx	0.68	0.62	0.06
Annual Disutility for Tx Injection	0.65	0.59	0.06
Hypoglycemia history Disutility	0.61	0.63	0.03
HbA1c Discontinuation Threshold	0.64	0.61	0.03
Diabetes duration (per year) Disutility	0.61	0.63	0.02
Age at diagnosis (per year ≥52) Disutility	0.61	0.63	0.02
BMI (per unit ≥32) Disutility	0.63	0.61	0.01
Tirzepatide HbA1c Change	0.63	0.62	0.01
Hispanic Disutility	0.62	0.62	0.01
Hypoglycemia event Disutility	0.62	0.62	0.01
Blindness history Disutility	0.62	0.62	0.01
Congestive heart failure history Disutility	0.62	0.62	0.01
Female Disutility	0.62	0.62	0.01
Current smoker Disutility	0.62	0.62	0.01
Tirzepatide Weight Change	0.62	0.62	0.01
Tirzepatide Initial Discontinuation	0.62	0.62	0.01

Unlike a typical cohort model, our probabilistic sensitivity analysis for this microsimulation is presented as the base case results in order to account for patient and risk equation uncertainty.

Scenario Analyses

Multiple scenario analyses can be found in Supplement E5. We sought to produce model estimates using a modified societal perspective and found a paucity of data to inform such calculations for a simulation. However, we present a calculated estimate of cost-effectiveness under a modified societal perspective using an estimate of productivity costs saved based on assumptions that fill in missing data. The results of these calculations are also presented in the Supplement.

Threshold Analyses

The annual drug costs at which tirzepatide would reach cost-effectiveness thresholds ranging from $50,000 to $200,000 per QALY gained as well as per evLYG, compared to background therapy, are presented below in Table 4.6.

Table 4.6. Cost per Outcome Threshold Analysis Results for Tirzepatide vs Background Therapy

	Net Price per Unit	Annual Price to Achieve $50,000 per outcome	Annual Price to Achieve $100,000 per outcome	Annual Price to Achieve $150,000 per outcome	Annual Price to Achieve $200,000 per outcome
QALY outcome – mean (95% credible range)	To be determined	$4,800 ($3,700 to $5,900)	$5,200 ($4,100 to $6,500)	$5,700 ($4,400 to $7,000)	$6,100 ($4,800 to $7,700)
evLY Gained outcome – mean (95% credible range)	To be determined	$5,000 ($3,900 to $6,100)	$5,700 ($4,400 to $7,000)	$6,300 ($4,800 to $7,900)	$7,000 ($5,300 to $8,900)

evLY Gained – equal-value life-years gained, QALY– quality-adjusted life-year
Net price for tirzepatide has not been publicly stated at the time of this report

Model Validation

We used several approaches to validate the microsimulation model's output. First, we provided the preliminary methods to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined the model approach, and will accept feedback on this draft report to allow us to refine data inputs used in the model. Second, we varied the model input parameters to evaluate the face validity of changes to those inputs on the results. We also performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we are also sharing the model with the manufacturers for external verification following the publication of this draft report.

For further model validation and calibration, we plan to compare the cardiovascular and renal trial outcomes versus model projections in the revised report. This comparison will be informed by microsimulations on modified patient populations and for a shorter time horizon to reflect specific trial conditions more accurately.

Uncertainty and Controversies

This model represents a simplified version of a complex disease and should therefore be interpreted with its limitations in mind. Cost and long-term outcome data for tirzepatide were unavailable at the time of the report and could not be used to validate its clinical results; any economic output for tirzepatide is based on a placeholder price and the results should not be interpreted as factual. Additionally, there are noted limitations to the UKPDS-OM2 risk equations used for this analysis, including that they were developed based on a patient cohort from the United Kingdom in decades past and may not fully capture the impact of weight loss on CV and renal outcomes. Our choice to use UKPDS-OM2 risk equations was made based on lack of feasible alternatives at the time, and adjustments were used in an attempt to ensure the model estimates aligns with clinical evidence. We plan to present shorter time horizon simulations, aligned with the cardiovascular and renal outcomes trials for semaglutide and empagliflozin, in the revised report in order to compare our model event outcomes with those found in the trials.

Finally, we acknowledge challenges in modeling tirzepatide given the immaturity of the evidence of its impact on micro- and macrovascular outcomes. In the draft threshold analyses, we compared tirzepatide to background therapy alone and estimated the health gains of tirzepatide through changes in intermediate outcomes. The scenario analysis that includes tirzepatide's changes in intermediate outcomes as well as reductions in cardiovascular outcomes (assuming the same hazard ratios as injectable semaglutide) provides estimates of the potential relative impact on health outcomes if the trends observed in tirzepatide's cardiovascular safety study are confirmed.

4.4 Summary and Comment

We used a patient-level microsimulation of T2DM patients taking an add-on therapy over a lifetime time horizon to assess the cost-effectiveness of the novel injectable agent tirzepatide in addition to background therapy against background therapy alone, injectable semaglutide, and empagliflozin. We found that tirzepatide produced a slightly lower point estimate for QALYs compared to injectable semaglutide, but higher versus empagliflozin and background therapy alone. Credible ranges for lifetime discounted QALYs did not overlap for tirzepatide versus background therapy alone but did overlap comparing tirzepatide to both injectable semaglutide and empagliflozin. The incremental cost per QALY gained for tirzepatide compared to empagliflozin and background therapy were under $100,000 when setting tirzepatide's placeholder price equal to semaglutide. Uncertainty analyses suggested a wide range of plausible cost-effectiveness estimates for tirzepatide.

5. Contextual Considerations and Potential Other Benefits

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

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on the severity of the condition being treated	Although there are multiple medication options for the treatment of T2DM, nearly half of patients have not reached adequate glycemic control.[1] Thus, additional options for treatment are beneficial.
Magnitude of the lifetime impact on individual patients of the condition being treated	Patients with inadequately controlled T2DM are at risk for microvascular and macrovascular complications, which can substantially affect both quality of life and longevity. Additionally, many patients with T2DM are overweight or obese, and weight loss may be of benefit to prevent complications of obesity.
Other (as relevant)	NA

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Prevention or delay of microvascular and macrovascular complications may allow for greater work or educational productivity.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Prevention or delay of microvascular and macrovascular complications may lessen caregiving burden over the lifetime.
Patients' ability to manage and sustain treatment given the complexity of regimen	The medication delivery device may be preferred by some patients compared with the delivery device of other GLP-1 RAs.
Health inequities	T2DM disproportionately affects minority populations, and significant disparities exist in prevalence, disease control, and rates of complications.[61] ICER calculated the Health Improvement Distribution Index, looking at the relative proportion of any health gains from treatment of T2DM for the following groups with a higher prevalence of T2DM than the general US population (see Supplement A1): American Indian/Alaska Native = 1.4 Hispanic = 1.2 Asian Indian = 1.2 Non-Hispanic Black = 1.1
Other (as relevant)	NA

The main potential other benefit of tirzepatide relates to its impact on obesity and obesity-related diseases and complications. The majority of patients in the US with T2DM are overweight or obese, and at risk for obesity-related complications – e.g., obstructive sleep apnea, nonalcoholic fatty liver disease, high blood pressure, cardiovascular disease, and osteoarthritis – any medication that induces weight loss could have beneficial effects outside of its impact on glycemic control. Tirzepatide appears to induce more substantial weight loss in patients than its comparator drugs, and thus may have an impact on obesity-related diseases as well.

Additionally, a substantial number of patients achieved near-normal glycemic control (defined as a HbA1c <5.7%) in SURPASS-2. Not only is this a boost to patients, who cite glycemic control as one of the more important outcomes for managing their diabetes, but it may also slow progression of disease, particularly if achieved early in the disease course.[19] Prevention of progression and potentially of development of the micro- and macrovascular complications of T2DM could both improve the productivity of patients and lessen caregiving burden. For example, prevention of diabetic neuropathy may lead to fewer amputations and thus less disability.

6. Health Benefit Price Benchmarks

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

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Using results from the cost-effectiveness model, we estimated the potential budget impact of adding tirzepatide for patients with T2DM with inadequate glycemic control on current background therapy. We used the tirzepatide placeholder price from the base-case analysis (placeholder price of $4,643.50 per year) and three threshold prices (at $50,000, $100,000, and $150,000 per QALY). Potential budget impact is defined as the total differential cost of using tirzepatide rather than the relevant existing therapy for the treated population, calculated as differential health care costs (including intervention costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon.

The analysis included the estimated number of individuals in the US who would be eligible for tirzepatide. To estimate the size of the potential candidate population for treatment, we used inputs for the total US adult population size (~265 million)[62], overall T2DM prevalence (14.6%)[63] proportion of patients with diagnosed T2DM (76.7%)[63], and the proportion of patients having failed background therapy and considering a second-line treatment and thus eligible for tirzepatide (16.2%).[64] Applying these sources results in estimates of 4,805,931 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate tirzepatide treatment in each of the five years, or approximately 961,186 patients per year. Tirzepatide drew market share proportionally from each of the model comparators over the five-year time horizon.

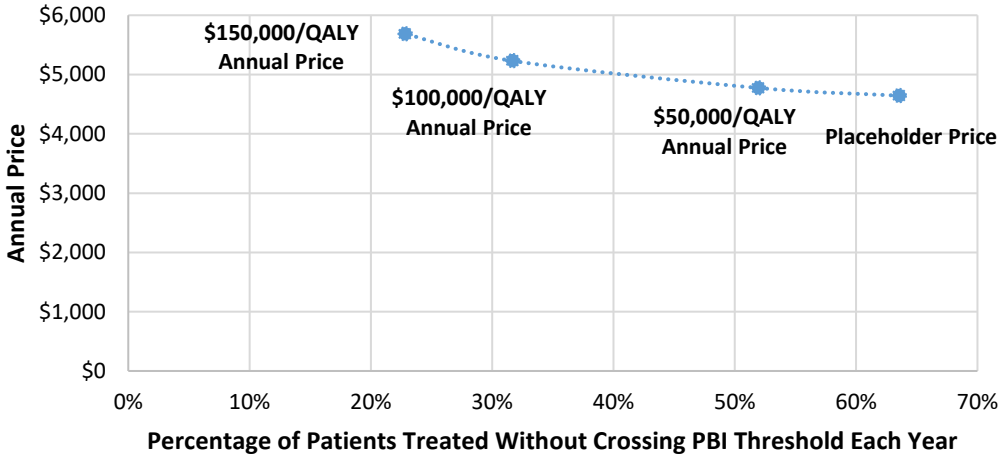
Market shares were derived from analyst projections based on primary market research, company reports, and key opinion leader surveys.[65] Specifically, we set the initial market shares for injectable semaglutide equal to a calculated 2021 market share for the GLP-1 RA class (15.1%), while the market share for empagliflozin was set to a calculated 2021 market share for the SGLT-2 inhibitor class (12.7%). The remaining market share was attributed to background therapy.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices within five years without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2021-2022, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $734 million per year for new drugs.

7.2. Results

Assuming the placeholder price of $4,643.50 per year, 63.6% of the eligible patients could be treated within five years (assuming 20% uptake each year), without crossing the ICER potential budget impact threshold of $734 million per year. In contrast, 51.9%, 31.7%, and 22.8% of eligible patients could be treated within five years without crossing the ICER potential budget impact threshold at the annual price to reach $50,000/QALY ($4,800), $100,000/QALY ($5,200), or $150,000/QALY ($5,700), respectively. Figure 7.1 depicts the potential budgetary impact of tirzepatide at the placeholder price and the three threshold prices.

Figure 7.1. Budgetary Impact of Tirzepatide in Adults with T2DM at Placeholder Price and Threshold Annual Prices



References

1. Centers for Disease Control and Prevention USDoHaHS. *National Diabetes Statistics Report, 2020.* Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services;2020.
2. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes.* 2008;26(2):77-82.
3. American Diabetes A. 1. Improving Care and Promoting Health in Populations: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S7-S13.
4. Caraballo C, Valero-Elizondo J, Khera R, et al. Burden and Consequences of Financial Hardship From Medical Bills Among Nonelderly Adults With Diabetes Mellitus in the United States. *Circ Cardiovasc Qual Outcomes.* 2020;13(2):e006139.
5. American Diabetes A. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S66-S76.
6. American Diabetes A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S98-S110.
7. American Diabetes A. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S111-S134.
8. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *The Lancet (British edition).* 2018;392(10160):2180-2193.
9. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes (SURPASS-2). *The New England journal of medicine.* 2021;385(6):503-515.
10. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6). *The New England journal of medicine.* 2016;375(19):1834-1844.
11. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG-OUTCOME). *The New England journal of medicine.* 2015;373(22):2117-2128.
12. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):323-334.
13. Hayes AJ, Leal J, Gray A, Holman R, Clarke P. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia.* 2013;56(9):1925-1933.
14. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.
15. Bae JP, Lage MJ, Mo D, Nelson DR, Hoogwerf BJ. Obesity and glycemic control in patients with diabetes mellitus: Analysis of physician electronic health records in the US from 2009-2011. *J Diabetes Complications.* 2016;30(2):212-220.
16. American Diabetes A. 8. Obesity Management for the Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S89-S97.
17. Piccolo RS, Subramanian SV, Pearce N, Florez JC, McKinlay JB. Relative Contributions of Socioeconomic, Local Environmental, Psychosocial, Lifestyle/Behavioral, Biophysiological, and Ancestral Factors to Racial/Ethnic Disparities in Type 2 Diabetes. *Diabetes Care.* 2016;39(7):1208-1217.

18. Meng YY, Diamant A, Jones J, et al. Racial and Ethnic Disparities in Diabetes Care and Impact of Vendor-Based Disease Management Programs. *Diabetes Care.* 2016;39(5):743-749.
19. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet.* 2010;376(9739):419-430.
20. American Diabetes A. Addendum. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43(Suppl. 1):S111-S134. *Diabetes Care.* 2020;43(8):1977-1978.
21. American Diabetes A. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2021. *Diabetes Care.* 2021;44(Suppl 1):S73-s84.
22. He X, Li J, Wang B, et al. Diabetes self-management education reduces risk of all-cause mortality in type 2 diabetes patients: a systematic review and meta-analysis. *Endocrine.* 2017;55(3):712-731.
23. Strawbridge LM, Lloyd JT, Meadow A, Riley GF, Howell BL. One-Year Outcomes of Diabetes Self-Management Training Among Medicare Beneficiaries Newly Diagnosed With Diabetes. *Med Care.* 2017;55(4):391-397.
24. Han Y, Xie H, Liu Y, Gao P, Yang X, Shen Z. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. *Cardiovasc Diabetol.* 2019;18(1):96.
25. Bradley C, Lewis KS. Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. *Diabet Med.* 1990;7(5):445-451.
26. Sun F, Chai S, Yu K, et al. Gastrointestinal adverse events of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes technology & therapeutics.* 2015;17(1):35-42.
27. Chaplin S. SGLT2 inhibitors and risk of genitourinary infections. *Prescriber.* 2016;27(12):26-30.
28. Douros A, Lix LM, Fralick M, et al. Sodium–glucose cotransporter-2 inhibitors and the risk for diabetic ketoacidosis: a multicenter cohort study. *Annals of Internal Medicine.* 2020;173(6):417-425.
29. Administration. UDoHaHSFaD. Guidance for Industry. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. In: Food and Drug Administration H, ed2008:77724-77725.
30. Gelhorn H, Balantac Z, Shinde S, Thieu VT, Boye KS. The Burden of Type 2 Diabetes and the Value of Achieving Near Normoglycemia from the Patient Perspective. *Diabetes Ther.* 2021;12(7):1821-1837.
31. Min T, Bain SC. The Role of Tirzepatide, Dual GIP and GLP-1 Receptor Agonist, in the Management of Type 2 Diabetes: The SURPASS Clinical Trials. *Diabetes therapy.* 2021;12(1):143-157.
32. Frias JP, Nauck MA, Van J, et al. Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: A 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. *Diabetes, obesity & metabolism.* 2020;22(6):938-946.
33. Trials C. A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT). U.S National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT04255433. Published 2021. Accessed2021.

34. Del Prato S, Kahn S. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *The Lancet.* 2021.
35. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™). *Cardiovascular diabetology.* 2014;13(1):1-8.
36. Association AD. 8. Cardiovascular Disease and Risk Management. *Diabetes Care.* 2016;39(Supplement 1):S60-S71.
37. Lilly E. Data on File. In:2021.
38. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA.* 2019;321(15):1466-1480.
39. Rind DM, Guzaukas G, Fazioli K, et al. *Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value.* Institute for Clinical and Economic Review;2019.
40. Lilly's tirzepatide achieves all primary and key secondary study outcomes against insulin glargine in adults with type 2 diabetes and increased cardiovascular risk in SURPASS-4 trial [press release]. Lilly2021.
41. Bain SC, Klufas MA, Ho A, Matthews DR. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: a review. *Diabetes, Obesity and Metabolism.* 2019;21(3):454-466.
42. FDA. OZEMPIC (semaglutide) Injection Package Insert. In. U.S Food & Drug Administration2021.
43. FDA. JARDIANCE (Empagliflozin tablets) Package Insert. In. U.S Food & Drug Administration2021.
44. US FDA grants Fast Track designation to Jardiance® for the treatment of chronic kidney disease [press release]. 2021.
45. American Diabetes A. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S135-S151.
46. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse effects of GLP-1 receptor agonists. *The review of diabetic studies: RDS.* 2014;11(3):202.
47. Heimburger SM, Bergmann NC, Augustin R, Gasbjerg LS, Christensen MB, Knop FK. Glucose-dependent insulinotropic polypeptide (GIP) and cardiovascular disease. *Peptides.* 2020;125:170174.
48. Jujic A, Atabaki-Pasdar N, Nilsson PM, et al. Glucose-dependent insulinotropic peptide and risk of cardiovascular events and mortality: a prospective study. *Diabetologia.* 2020;63(5):1043-1054.
49. Kahles F, Ruckbeil MV, Arrivas MC, et al. Association of Glucose-Dependent Insulinotropic Polypeptide Levels With Cardiovascular Mortality in Patients With Acute Myocardial Infarction. *J Am Heart Assoc.* 2021;10(13):e019477.
50. Mori Y, Matsui T, Hirano T, Yamagishi SI. GIP as a Potential Therapeutic Target for Atherosclerotic Cardiovascular Disease-A Systematic Review. *Int J Mol Sci.* 2020;21(4).
51. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9(10):653-662.
52. Laiteerapong N, Cooper JM, Skandari MR, et al. Individualized Glycemic Control for U.S. Adults With Type 2 Diabetes: A Cost-Effectiveness Analysis. *Ann Intern Med.* 2018;168(3):170-178.
53. Guzauskas GF, Rind DM, Fazioli K, Chapman RH, Pearson SD, Hansen RN. Cost-effectiveness of oral semaglutide added to current antihyperglycemic treatment for type 2 diabetes. *Journal of Managed Care & Specialty Pharmacy.* 2021;27(4):455-468.

54. Shao H, Fonseca V, Stoecker C, Liu S, Shi L. Novel risk engine for diabetes progression and mortality in USA: building, relating, assessing, and validating outcomes (BRAVO). *Pharmacoeconomics.* 2018;36(9):1125-1134.
55. Hong D, Si L, Jiang M, et al. Cost effectiveness of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors: a systematic review. *Pharmacoeconomics.* 2019;37(6):777-818.
56. Reifsnider OS, Kansal AR, Gandhi PK, et al. Cost-effectiveness of empagliflozin versus canagliflozin, dapagliflozin, or standard of care in patients with type 2 diabetes and established cardiovascular disease. *BMJ Open Diabetes Research and Care.* 2021;9(1):e001313.
57. Willis M, Asseburg C, Nilsson A, Johnsson K, Kartman B. Multivariate Prediction Equations for HbA1c Lowering, Weight Change, and Hypoglycemic Events Associated with Insulin Rescue Medication in Type 2 Diabetes Mellitus: Informing Economic Modeling. *Value Health.* 2017;20(3):357-371.
58. SSR Health L. https://www.ssrhealth.com/. Published 2018. Accessed.
59. Ward A, Alvarez P, Vo L, Martin S. Direct medical costs of complications of diabetes in the United States: estimates for event-year and annual state costs (USD 2012). *J Med Econ.* 2014;17(3):176-183.
60. Yang W, Cintina I, Hoerger T, et al. Estimating costs of diabetes complications in people< 65 years in the US using panel data. *Journal of Diabetes and its Complications.* 2020;34(12):107735.
61. Peek ME, Cargill A, Huang ES. Diabetes health disparities: a systematic review of health care interventions. *Med Care Res Rev.* 2007;64(5 Suppl):101S-156S.
62. US Census Bureau. 2017 National Population Projections Datasets. Projected Population by Single Year of Age, Sex, Race, and Hispanic Origin for the United States: 2016 to 2060. 2017.
63. Wang L, Li X, Wang Z, et al. Trends in Prevalence of Diabetes and Control of Risk Factors in Diabetes Among US Adults, 1999-2018. *JAMA.* 2021;326(8):704-716.
64. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. In: Prevention CfDCa, ed2018.
65. Datamonitor. Patient-Based Forecast Model - Diabetes Type 2. 2021.
66. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S14-S31.
67. Group UPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The lancet.* 1998;352(9131):837-853.
68. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;139(25):e1082-e1143.
69. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.
70. Tsai IT, Wang CP, Lu YC, et al. The burden of major adverse cardiac events in patients with coronary artery disease. *BMC Cardiovasc Disord.* 2017;17(1):1.
71. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ.* 1992;305(6846):160-164.

72. Kolotkin RL, Head S, Brookhart A. Construct validity of the Impact of Weight on Quality of Life Questionnaire. *Obes Res.* 1997;5(5):434-441.
73. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of Real-time Continuous Glucose Monitoring With Glycemic Control and Acute Metabolic Events Among Patients With Insulin-Treated Diabetes. *JAMA.* 2021;325(22):2273-2284.
74. Martens TW, Beck RW, Bergenstal RM. Continuous Glucose Monitoring and Glycemic Control in Patients With Type 2 Diabetes Treated With Basal Insulin-Reply. *JAMA.* 2021;326(13):1330-1331.
75. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA.* 2019;322(12):1155-1166.
76. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care.* 2010;33(8):1859-1864.
77. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA.* 2007;298(10):1189-1195.
78. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet.* 2005;366(9493):1279-1289.
79. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* 2009;373(9681):2125-2135.
80. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care.* 2008;31(5):845-851.
81. Pratley RE, Salsali A. Inhibition of DPP-4: a new therapeutic approach for the treatment of type 2 diabetes. *Curr Med Res Opin.* 2007;23(4):919-931.
82. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA.* 2007;298(2):194-206.
83. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol.* 2021;6(2):148-158.
84. Ueda P, Svanstrom H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ.* 2018;363:k4365.
85. Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. *Diabetes Spectr.* 2017;30(3):202-210.
86. Samms RJ, Coghlan MP, Sloop KW. How May GIP Enhance the Therapeutic Efficacy of GLP-1? *Trends Endocrinol Metab.* 2020;31(6):410-421.
87. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. *Endocr Pract.* 2020;26(1):107-139.
88. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *European heart journal.* 2020;41(2):255-323.
89. Excellence NIfHaC. Type 2 diabetes in adults: management. In:2015.

90. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
91. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current. Published 2020. Accessed.
92. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine.* 2009;6(7):e1000097.
93. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. Published 2008. Accessed.
94. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care.* 2010;48(6 Suppl):S145-152.
95. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. https://icer.org/evidence-rating-matrix/. Published 2020. Updated January 31, 2020. Accessed.
96. Ahrén BP, Masmiquel LP, Kumar HM, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *The lancet Diabetes & endocrinology.* 2017;5(5):341-354.
97. Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide versus Empagliflozin in Patients with Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care.* 2019:dc190883.
98. Ahren B, Johnson SL, Stewart M, et al. HARMONY 3: 104-Week Randomized, Double-Blind, Placebo- and Active-Controlled Trial Assessing the Efficacy and Safety of Albiglutide Compared With Placebo, Sitagliptin, and Glimepiride in Patients With Type 2 Diabetes Taking Metformin. *Diabetes care.* 2014;37(8):2141-2148.
99. Salsali A, Kim G, Woerle HJ, Broedl UC, Hantel S. Cardiovascular safety of empagliflozin in patients with type 2 diabetes: a meta-analysis of data from randomized placebo-controlled trials. *Diabetes, obesity & metabolism.* 2016;18(10):1034-1040.
100. Shi F-H, Li H, Cui M, Zhang Z-L, Gu Z-C, Liu X-Y. Efficacy and Safety of Once-Weekly Semaglutide for the Treatment of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in pharmacology.* 2018;9:576-576.
101. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
102. Lundqvist A, Steen Carlsson K, Johansen P, Andersson E, Willis M. Validation of the IHE cohort model of type 2 diabetes and the impact of choice of macrovascular risk equations. *PLoS One.* 2014;9(10):e110235.
103. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE diabetes model. *Value in Health.* 2014;17(6):714-724.
104. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. *American journal of preventive medicine.* 2007;32(4):328-333.
105. Weng L-C, Preis SR, Hulme OL, et al. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. *Circulation.* 2018;137(10):1027-1038.
106. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *Journal of diabetes and its complications.* 2018;32(5):501-511.
107. Neuwahl SJ, Zhang P, Chen H, et al. Patient Health Utility Equations for a Type 2 Diabetes Model. *Diabetes Care.* 2021;44(2):381-389.

108. Shao H, Yang S, Fonseca V, Stoecker C, Shi L. Estimating quality of life decrements due to diabetes complications in the United States: the Health Utility Index (HUI) diabetes complication equation. *Pharmacoeconomics.* 2019;37(7):921-929.
109. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *The European Journal of Health Economics.* 2011;12(3):219-230.
110. Sullivan PW, Ghushchyan VH. EQ-5D scores for diabetes-related comorbidities. *Value in health.* 2016;19(8):1002-1008.
111. Dall TM, Yang W, Gillespie K, et al. The economic burden of elevated blood glucose levels in 2017: diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes. *Diabetes care.* 2019;42(9):1661-1668.
112. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value Health.* 2019;22(8):931-941.
113. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/our-approach/methods-process/value-assessment-framework/. Published 2020. Accessed.
114. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value Health.* 2018;21(3):258-265.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Diagnosis of Type 2 Diabetes Mellitus (T2DM): T2DM is characterized by progressive loss of adequate insulin secretion by pancreatic beta cells, frequently on the background of insulin resistance.[66] The diagnosis is made if any of the following criteria are met: (a) fasting plasma glucose ≥ 126 mg/dL; (b) 2-hour post-prandial glucose ≥ 200 mg/dL during 75-gram oral glucose tolerance test; (c) HbA1c ≥ 6.5%; or (d) random plasma glucose ≥ 200 mg/dL and symptoms of hyperglycemia.

Glycated Hemoglobin (HbA1c): Blood test that measures the amount of glycated red blood cells in the blood. It reflects average blood sugar levels over the past 2-3 months and increases as the amount of glucose increases in the blood. Patients with HbA1c ≥ 6.5% are considered to have diabetes.

Microvascular complications: Persistent exposure to high levels of blood glucose can lead to damage to small blood vessels in the eyes, kidney, and nerves.

- Retinopathy (eye): Most common microvascular complication, causing around 10,000 new cases of blindness each year in the US.[2] Most cases develop within 7-20 years after diagnosis.[67]
- Nephropathy (kidney): Leading cause of renal failure in the US, can be present at diagnosis. [2,45] Characterized by elevated levels of protein in the urine and/or decreased estimated glomerular filtration rate (eGFR).[45]
- Neuropathy (nerves): Characterized by symptoms or signs of peripheral nerve dysfunction (e.g., burning, tingling, numbness, sensory loss to light touch, vibration or temperature, autonomic dysfunction) in people with diabetes, after excluding other causes.[45] Can lead to foot ulcers, injury from falls, and ultimately limb amputation.[2]

Macrovascular complications: Diseases characterized by atherosclerosis, including coronary artery disease and cerebrovascular disease. Patients with T2DM have a much higher risk of cardiovascular events such as myocardial infarction or stroke, and cardiovascular death is the most common cause of death in patients with diabetes.[2]

Cardiovascular Outcomes Trial (CVOT): Long-term, prospective trials of diabetes drugs specifically examining cardiovascular safety. CVOTs became required by the FDA in 2008 for the approval of new diabetes drugs due to cardiovascular safety concerns raised by rosiglitazone, a thiazolidinedione.[29] Trial results must demonstrate that the upper bound of the 95% confidence interval of the hazard ratio for cardiovascular events is less than 1.8 for a drug to be considered safe from a cardiovascular perspective. CVOTs have been conducted for newer diabetes drugs, including DPP-4 inhibitors, GLP-1 RA, and SGLT-2 inhibitors.

Atherosclerotic Cardiovascular Disease (ASCVD): Disease of the arteries caused by plaque buildup in artery walls. ASCVD includes the clinical conditions of coronary artery disease, acute coronary syndromes, stroke, transient ischemic attack, peripheral vascular disease, coronary or other arterial revascularization, and aortic aneurysm.[68] Patients with diabetes are at higher than normal risk for ASCVD.[69]

Major Adverse Cardiovascular Events (MACE): The major causes of morbidity and death in patients with ASCVD, and an often-used endpoint in clinical trials. There is no standard definition of MACE, but in general it can include: fatal and non-fatal myocardial infarction, heart failure, recurrent angina pain, repeat hospitalization for cardiovascular-related illness, repeat percutaneous coronary intervention, coronary bypass surgery, fatal and non-fatal stroke, and all-cause mortality.[70] For diabetes drugs, 3-point MACE (MACE-3) is often used as an endpoint in CVOT, including non-fatal myocardial infarction (may or may not include silent infarction), non-fatal stroke, and cardiovascular mortality.

Congestive Heart Failure: A chronic condition where the heart does not pump enough blood for the body's needs, leading to inadequate blood flow to vital organs (e.g., kidneys) and buildup of fluid in other organs (e.g., lungs). This can happen when the heart muscle is weakened or is too stiff. The most common symptoms of heart failure are shortness of breath, leg swelling, and fatigue.

Chronic kidney disease (CKD): A chronic condition where kidney function is decreased, resulting in buildup of waste and fluid in the body. It is defined as a reduction in eGFR to 60 mL/min/1.73 m^2 or less and/or the presence of protein in the urine. Symptoms of CKD often do not occur until the advanced stages, and can include edema, loss of appetite, nausea, fatigue, high blood pressure, anemia, high potassium, and bone disease. Diabetes is the leading cause of CKD in the US.[2]

Short Form (36) Health Survey (SF-36): A 36-item self-reported questionnaire of health-related quality of life. It includes questions about general health, activity limitations, physical and emotional health, social activities, and pain.[71] It is often used as a quality-of-life measure in clinical trials and is not specific to any health condition.

Diabetes Treatment Satisfaction Questionnaire (DTSQ): An 8-item self-reported questionnaire of psychological well-being (depression, anxiety, and positive well-being) and treatment satisfaction in patients with T2DM.[25] It is widely used in clinical trials to assess the impact of diabetes interventions on quality of life.

Impact of Weight on Quality-of-Life Questionnaire: A 74-item self-reported questionnaire assessing the effects of obesity on health-related quality of life. The scale measures the impact of obesity on physical function, self-esteem, sexual life, public distress, and work.[72]

Continuous Glucose Monitor (CGM): A non-invasive device that measures interstitial blood glucose levels constantly through skin sensors, providing real-time information about blood glucose levels. Use of CGMs can result in better glycemic control compared with regular blood glucose monitoring in patients with T2DM on insulin therapy.[73,74]

Health Improvement Distribution Index: The Health Improvement Distribution Index identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The Health Improvement Distribution Index is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if the disease prevalence was 10% in poor Americans whereas the disease prevalence across all Americans was 4%, then the Health Improvement Distribution Index would be 10%/4% = 2.5. For interventions known to increase health in this disease and that accomplish equal access across the entire population, poor Americans would receive 2.5 times the health improvements as compared to the same sized group of Americans without regard to economic status. Health Improvement Distribution Indexes above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits (Section 5).

For this calculation, we used data from the Centers for Disease Control 2020 National Diabetes Statistics Report.[1] We used the overall US population prevalence of diagnosed diabetes, 10.2%, as the denominator. We performed calculations for the following subgroups:

- American Indian/Alaska Native: 14.7%/10.2% = 1.4
- Asian Indian: 12.6%/10.2% = 1.2
- Hispanic: 12.5%/10.2% = 1.2
- Black: 11.7%/10.2% = 1.1

A2. Drug Classes for the Treatment of Type 2 Diabetes

Metformin: An orally administered biguanide that decreases glucose production and absorption and improves insulin sensitivity. It is recommended as initial pharmacotherapy for patients with T2DM due to its efficacy and favorable safety profile.[5] It decreases HbA1c by 1.1% on average without significant risk of hypoglycemia. Additionally, it is associated with modest weight loss and may improve cardiovascular outcomes, though there are no direct cardiovascular outcomes trials.[24] Side effects from metformin are mainly gastrointestinal; there is also a rare risk of lactic acidosis and the drug should be discontinued in patients with severe chronic kidney disease. Metformin is recommended to be continued as long as it is tolerated and not contraindicated.[5]

Sulfonylureas (SU): Oral hypoglycemic agents such as glyburide and glipizide that increase insulin secretion by stimulating pancreatic beta cells. They lower HbA1c by 1-2%. The most common side effects are hypoglycemia and weight gain. Sulfonylureas may be associated with progressive dysfunction of pancreatic beta cells and worsening diabetes control in the long-term. Sulfonylureas do not appear to have an impact on cardiovascular outcomes.[75]

Thiazolidinediones (TZD): Oral hypoglycemic agents such as pioglitazone that lower blood glucose by decreasing insulin resistance and decreasing glucose production in the liver. TZDs lower HbA1c by around 1-1.25%[76] , and also have favorable effects on lipids and hepatic steatosis. TZDs have mixed cardiovascular data. Rosiglitazone has been associated with an increased risk of myocardial infarction[77], however, pioglitazone has been shown to decrease fatal and non-fatal stroke in patients with previous strokes.[78] TZDs are also associated with weight gain and fluid retention, and an increased incidence of heart failure and heart failure hospitalizations.[78,79] There is also an increased risk of bone fractures with long-term use of TZDs.[80]

Dipeptidyl peptidase-4 (DPP-4) inhibitors: Oral hypoglycemic agents such as sitagliptin, saxagliptin, linagliptin, and alogliptin that lower blood glucose by inhibiting the activity of the DPP-4 enzyme in the plasma. Inhibition of DPP-4 stops degradation of incretins such as GLP-1 and GIP, which in turn increases insulin secretion and decreases gastric emptying.[81] DPP-4 inhibitors lower HbA1c on average by around 0.75%.[82] Hypoglycemia is rare, and they are considered weight neutral. However, DPP-4 inhibitors do not appear to impact cardiovascular outcomes.[75] Common side effects include runny nose, headache, and diarrhea. DPP-4 inhibitors have also been associated with more severe side effects such as severe joint pains, pancreatitis, angioedema, and Stevens-Johnson syndrome.

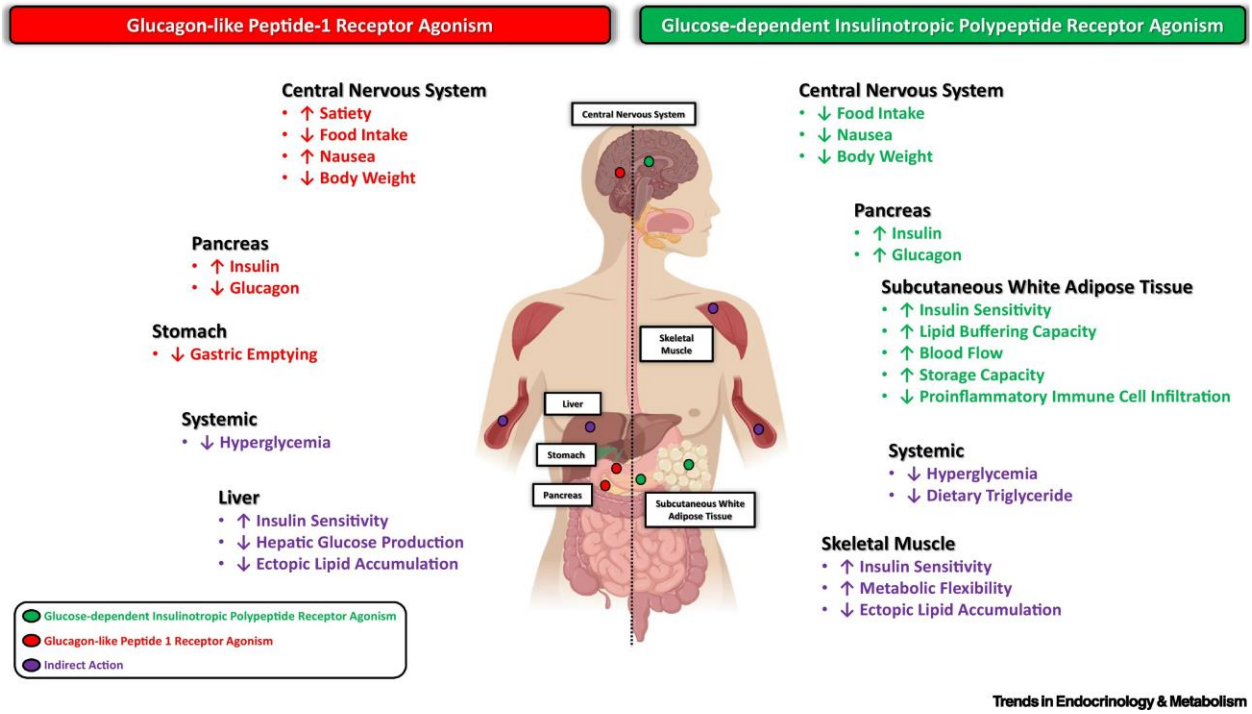
Sodium-glucose co-transporter 2 (SGLT-2) inhibitors: Oral hypoglycemic agents such as empagliflozin, canaglifozin, and dapagliflozin. SGLT-2 is a protein that is involved in the reabsorption of glucose filtered by the kidneys, and in patients with T2DM, SGLT-2 appears to be upregulated, increasing the rate of renal glucose reabsorption. SGLT-2 inhibitors block glucose reabsorption, resulting in loss of glucose in the urine. As add-on therapy to metformin and/or sulfonylureas, SGLT-2 inhibitors lowered HbA1c by up to an additional 1%. Hypoglycemia is rare with SGLT-2 inhibitors and modest weight loss has been observed. SGLT-2 inhibitors have been shown to reduce cardiovascular events, particularly hospitalization for heart failure and kidney disease.[83] Side effects of SGLT-2 inhibitors include dehydration, urinary tract infections, genital

yeast infections, acute kidney injury and increased LDL-C. More severe side effects such as urosepsis and ketoacidosis have also been noted, as well as an association with increased diabetic foot amputations.[84]

GLP-1 receptor agonists (GLP-1 RA): Oral and injectable hypoglycemic agents such as semaglutide (has both oral and injectable forms), dulaglutide, exenatide, liraglutide. GLP-1 is an incretin that stimulates release of insulin from pancreatic beta cells in response to glucose. It has also been shown to slow gastric emptying, reduce food intake, and inhibit inappropriate post-meal glucagon release (refs). Injectable GLP-1 RA can be administered twice daily, daily or weekly; oral semaglutide is taken daily. GLP-1 RA have been shown to lower HbA1c (0.8-1.6%), weight (1-3 kg), blood pressure and lipids. Additionally, cardiovascular outcomes trials have demonstrated cardiovascular and renal benefits for some GLP-1 RA.[10] The most prominent side effects are gastrointestinal, and hypoglycemia is rare. There is a risk of developing thyroid C-tumors, though this has not been seen in clinical practice.[85]

Glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist (GIP/GLP-1 RA): Dual agonist targeting two incretins, GIP and GLP-1, both of which are released after meals to facilitate insulin secretion. Tirzepatide, an injectable agent, is currently the only member of this class. The dual receptor agonism leads to a decrease in blood sugar through an increase in insulin secretion and increase in insulin sensitivity in the liver and skeletal muscles. Both GLP-1 and GIP have additional impacts on other tissues, as depicted in Figure A1. For example, both GLP-1 and GIP mediate weight loss through effects on satiety centers in the central nervous system. GLP-1 RA additionally decreases gastric emptying, and GIP has impacts on the subcutaneous white adipose tissue.

Figure A1. Pleiotropic Effects of Dual GIP Inhibition and GLP-1 Receptor Agonism in the Treatment of T2DM.[86]



Insulin: Insulin is produced in pancreatic beta cells and controls the amount of blood glucose in the bloodstream, helps promote storage of glucose in the liver, adipose tissue, and muscles, and regulates metabolism of carbohydrates, fats, and proteins. There are short, intermediate, and long-acting insulins, delivered mainly by injection, which are used alone or in combination by patients with T2DM to help control blood sugar levels. The main side effects of insulin are hypoglycemia and weight gain.

A3. Potential Cost-Saving Measures in Type 2 Diabetes

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for T2DM (e.g., reduction in disability), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of T2DM beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with T2DM that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

ICER engaged with individual patients, patient groups, including representatives from diabetes and kidney disease advocacy organizations, and clinical experts to gather information to better understand patient experiences with the T2DM. In total, we spoke with five individual patients and seven advocacy organizations via focus groups and conference calls. We also spoke with three clinical experts throughout the review process. We also reviewed research literature suggested by or provided to ICER by advocacy organizations.

Patients and advocacy groups provided information on the impact of T2DM on patients throughout the disease course, particularly concerning aspects of the disease and caregiving that are not well-reflected in the current literature. These organizations also assisted with literature review to find information that was considered for inputs into the economic model.

C. Clinical Guidelines

Clinical practice guidelines for the treatment of T2DM have been issued by several US and non-US-based organizations. These guidelines are summarized below.

The American Diabetes Association (ADA)[3,6]

The ADA's Standards of Medical Care in Diabetes guidelines are updated yearly and include recommendations on diagnosis and treatment of T2DM and its complications. The guidelines recommend that at time of diagnosis of T2DM, all patients, except when contraindicated, should be started on metformin in addition to comprehensive lifestyle modifications (e.g., healthy eating patterns, medical nutrition therapy, regular physical activity, weight management, smoking cessation).[66] A recommended HbA1c target is less than 7.0% for most nonpregnant adults. However, the guidelines suggest accounting for patient-specific factors, including but not limited to risk of hypoglycemia, comorbidities, disease duration, and patient preference, through which a patients' individualized target HbA1c may be higher or lower than 7.0%.[5] Dual pharmacologic therapy should be considered at initiation of newly diagnosed T2DM patients if their HbA1c is greater than or equal to 1.5% of the HbA1c target. These guidelines recommend a patient-centered approach to help guide selection of pharmacologic agents with considerations for comorbidities, risk of hypoglycemia, risk of side effects, cost, and impact on patient weight, along with patient preferences.

If the patient does not have chronic kidney disease (CKD), atherosclerotic cardiovascular disease (ASCVD), or concerns regarding weight management, and the HbA1c target is not achieved after three months of therapy, it is recommended to have a combination of metformin and any of six preferred medication classes which include basal insulin, DPP-4 inhibitors, GLP-1 RA, SGLT-2 inhibitors, sulfonylureas, or thiazolidinediones, dependent upon patient factors and drug-specific effects.[5] When there is a compelling need to either minimize weight gain or help promote weight loss, use of either GLP-1 RA or SGLT-2 inhibitors are preferred.

For T2DM patients who also have established ASCVD or multiple ASCVD risk factors, and who do not achieve HbA1c target after three months, use of either SGLT-2 inhibitors or GLP-1 receptor agonists are recommended as part of the treatment regimen. Among T2DM patients who have established ASCVD and heart failure or are at high risk of developing heart failure, use of SGLT-2 inhibitors are preferred. For T2DM patients who also have CKD, use of GLP-1 RA or SGLT-2 inhibitors are preferred.[6]

American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE)[87]

The AACE and ACE published a Comprehensive Type 2 Diabetes Management Algorithm in 2019. The guidelines recommend that in addition to promoting lifestyle optimization measures, clinicians should individualize both glycemic targets and choice of therapy. Choice of therapy should be patient-centered, consider ASCVD, heart failure, and CKD status, and achieved through shared decision-making. A HbA1c ≤ 6.5% is considered optimal if it can be achieved in a safe and affordable manner and glycemic therapy should be evaluated frequently (e.g., every 3 months) so that glycemic targets should be achieved as soon as possible. Continuous glucose monitoring is highly recommended to assist patients in reaching glycemic targets.

Choice of therapy is based on comorbidities and HbA1c status at initiation of therapy. For patients with established ASCVD or high risk of ASCVD, CKD stage 3, or heart failure with reduced ejection fraction, a long-acting GLP-1 RA or SGLT-2 inhibitor with proven efficacy in these conditions is preferred. For patients with a HbA1c ≥ 7.5%-9.0% or HbA1c ≥ 9.0% without symptoms at initiation of therapy, dual therapy with metformin and another agent is recommended, with the addition of a third agent if glycemic control is not achieved within 3 months. For patient with a HbA1c > 9.0% with symptoms, insulin with or without other agents is preferred.

The European Society of Cardiology (ESC) and the European Association of the Study of Diabetes (EASD)[88]

The ESC and EASD guidelines on diabetes, pre-diabetes, and CVD recommend the use of metformin along with lifestyle modifications (e.g., healthy eating patterns, regular physical activity, smoking cessation, weight management) as first-line therapy in patients with T2DM without established ASCVD or at high CV risk.[88] A recommended HbA1c target is less than 7.0% for most adults, however, target goals should be individualized on a per-patient basis.

For patients with T2DM and CVD or at high CV risk, the use of GLP-1 receptor agonists or SGLT-2 inhibitors are recommended to reduce the risk of CV events. For patients with T2DM and heart failure, SGLT-2 inhibitors are recommended to reduce the risk of hospitalization from heart failure. Saxagliptin is not recommended for use in patients with heart failure. For patients with T2DM and CKD, SGLT-2 inhibitors are recommended to reduce progression of CKD.

National Institute for Health and Care Excellence (NICE)[89]

NICE published guidelines for Type 2 diabetes in adults in 2015, and updated the guidelines in 2019. Along with evidence-based patient education delivered by trained educators, a personalized diabetes management plan including advice about diet, exercise, and weight loss, the NICE guideline recommends metformin as initial drug treatment. HbA1c targets should be individualized, based on risk of hypoglycemia (HbA1c ≤ 6.5% in patients who are not on drugs that cause hypoglycemia and ≤ 7.0% if patients are on drugs that cause hypoglycemia). HbA1c targets can be relaxed in patients for whom tight glucose control is not appropriate.

If metformin is not sufficient to achieve the glycemic target, the guidelines recommend dual therapy with the addition of a sulfonylurea, DPP-4 inhibitor, pioglitazone or SGLT-2 inhibitor. Triple therapy with metformin and two of the following: DPP-4 inhibitor, sulfonylurea, and/or pioglitazone, or starting insulin is recommended as a second intensification step. GLP-1 RA are recommended only if metformin + two other oral drugs is not effective, particularly in patients who are obese or have obesity-related complications, or have relative contraindications to insulin (e.g., patients in whom insulin therapy would have significant occupational implications).

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

Our intervention of interest for this review was injectable tirzepatide (Eli Lilly) added to background therapy (metformin +/- sulfonylureas or thiazolidinediones).

Comparators

We compared tirzepatide to background therapy and each of the following add-on agents:

- Semaglutide (Ozempic®, Novo Nordisk), an injectable GLP-1 receptor agonist
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), an oral SGLT-2 inhibitor

Outcomes

The outcomes of interest are described in the list below.

- Glycated hemoglobin (HbA1c) levels
- Fasting plasma glucose
- Body weight
- Waist circumference
- Blood pressure
- Percentage of patients achieving HbA1C targets of <7.0%, ≤6.5%, and/or <5.7%
- Lipid profile (e.g., Total Cholesterol, Low-Density Lipoprotein Cholesterol, High-Density Lipoprotein Cholesterol, and Triglycerides)
- Use of rescue medication (e.g., additional glucose-lowering medication)
- Health-related quality of life and activities of daily living (e.g., Diabetes Treatment Satisfaction Questionnaire (DTSQ), EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D), Impact of Weight on Quality of Life Questionnaire–Lite (IWQOL-Lite), Short Form Health Survey (SF-36))
- Macrovascular outcomes including:
  - All-cause mortality
  - Cardiovascular mortality
  - Stroke

        - Myocardial infarction
        - Heart failure requiring hospitalization or an urgent heart failure visit
    - Microvascular outcomes including:
        - Retinopathy
        - Nephropathy
        - Neuropathy
    - Adverse events including:
        - Hypoglycemia
        - Pancreatitis
        - Urogenital infections
        - Gastrointestinal effects
        - Fractures
        - Discontinuation (all-cause, due to adverse events)
        - Serious adverse events including death

Timing

Evidence on intervention effectiveness and harms was derived from studies of at least 3 months' duration.

Settings

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

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size were included.

Table D1.1 PRISMA 2009 Checklist

		Checklist Items
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for T2DM followed established best research methods.[90,91] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[92] The PRISMA guidelines include a checklist of 27 items, which are described further in Table D1.

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

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

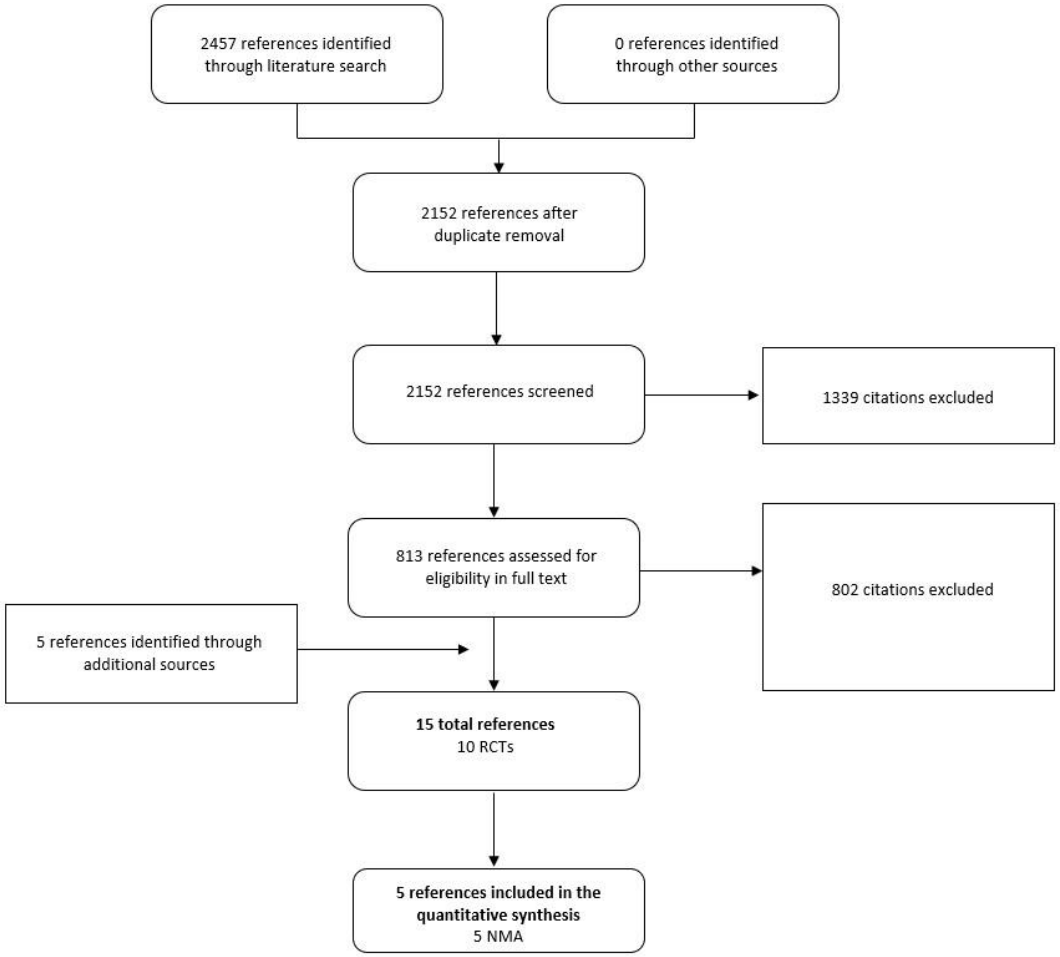
Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, and EBM Reviews - Cochrane Central Register of Controlled Trials

	Search Terms
1	exp Diabetes Mellitus, Type 2/
2	(((adult or ketosis-resistant or matur* or late or "non-insulin depend*" or "noninsulin depend*" or slow or stable or "type 2" or "type II" or lipoatrophic) adj3 diabet*) or T2D* or NIDDM).ti,ab.
3	1 or 2
4	(tirzepatide or "LY3298176" or LY3298176).ti,ab.
5	(semaglutide or "nn 9535'" or nn9535 or ozempic).ti,ab.
6	(empagliflozin or "BI 10773" or BI10773 or jardiance).ti,ab.
7	4 or 5 or 6
8	3 and 7
9	(address or autobiography or bibliography or biography or case reports or clinical trial phase i or comment or conference review or congress or consensus development conference or duplicate publication or dictionary or directory or editorial or guideline or interview or lecture or legal case or legislation or letter or meta analysis or news or newspaper article or note or patient education handout or periodical index or personal narrative or portrait or practice guideline or review or systematic review or video-audio media).pt.
10	conference abstract.pt.
11	8 not (9 or 10)
12	(clinical and trial).ti,ab. or exp 'clinical trials as topic'/ or clinical trial.pt. or random*.ti,ab. or exp 'random allocation'/ or tu.xs
13	11 and 12
14	limit 13 to english language
15	(animals not (human and animals)).sh.
16	14 not 15
17	remove duplicates from 16

Table D1.3. Search Strategy of EMBASE SEARCH

	Search Terms
1	'non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'
2	(((adult OR 'ketosis resistant' OR matur* OR late OR 'non-insulin depend*' OR 'noninsulin depend*' OR slow OR stable OR 'type 2' OR 'type ii' OR lipoatrophic) NEAR/3 diabet*):ti,ab) OR t2d*:ti,ab OR niddm:ti,ab
3	#1 or #2
4	'tirzepatide'/exp
5	'tirzepatide':ti,ab OR 'LY3298176':ti,ab OR 'LY3298176':ti,ab
6	'semaglutide'/exp
7	Semaglutide:ti,ab OR 'nn 9535':ti,ab OR 'nn9535':ti,ab OR 'ozempic':ti,ab
8	'empagliflozin'/exp
9	empagliflozin:ti,ab OR bi10773:ti,ab OR 'bi 10773':ti,ab OR 'jardiance':ti,ab
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
11	#3 AND #10
12	#11 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'network meta-analysis'/de OR 'nonhuman'/de OR 'phase 1 clinical trial (topic)'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'systematic review'/de OR 'systematic review (topic)'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
13	'clinical':ti,ab AND 'trial':ti,ab OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk OR 'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp
14	#12 AND #13
15	#14 AND [english]/lim
16	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
17	#15 NOT #16
18	#17 NOT [medline]/lim

Figure D1.1 PRISMA Flow Chart Showing Results of Literature Search for Tirzepatide for Type 2 Diabetes



Study Selection

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

Tirzepatide

There are four tirzepatide trials, two Phase 2 trials that compare tirzepatide to background therapy and two Phase 3 trials that compare tirzepatide against injectable semaglutide and tirzepatide against insulin glargine.

NMA Linkages

A total of four references relating to four RCTs were used as linkages for the NMA. Two RCTs related to oral semaglutide, one RCT related to injectable semaglutide, and one RCT contained a placebo and sitagliptin arm.

CVOTs

A total of two references relating to two RCTs evaluating cardiovascular outcomes. One RCT reviewed empagliflozin and the second reviewed injectable semaglutide.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Table D4.1).[93] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

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

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

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

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

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[94,95]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for tirzepatide, semaglutide, and empagliflozin using the clinicaltrials.gov database of trials. We searched for studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Section D4) and synthesized qualitatively in the body of the review. In addition, we evaluated the comparative efficacy of tirzepatide, injectable semaglutide, empagliflozin, and background therapy by means of network meta-analysis (NMA), where feasible. Based on data availability, our NMA evaluated HbA1c, body weight, LDL, and SBP outcomes at 40 weeks. Network Meta-Analysis Supplemental Information below (Section D2) contains a detailed description of the NMA methods. Due to inconsistent or limited data reporting, other outcomes were only described narratively in the body of the report or in Section D4 of the Report Supplement.

D2. Network Meta-Analysis Supplemental Information

NMA Methods

We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Trials deemed sufficiently similar in terms of population, intervention type, duration, and outcome definitions were included in the NMAs. Based on data availability, we developed quantitative, indirect comparisons of tirzepatide, injectable semaglutide, empagliflozin, and background therapy using a Bayesian NMA for outcomes of change in HbA1c, weight, LDL, and SBP at 40 weeks in adult patients with T2DM. The primary endpoints of the tirzepatide trial, SURPASS-2 was measured at 40 weeks, PIONEER-2 and 3 were measured at 52 weeks, SUSTAIN-2 at 56 weeks, and HARMONY-3 at 104 weeks. We received academic-in-confidence outcomes data at week 40 from manufacturers of four of the five trials in the NMA. We were unable to access week 40 data from the HARMONY-3 trial. Thus, we used digitized estimates from published figures to calculate change in HbA1c and weight at week 40; we were limited to using change from baseline to week

104 for the LDL and SBP outcomes. For the outcomes of HbA1c and weight, results were reported using the treatment-regimen or equivalent estimand. For the outcome of LDL, results were reported using the efficacy estimand for SURPASS-2 and treatment-regimen estimand equivalent for SUSTAIN-2, PIONEER-2 and 3.

All four outcomes were analyzed as continuous outcomes using a generalized linear model with identity link (Tables D2.1-2.3). All NMAs were conducted using the IndiRect NMA platform (CRG-EVERSANA, 2020™). For all analyses, we used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and based inferences on an additional 50,000 iterations using three chains. Convergence of chains was through visual examination of the Brook–Gelman–Rubin diagnostic and historical plots. We presented results for both the fixed effects and random effects models; both models had a similar goodness of fit to the data as evaluated by the deviance information criterion.

For the draft report, we limit our presentation of NMA results in Table D2.4 to only include point estimates between tirzepatide and background therapy/placebo, and tirzepatide and empagliflozin, with footnote notations for statistically significant values at 95% confidence for a fixed effects and random effects (assuming noninformative priors) models. Prior to the draft report posting, we received feedback from reviewers that a random effects model assuming evidence-based priors would best fit this sparse network. We plan to run a random effects model that uses evidence-based priors and will report the 95% credible intervals for this model in the NMA. Once the findings from the additional NMA model are available, we will post an amendment to the NMA results in Table D2.4.

Table D2.1. NMAs Conducted & Presented

Outcome	Model	Number of trials
Change from Baseline in HbA1c (%)	Generalized linear model with identity link	5
Change from Baseline in Body Weight (kg)		
Change from Baseline in LDL (mg/dL)		
Change from Baseline in SBP (mmHg)		

HbA1c: hemoglobin A1c, kg: kilogram, LDL: low-density lipoprotein, mg/dL: milligram/deciliter, mmHg: millimeters of mercury, SBP: systolic blood pressure

Table D2.2. Data Inputs for NMA of HbA1c and Body Weight Loss

		HbA1C (%)			Body Weight (kg)		
Trial	**Name**	**N**	**Mean**	**Standard Error**	**N**	**Mean**	**Standard Error**
SURPASS-2	TZP		-2.3			-11.2	
	SEM		-1.86			-5.7	
SUSTAIN 2	SEM						
	SITA						
PIONEER_2	OSEM						
	EMPA						
PIONEER 3	OSEM						
	SITA						
HARMONY 3*	PBO	101	0	0.13	101	2.2	1
	SITA	302	-0.5	0.07	302	0.4	0.95

EMPA: empagliflozin, kg: kilogram, N: number, OSEM: oral semaglutide, PBO: placebo, SEM: semaglutide, SITA: sitagliptin, TZP: tirzepatide

*Values from HARMONY 3 were digitized by ICER staff

Table D2.3. Data Inputs for NMA of LDL and SBP

		LDL Cholesterol (mg/dL)			Systolic Blood Pressure (mmHg)		
Trial	**Name**	**N**	**Mean**	**Standard Error**	**N**	**Mean**	**Standard Error**
SURPASS-2	TZP		-4.5			-6.5	
	SEM		-5.6			-3.6	
SUSTAIN 2	SEM						
	SITA						
PIONEER 2	OSEM						
	EMPA						
PIONEER 3	OSEM						
	SITA						
HARMONY 3*	PBO	101	-1.2	2.7	101	2.2	1.39
	SITA	302	-1.9	1.34	302	0.2	0.85

EMPA: empagliflozin, LDL: low-density lipoprotein, mg/dL: milligrams per deciliter, N: number, OSEM: oral semaglutide, PBO: placebo, SBP: systolic blood pressure, SEM: semaglutide, SITA: sitagliptin, TZP: tirzepatide

*Note: For LDL and SBP, mean values of change were calculated from baseline to week 104

Table D2.4. NMA Point Estimates for Change in HbA1c, Body Weight, LDL and SBP at Week 40 Between Tirzepatide versus Background Therapy/ Empagliflozin

	TZP vs BT	TZP vs EMPA
Mean Difference of Change in HbA1c, %,	-1.72†	-1.12†
Mean Difference of Change in Body Weight, kg	-11.51†*	-7.24†*
Mean Difference of Change in LDL, mg/dL	-4.34†	-7.53†*
Mean Difference of Change in SBP, mmHg	-7.46†*	-2.59†

BT: background therapy, EMPA: empagliflozin; HbA1c: hemoglobin A1c, kg: kilogram, mg/dL: milligram per deciliter, TZP: tirzepatide

*95% credible interval of this point estimate does not contain zero for the random effects model

†95% credible interval of this point estimate does not contain zero for the fixed effects model

D3. Additional Clinical Evidence

Trials of Tirzepatide

We identified four relevant trials of tirzepatide for treatment of T2DM.[8,9,32,34] The key trials are described in detail below and additional details can be found in Evidence Table D4.3-6. Frias 2018, Frias 2020, and SURPASS-2 have been published and the data for these trials are informed by the clinical trial report. We also identified SURPASS-4 which includes an assessment of the cardiovascular safety of tirzepatide compared with insulin glargine.

Phase 2 (Frias 2018 and 2020)

Frias 2018 and 2020 are two phase 2 trials exploring the efficacy and safety of tirzepatide in patients with T2DM. Frias 2018 was a 26-week randomized, double-blind study where participants were randomized 1:1:1:1 to 1 mg (n=52), 5 mg (n=55), 10 mg (n=51), 15 mg (n=53) of tirzepatide, 1.5 mg of dulaglutide (n=52), or placebo (n=51). For the purposes of this review, only the 5, 10, and 15 mg tirzepatide arms were included as Ely Lilly is not seeking FDA approval for the 1 mg dose. Patients were eligible for the study if they were 18-75 years old with T2DM for at least 6 months, that was inadequately controlled with diet and exercise alone or with stable metformin therapy for at least 3 months before screening, and a BMI of 23-50 kg/m^2. The primary outcome was change in HbA1c from baseline at 26 weeks. Secondary outcomes include change in HbA1c at week 12, change in mean bodyweight, and waist circumference from baseline to weeks 12 and 26.

Frias 2020 was a phase 2 dose-ranging study, where patients were randomized to either placebo or one of three tirzepatide doses. For the purpose of this review, the 12 mg arm was not reported on, as Eli Lilly will not be seeking FDA approval for this dose. The two 15 mg arms had different dose

titration regimens; the 15 mg-1 group was 2.5 mg for two weeks followed by 5 mg for 2 weeks, 10 mg for 4 weeks and then 15 mg for the final 4 weeks. The 15 mg-2 arm was 2.5 mg for 4 weeks, followed by 7.5 mg for 4 weeks, and then 15 mg for the final 4 weeks. Inclusion criteria and outcomes were similar to the 2018 study. The timepoint of interest was 12 weeks.

Additional baseline characteristics are available in Evidence Table D4.3.

SURPASS-2

The SURPASS-2 trial was a phase 3, head-to-head open-label trial exploring the efficacy and safety of tirzepatide compared to injectable semaglutide. Patients were randomized 1:1:1:1 to tirzepatide 5 mg (n= 470), 10 mg (n= 469), 15 mg (n= 470) or semaglutide 1mg (n= 469) every week for 40 weeks followed by a 4-week safety period. 1,878 patients included in the study were adults with T2DM that were inadequately controlled with metformin at a dose of at least 1500 mg per day. Included patients also had HbA1c levels of 7.0 to 10.5% and a BMI of ≥ 25 kg/m^2 with a stable weight in the past three months. Patients with type 1 diabetes, an eGFR below 45 mL/min/1.73 m^2, and a history of pancreatitis were excluded from the study. Included patients had a mean age of 56.6 years, with 53% identifying as female, 82.6% white, an average weight of 93.7 kg, and an eGFR of 96.0 mL/min/1.73 m^2. Additional baseline characteristics are available in Evidence Table D4.3.

The primary endpoint was change in HbA1c from baseline to week 40. Secondary endpoints include change from body weight, and attainment of HbA1c targets of less than 7.0% and less than 5.7%.

SURPASS-4

SURPASS-4 was an open-label Phase 3 study exploring the efficacy and cardiovascular safety of tirzepatide (5, 10 and 15 mg) versus insulin glargine in patients with T2DM. Patients were randomized to either a tirzepatide arm (n= 995) or insulin glargine (n= 1000) for 52-weeks for the primary efficacy endpoint, with an additional variable treatment period of up to 52 additional weeks. The median study duration was 85 weeks. Study participants were adults with T2DM inadequately controlled with any of three oral glucose-lowering medications (i.e., metformin, sulfonylurea, or an SGLT-2 inhibitor), a BMI of 25 kg/m^2 or more and stable weight and increased risk of CV events. Patients with type 1 diabetes or a history of pancreatitis were not included in the study. Included patients had a mean disease duration of 10.5 years, baseline HbA1c of 8.52%, and a baseline weight of 90.3 kg. 87% of patients had a history of cardiovascular disease.

The primary endpoint was change in HbA1c from baseline to 52 weeks. Key secondary endpoints include change in bodyweight at 52 and achievement of HbA1c target of less than 7%. A prespecified cardiovascular risk comparison between tirzepatide and insulin glargine was also conducted and assessed MACE-4. Additional outcomes are available in Evidence Table D4.12.

Trials of NMA Linkage Studies

We identified four trials to provide linkages for the NMA.[38,96-98] The trials are described in detail below and additional details can be found in Evidence Table D4.7-9. All trials are published and are informed by the respective clinical trial reports.

SUSTAIN-2

SUSTAIN-2 was a phase 3a, randomized, double blind, multicenter trial, assessing the efficacy and safety of semaglutide versus sitagliptin in patients with T2DM inadequately controlled on metformin, thiazolidinediones, or both. Included patients were adults with T2DM with insufficient glycemic control for 90 days prior to screening and were on stable treatment with metformin, pioglitazone, rosiglitazone, or metformin and rosiglitazone. Patients were excluded if they were on other glucose lowering drugs not described above, had a history of chronic or acute pancreatitis, impaired renal function, or heart failure at any time. 1,231 patients were randomized 2:2:1:1 to 0.5 mg semaglutide (n=409), 1.0 mg semaglutide (n= 409) or two arms of 100 mg sitagliptin that were pooled for analysis (n=407). Included patients had a mean age of 55.1, years, HbA1c of 64.7mmol/mol, 49.5% female, 68.5% white and an eGFR of 97.50 mL/min/1.73 m^2. Additional baseline characteristics are available in Evidence Table D4.7.

The primary outcome was change in HbA1c from baseline at week 56. Secondary endpoints include change in bodyweight, proportion of patients who achieved an HbA1c of less than 7.0% and HbA1c of 6.5%.

PIONEER 2 and PIONEER 3

PIONEER 2 and 3 have been previously described in the 2019 T2DM ICER report.[39] A brief description is provided below.

The PIONEER program was comprised of ten trials (PIONEER 1-10). The PIONEER trials included in this review (PIONEER 2 and 3) were multinational RCTs comparing oral semaglutide to sitagliptin, empagliflozin, liraglutide, and placebo. PIONEER 2 compared oral semaglutide 14 mg to empagliflozin 25 mg added to metformin and PIONEER 3 compared oral semaglutide 3, 7, and 14 mg to sitagliptin 100 mg added to metformin ± sulfonylurea (47%). Key exclusion criteria included: renal impairment (eGFR <60 mL/min/1.73 m^2); MI, stroke, hospitalization for unstable angina, or transient ischemic attack within 180 days; stage IV heart failure; and history of pancreatitis. Baseline characteristics are available in Evidence Table D4.7.

HARMONY-3

The HARMONY 3 trial was a phase 3 randomized, double-blind, placebo-controlled study and evaluated the efficacy and safety of albiglutide with daily sitagliptin, daily glimepiride, and placebo

in patients with type 2 diabetes. For the purpose of this review, we only used the placebo and sitagliptin arms for the NMA. Patients were eligible to be enrolled if they were adults with T2DM and experienced inadequate glycemic control while taking background metformin at least 3 months before screening. Patients also had to have a HbA1c of 7.0% to 10% and a BMI of 20 to 45 kg/m^2. 1049 patients met the criteria (placebo, n= 101 and sitagliptin, n= 302) with a mean age of 54.3 to 56.1, and a mean duration of diabetes from 5.8 to 6.7 years. Additional baseline characteristics are available in Evidence Table D4.7.

The primary outcome was change in HbA1c from baseline to week 104. The secondary endpoints include change from baseline for HbA1c and weight.

Cardiovascular Outcomes Trials (CVOT)

We identified two relevant trials exploring the efficacy of semaglutide and empagliflozin on cardiovascular outcomes.[10,11] The trials are described below with additional details on study design available in Evidence Table D4.2.

SUSTAIN-6

The SUSTAIN-6 trial was a phase 3 randomized, double-blind, placebo-controlled trial evaluating the cardiovascular safety of semaglutide in patients with T2DM. Patients were randomized 1:1:1:1 to either 0.5 or 1.0 mg injectable semaglutide or a matched placebo for 104 weeks with a 5-week follow up period. 3,297 met the inclusion criteria of T2DM and HbA1c levels of 7%, and no previous treatment with an antihyperglycemic drug, or more than two oral antihyperglycemic agents with or without basal or premixed insulin. Patients were also included if they were 50+ years of age with established CVD, chronic heart failure, or chronic kidney disease of stage three or higher. Included patients had a mean age of 64.6 years, an average disease duration of 13.8 years and an average Hba1c level of 8.7%. Additional baseline characteristics are available in Evidence Table D4.10.

The primary composite outcome was first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke (MACE-3). A key secondary outcome was first occurrence of an expanded composite CV outcome (death from CV causes, nonfatal MI, nonfatal stroke, revascularization and hospitalization for unstable angina or heart failure).

EMPA-REG-OUTCOME

The EMPA-REG-OUTCOME trial was a phase 3 trial evaluating the efficacy and safety of empagliflozin added to standard of care on cardiovascular morbidity and mortality in patients with T2DM and high cardiovascular risk. Patients were eligible for the trial if they were 18 or older with T2DM, a BMI of 45 kg/m^2 or less and eGFR of at least 30 mL/min/1.73m^2 and established CVD. Included patients were randomized 1:1:1 to either two doses of EMPA (N= 4687) or placebo (N= 2133). The baseline characteristics were well balanced, with a mean age of 63.1, mean weight of

86.3 kg and a HbA1c of 8.07%. Median observation time was 3.1 years. Additional baseline characteristics are available in Evidence table D4.10.

The primary outcome was MACE-3. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina.

D4. Evidence Tables

Table D4.1. Study Quality

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding	Clear Definition of Intervention	Clear Definitions of Outcomes	Selective Outcome Reporting	Measurements Valid	Intention-to-treat Analysis	Approach to Missing Data	USPSTF Rating
Tirzepatide										
Frias 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	LOCF	Good
Frias 2020	Yes	No	Yes	Yes	Yes	No	Yes	mITT	MMRM	Fair
SURPASS-2	Yes	Yes	Open-label	Yes	Yes	No	Yes	mITT	MMRM	Good
SURPASS-4	Yes	Yes	Open-label	Yes	Yes	No	Yes	mITT	MMRM	Good
Injectable Semaglutide										
SUSTAIN-2	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	MI	Good
SUSTAIN-6	Yes	Yes	Yes	Yes	Yes	No	Yes	ITT	MAR	Good
Oral Semaglutide*										
PIONEER 2	Yes	Yes	Open-label	Yes	Yes	No	Yes	ITT	MI	Good
PIONEER 3	Yes	Yes	Yes	Yes	Yes	No	Yes	ITT	MI	Good
Empagliflozin										
EMPA-REG-OUTCOME	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	LOCF	Good
Sitagliptin*										
HARMONY 3	Yes	Yes	Yes	Yes	Yes	No	Yes	ITT	LOCF	Good

Studies with an asterisk (*) were used as linkages for the NMA. ITT = intention-to-treat analysis, LOCF = last observation carried forward, MAR= missing at random, MI = multiple imputation, mITT = modified intention-to-treat analysis, MM = mixed-effects model, MMRM = mixed-effects model repeated measure, NR: not reported

Table D4.2. Study Design

Trial	Interventions	Background Therapy	Inclusion Criteria	Study Length	Primary Key Outcome	Key Secondary Outcomes
Tirzepatide						
Phase 2 Frias 2018 N= 318 18 to 75 years	PBO TZP 1 mg TZP 5 mg TZP 10 mg TZP 15 mg DUA 1.5 mg	+/- MET	Have had T2DM for ≥ 6 months according to WHO classification Have HbA1c of 7.0% to 10.5% If on MET, have been treated with stable doses of MET for at least 3 months Have BMI ≥23 and <50 kg/m^2	26 weeks	Primary Change in HbA1c from baseline to Week 26 Bayesian Dose Response	Secondary Percentage of participants with 5% or greater body weight loss from baseline Percentage of participants with 10% or greater body weight loss from baseline Percentage of participants reaching the HbA1c target of ≤6.5% Percentage of participants reaching the HbA1c target of <7.0%
Phase 2 Frias 2020 N= 111 18 to 75 years	TZP 12 mg TZP 15 mg-1 TZP 15 mg-2 PBO	+/- MET	Have T2DM for ≥6 months according to ADA 2017 Have HbA1c of 7.0% to 10.5% If on MET, have been treated with stable doses of MET for at least 30 months Have a BMI between 23 and 45 kg/m^2	12 weeks	Primary Change from baseline in HbA1c	Secondary Change from baseline in body weight Change from baseline in waist circumference Number of participants with anti-drug antibodies Number of episodes of total hypoglycemia episodes Pharmacokinetics (PK): Average trough concentration

						(Conctrough) of tirzepatide
SURPASS-2 Frias 2021 N= 1,879 18 and older	TZP 5 mg TZP 10 mg TZP 15 mg SEM 1 mg	MET	Have been diagnosed with T2DM Have HbA1c between ≥7.0% and ≤10.5% Be on stable treatment with unchanged dose of metformin >1500 mg/day for at least 3 months prior to screening Be of stable weight (±5%) for at least 3 months before screening	40 weeks	<u>Primary</u> Change from Baseline in HbA1c to week 40	<u>Secondary</u> Mean change from baseline in daily average 7-Point SMBG values Percentage of participants who achieved weight loss ≥5% Rate of documented symptomatic hypoglycemic episodes Change from baseline in body weight Percentage of participants achieving an HbA1c target value of <7%
SURPASS-4 Del Proto 2021 N= 1878 18 and older	TZP 5mg TZP 10mg TZP 15mg Insulin glargine SC once daily	OADs (MET, SGLT-2 inhibitors, and/or SU)	Have been diagnosed with T2DM Have HbA1c between ≥7.5% and ≤10.5% Be on stable treatment with unchanged dose of at least 1 and no more than 3 types of OADs, which may only include metformin, SGLT-2 inhibitors, and/or SU for at least 3 months before screening Have increased risk for CV events Be of stable weight (± 5%)	52 weeks	<u>Primary</u> Change from baseline in HbA1c to week 40	<u>Secondary</u> Change from baseline in body weight Percentage of participants with HbA1c of <7.0% Change from baseline in fasting serum glucose Change from Baseline in HbA1c (5 mg)

Injectable Semaglutide						
SUSTAIN-2 Ahren 2017 N= 1231 18 and older	SEM 0.5 mg SEM 1.0 mg SITA 100 mg + PBO 0.5 mg SITA 100 mg + PBO 1.0 mg	MET ± TZD	Japan: Age minimum 20 years Subjects diagnosed with T2DM and on stable treatment in a period of 90 days prior to screening with either MET above or equal to 1500 mg (or maximum tolerated dose), pioglitazone above or equal to 30 mg (or maximum tolerated dose), rosiglitazone above or equal to 4 mg (or maximum tolerated dose) or a combination of either MET/pioglitazone or MET/rosiglitazone (doses as for individual therapies)	56 weeks	<u>Primary</u> Change from Baseline in HbA1c	<u>Secondary</u> Change in body weight from baseline Change in FPG from baseline Change in PRO questionnaire Change in systolic and diastolic blood pressure from baseline Subjects who achieve HbA1c below or equal to 6.5% (48 mmol/mol) target (yes/no)
SUSTAIN-6 Marso 2016 N= 3260 50 and older	SEM 0.5 mg SEM 1.0 mg PBO 0.5 mg SC QW PBO 1.0 mg SC QW	Naïve or treated with OADs or insulin	Men and women with T2DM Age above or equal to 50 years at screening and clinical evidence of cardiovascular disease or age above or equal to 60 years at screening and subclinical evidence of cardiovascular disease Anti-diabetic drug naïve, or treated with one or two OADs HbA1c above or equal to 7.0% at screening	148 weeks	<u>Primary</u> Time from randomization to first occurrence of a MACE	<u>Secondary</u> Change from baseline: urinary albumin to creatinine ratio Change from baseline: vital signs Time from randomization to first occurrence of an expanded composite cardiovascular outcome Change from baseline: HbA1c Change from baseline: Lipid profile

						Change from baseline FBG
Oral Semaglutide						
PIONEER 2 NCT02893328 Rodbard et al N=822 18 and older	SEM 14 mg EMPA 25 mg	MET	Male or female, age above or equal to 18 years at the time of signing informed consent Diagnosed with T2DM at least 90 days prior to day of screening HbA1c of 7.0 to 10.5% (53-91 mmol/mol) Stable daily dose of metformin (at least 1500 mg or MTD) at least 90 days prior to the day of screening	52 weeks	<u>Primary</u> Change in HbA1c (week 0 to 26)	<u>Secondary</u> Change in body weight (kg) (week 0 to 26) Change in HbA1c (week 0 to 52) Change in body weight (kg) (week 0 to 52) Change in FPG
PIONEER 3 NCT026865 Rosenstock et al N=1864 18 and older	SEM 3 mg SEM 7 mg SEM 14 mg SITA 100 mg	MET +/- SU	Male or female, age at least 18 years at the time of signing informed consent Diagnosed with T2DM for at least 90 days prior to day of screening HbA1c 7.0-10.5% (53-91 mmol/mol) Stable daily dose of MET (at least 1500 mg or MTD) within 90 days prior to the day of screening	78 weeks	<u>Primary</u> Change in HbA1c (week 0 to 26)	<u>Secondary</u> Change in body weight (week 0 to 26) Change in HbA1c (weeks 0 to 52, 78) Change in body weight (kg) (weeks 0 to 52,78) Change in body weight (%) Change in FPG Change in BMI Change in waist circumference
Empagliflozin						

EMPA REG OUTCOME (CVOT) NCT01131676 Zinman et al N=7064	EMPA 10 mg EMPA 25 mg PBO	Naïve or pre-treated with any background therapy	Diagnosis of T2DM Male or female patients on diet and exercise regimen who are drug naive or pre-treated with any background therapy Antidiabetic therapy has to be unchanged for 12 weeks prior to randomization HbA1c of ≥7.0% and ≤10% for patients on background therapy or HbA1c ≥ 7.0% and ≤9.0% for drug naive patients Age ≥18 years BMI ≤45 kg/m^2 at Visit 1	Up to 4.6 years	<u>Primary</u> Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint (MACE-3): CV Death (including fatal stroke and fatal MI) Non-fatal MI (excluding silent MI) Non-fatal Stroke	<u>Secondary</u> Percentage of participants with the composite of all events adjudicated (MACE-4): CV Death (including fatal stroke and fatal MI) Non-fatal MI (excluding silent MI) Non-fatal stroke Hospitalization for Unstable Angina Pectoris Percentage of participants with silent MI

BMI: body mass index, CVOT: cardiovascular outcomes trial, DUA: dulaglutide, EMPA: empagliflozin, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, MACE: major adverse cardiovascular event, MACE-3: 3-point MACE, MACE-4: 4-point MACE, MET: metformin, mg: milligram, MTD: maximum tolerated dose, OAD: oral antidiabetic drug, PBO: placebo, PK: pharmacokinetics, PRO: patient-reported outcomes, QW: once weekly, SC: subcutaneous, SEM: semaglutide, SGLT-2: sodium-dependent glucose co-transporter-2, SIT: sitagliptin, SMBG: self-monitoring of blood glucose, SU: sulfonylurea, TZP: tirzepatide, T2DM: type 2 diabetes mellitus

Table D4.3. Baseline Characteristics – Tirzepatide[8,9,32,34]

Study		Frias 2018				Frias 2020			SURPASS -2				SURPASS-4				
Arm		PBO	TZP 5 mg	TZP 10 mg	TZP 15 mg	PBO	TZP 15 mg-1	TZP 15 mg-2	TZP 5 mg	TZP 10 mg	TZP 15 mg	SEM 1 mg	TZP 5 mg	TZP 10 mg	TZP 15mg	Insulin G	Overal l
N		51	55	51	53	26	28	28	470	469	470	469	329	328	338	1000	1995
Age, y	Mean (SD)	56.6 (8.9)	57.9 (8.2)	56.5 (9.9)	56.0 (7.6)	56.0 (10.13)	55.5 (8.54)	56.6 (9.21)	56.3 (10.0)	57.2 (10.5)	55.9 (10.4)	56.9 (52)	62.9 (8.6)	63.7 (8.7)	63.7 (8.6)	63.8 (8.5)	63.6 (8.6)
Sex, n (%)	Men	29 (57)	34 (62)	30 (59)	22 (42)	12 (46.2)	16 (57.1)	23 (82.1)	205 (43.6)	238 (50.7)	214 (45.5)	225 (48)	198 (60)	209 (64)	203 (60)	636 (64)	1246 (62)
	Women	22 (43)	21 (38)	21 (41)	31 (59)	NR	NR	NR	265 (56.4)	231 (49.2)	256 (54.5)	244 (52.0)	131 (40)	119 (36)	135 (40)	364 (36)	749 (38)
Diabetes Duration, y	Mean	8.6	8.9	7.9	8.5	8.8	8.2	8.9	9.1	8.4	8.7	8.3	9.8	10.6	10.4	10.7	10.5
	SD	7	5.7	5.8	6.1	6.43	4.87	6.35	7.16	5.9	6.85	5.8	6.2-15.3	6.5-16.2	5.5-15.7	6.3-16.5	6.2-15.9
HbA1c mean (SD)	%	8.0 (0.9)	8.2 (1.0)	8.2 (1.1)	8.1 (1.1)	8.2 (1.2)	8.5 (1.2)	8.4 (1.1)	8.3 (1.1)	8.3 (1.0)	8.3 (1.0)	8.3 (1.0)	8.52 (0.84)	8.59 (0.91)	8.52 (0.98)	8.50 (0.85)	8.52 (0.88)
Weight, kg	Mean	91.5	92.8	92.7	89.1	89.6	88.7	89.6	92.5	94.8	93.8	93.7	90.3	90.6	90	90.2	90.3
	SD	23.1	19	19.5	22.7	23.7	18.21	16.91	21.76	22.71	21.83	21.12	20.32	18.21	16.34	19	18.66
BMI, kg/m^2	Mean (SD)	32.4 (6.0)	32.9 (5.7)	32.6 (5.8)	32.2 (6.2)	32.5 (5.7)	32.0 (5.56)	31.1 (4.21)	33.8 (6.85)	34.3 (6.60)	34.5 (7.11)	34.2 (7.15)	32.6 (6.06)	32.8 (5.51)	32.5 (5.02)	34.5 (5.55)	32.6 (5.54)
Waist cm	Mean (SD)	107.7 (2.06)	110.1 (2.0)	109.6 (2.04)	107.6 (2.17)	109.1 (15.38)	107.0 (12.65)	105.1 (12.19)	108.06 (14.81)	110.55 (16.05)	109.55 (15.60)	109.04 (14.90)	NR	NR	NR	NR	NR
eGFR	Mean (SD)	95.3 (15.3)	92.2 (17.2)	93.7 (18.6)	91.8 (17.9)	NR	NR	NR	96.6 (17.51)	95.5 (16.62)	96.3 (16.92)	95.6 (17.25)	80.3 (22.66)	81.4 (20.44)	81.6 (21.22)	81.5 (20.78)	81.3 (21.11)
Metformin use, N (%)	Yes	47 (92.2)	49 (89.1)	44 (86.3)	51 (96.2)	23 (88.5)	25 (89.3)	23 (82.1)	470 (100)	469 (100)	470 (100)	469 (100)	306 (93)	316 (96)	317 (94)	954 (95)	1893 (95)
Ethnicity, N (%)	Hispanic	27 (59)	22 (49)	26 (57)	23 (46)	NR	NR	NR	325 (69.1)	322 (68.7)	334 (71.1)	336 (71.6)	NR	NR	NR	NR	NR
	Non-Hispanic	19 (41)	23 (51)	20 (44)	27 (54)	NR	NR	NR	145 (30.9)	147 (31.3)	136 (28.9)	133 (28.4)	NR	NR	NR	NR	NR

Race, N (%)	American Indian/ Alaska Native	NR	NR	NR	NR	NR	NR	NR	53 (11.3)	53 (11.3)	57 (12.1)	45 (9.6)	NR	NR	NR	NR	NR
	Black	2 (4)	6 (11)	7 (14)	6 (11)	NR	NR	NR	28 (6.0)	21 (4.5)	15 (3.2)	15 (3.2)	13 (4)	17 (5)	11 (3)	32 (3)	73 (4)
	Asian	1 (2)	0	1 (2)	1 (2)	NR	NR	NR	6 (1.3)	11 (2.3)	5 (1.1)	3 (0.6)	15 (5)	16 (5)	8 (2)	31 (3)	70 (4)
	White	41 (80)	46 (84)	37 (74)	43 (81)	NR	NR	NR	382 (81.3)	376 (80.2)	334 (71.1)	336 (71.6)	260 (79)	259 (79)	285 (85)	825 (83)	1629 (82)

A dulaglutide arm and 1mg tirzepatide arm in Frias 2018 and 12mg Tirzepatide arm in Frias 2020 are also available. Frias 2020 has two 15-mg arms following two different dosing schedules. N: number, NR: not reported, PBO: placebo, SD: standard deviation, TZP: tirzepatide

Table D4.4. Outcomes– Tirzepatide Phase 2 Trials [8,32]

Study		Frias 2018				Frias 2020			
Arm		PBO	TZP 5 mg	TZP 10 mg	TZP 15 mg	PBO	TZP 12 mg	TZP 15 mg-1	TZP 15 mg-2
N		51	55	51	53	26	29	28	28
Timepoint		26 wks				12 wks			
Glycemia endpoints									
HbA1c, %	Mean, Change from BL	0.1	-1.6	-2	-2.4	0.2	-1.7	-2	-1.8
	ETD	NR	NR	NR	NR	REF	-1.9	-2.2	-2
	95% CI (ETD)	REF	-1.88 to -1.46	-2.04 to -1.61	-2.11 to -1.67	REF	-2.5 to -1.4	-2.8 to -1.7	-2.5 to -1.4
	P-Value (ETD)	REF	<0.0001	<0.0001	<0.0001	REF	<0.001	<0.001	<0.001
Lipid Levels									
Triglycerides, mg/dL	Change from BL	26.6	-44.3	-62	-70.9	NR	NR	NR	NR
Total Cholesterol, mg/dL	Change from BL	11.6	-3.9	-11.6	-11.6	NR	NR	NR	NR
HDL Cholesterol, mg/dL	Change from BL	0	0	0	3.9	NR	NR	NR	NR
LDL Cholesterol, mg/dL	Change from BL	7.7	0	0	-3.9	NR	NR	NR	NR
Body Weight Endpoints									
Weight, kg	Change from BL	-0.4	-4.8	-8.7	-11.3	-0.5	-5.3	-5.5	-5.7
	ETD	NR	NR	NR	NR	REF	-4.8	-5	-5.2
	95% CI	NR	NR	NR	NR	REF	-7.1 to -2.6	-7.2 to -2.7	-7.5 to -2.9
	P-Value	NR	NR	NR	NR	REF	<0.001	<0.001	<0.001
Mean Waist Circumference	Change from BL, cm	-1.3	-5.1	-7.4	-10.2	-2.5	-4.8	-4.9	-4.9
	ETD	NR	NR	NR	NR	REF	-2.2	-2.4	-2.4
	95% CI	NR	NR	NR	NR	REF	-4.7 to 0.2	-4.9 to 0.1	-4.9 to -0.2
	P-Value	NR	NR	NR	NR	REF	0.075	0.065	0.065
Blood Pressure and Pulse Rate									

DBP, mmHg	Change from BL	0.8 (1.26)	-0.7 (1.18)	-0.2 (1.22)	-0.7 (1.27)	NR	NR	NR	NR
	ETD	NR	NR	NR	NR	NR	NR	NR	NR
	95% CI	NR	NR	NR	NR	NR	NR	NR	NR
	P-Value	NR	NR	NR	NR	NR	NR	NR	NR
SBP, mmHg	Change from BL	1.7 (1.98)	-2.6 (1.86)	-1.3 (1.92)	-1.0 (2.00)	NR	NR	NR	NR
	ETD	NR	NR	NR	NR	NR	NR	NR	NR
	95% CI	NR	NR	NR	NR	NR	NR	NR	NR
	P-Value	NR	NR	NR	NR	NR	NR	NR	NR
Achieving HbA1C targets									
<7%	N (%)	6 (11.8)	38 (69.1)	45 (90)	41 (77.4)	NR	NR	NR	NR
	OR (95% CI)	REF	20.98 (7.28 to 60.50)	89.44 (24.41 to 327.76)	33.63 (11.02 to 102.62)	NR	NR	NR	NR
	P value	REF	<0.0001	<0.0001	<0.0001	NR	NR	NR	NR
<6.5%	N (%)	1 (2)	35 (63.6)	41 (82)	31 (58.5)	NR	NR	NR	NR
	OR (95% CI)	REF	73.64 (12.92 to 419.77)	200.87 (32.74 to >999)	56.95 (10.01 to 323.97)	NR	NR	NR	NR
	P value	REF	<0.0001	<0.0001	<0.0001	NR	NR	NR	NR
<5.7%	N (%)	1 (2)	2 (3.6)	9 (18)	16 (30.2)	NR	NR	NR	NR
	OR (95% CI)	REF	1.60 (0.21 to 12.26)	7.75 (1.33 to 44.97)	14.42 (2.61 to 79.75)	NR	NR	NR	NR
	P value	REF	0.6506	0.0225	0.0022	NR	NR	NR	NR
Achieving bodyweight targets									
≥5%	N (%)	0 (0)	26 (47.3)	36 (70.6)	33 (62.3)	NR	NR	NR	NR
	OR (95% CI)	REF	90.91 (5.45 to >999)	236.84 (13.99 to >999)	161.12 (9.62 to >999)	NR	NR	NR	NR
	P value	REF	0.0017	0.0002	0.0004	NR	NR	NR	NR
≥10 %	N (%)	0 (0)	9 (16.4)	20 (39.2)	20 (37.7)	NR	NR	NR	NR

	OR (95% CI)	REF	20.82 (1.22 to 355.42)	67.57 (4.07 to >999)	66.20 (3.99 to >999)	NR	NR	NR	NR
	P value	REF	0.036	0.0033	0.0034	NR	NR	NR	NR
≥15 %	N (%)	0 (0)	3 (5.5)	11 (21.6)	13 (24.5)	NR	NR	NR	NR
	OR (95% CI)	REF	NR	NR	NR	NR	NR	NR	NR
	P value	REF	NR	NR	NR	NR	NR	NR	NR

A dulaglutide arm in Frias 2018 and 12 mg Tirzepatide arm in Frias 2020 are also available. Frias 2020 has two 15-mg arms following two different dosing schedules. BL: baseline, CI: confidence interval, DBP: diastolic blood pressure, ETD: estimated treatment difference, N: number, NR: not reported, OR: odds ratio, PBO: placebo, REF: reference, SBP: systolic blood pressure, SD: standard deviation, TZP: tirzepatide

Table D4.5. Outcomes– Tirzepatide Phase 3 Trials[9,34]

Study		**SURPASS-2**				**SURPASS-4**			
Arm		TZP 5 mg	TZP 10 mg	TZP 15 mg	SEM 1 mg	TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin Glargine
N		470	469	470	469	328	326	337	998
Timepoint		40 wks				52 wks			
Glycemia endpoints									
HbA1c, %	Mean, Change from BL	-2.01	-2.24	-2.3	-1.86	-2.24	-2.43	-2.58	-1.44
	ETD	-0.15	-0.39	-0.45	REF	-0.80	-0.99	-1.14	REF
	95% CI (ETD)	-0.28 to -0.03	-0.51 to -0.26	-0.57 to -0.32	REF	-0.92 to -0.68	-1.11 to -0.87	-1.26 to -1.02	REF
	P-Value (ETD)	0.02	<0.001	<0.001	REF	<0.0001	<0.0001	<0.0001	REF
Lipid levels, mg/dL									
Triglycerides	Change from BL	-31.4*	-40*	-41.1*	-19.1*	-16.3	-20.1	-22.5	-6.4
Total Cholesterol	Change from BL	-9.4*	-10.2*	-10.7*	-8.2*	-5.2	-5.5	-5.6	0
HDL Cholesterol	Change from BL	2.9*	3.4*	3*	1.9*	6.7	9.7	10.8	2.9

Study		SURPASS-2				SURPASS-4			
Arm		TZP 5 mg	TZP 10 mg	TZP 15 mg	SEM 1 mg	TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin Glargine
LDL Cholesterol	Change from BL	-6.7*	-4.9*	-4.5*	-5.6*	-6.8	-8.3	-7.9	1.4
Body Weight Endpoints									
Weight, kg	Change from BL	-7.6	-9.3	-11.2	-5.7	-7.1	-9.5	-11.7	1.9
	ETD	-1.9	-3.6	-5.5	REF	-9.0	-11.4	-13.5	REF
	95% CI	-2.8 to -1.0	-4.5 to -2.7	-6.4 to -4.6	REF	-9.8 to -8.3	-12.1 to -10.6	-12.1 to -10.6	REF
	P-Value	<0.001	<0.001	<0.001	REF	<0.0001	<0.0001	<0.0001	REF
Mean Waist Circumference, cm	Change from BL	-6.9*	-9.6*	-9.9*	-5.6*	-8.41†	-8.27†	-9.46†	1.4†
	ETD	NR	NR	NR	NR	NR	NR	NR	NR
	95% CI	NR	NR	NR	NR	NR	NR	NR	NR
	P-Value	NR	NR	NR	NR	NR	NR	NR	NR
Blood pressure and pulse rate									
DBP, mmHg	Change from BL	-4.5	-5.3	-6.5	-3.6	1†	0.94†	0.8†	-0.72†
	ETD	NR	NR	NR	NR	NR	NR	NR	NR
	95% CI	NR	NR	NR	NR	NR	NR	NR	NR
	P-Value	NR	NR	NR	NR	NR	NR	NR	NR
SBP, mmHg	Change from BL	NR	NR	NR	NR	-1.65†	-4.33†	-4.59†	-1.2†
	ETD	NR	NR	NR	NR	NR	NR	NR	NR
	95% CI	NR	NR	NR	NR	NR	NR	NR	NR
	P-Value	NR	NR	NR	NR	NR	NR	NR	NR
Achieving HbA1c targets									
<7%	N (%)	394 (85.5) *	408 (88.9) *	428 (92.2) *	374 (81.1) *	264 (88)	283 (88)	303 (91)	496 (51)
	OR (95% CI)	1.54 (1.06 to 2.23)	2.14 (1.44 to 3.17)	3.03 (1.97 o 4.66)	REF	4.78 (3.47 to 6.58)	9.23 (6.31 to 13.49)	11.87 (7.88 to 17.89)	REF
	P value	NR	NR	NR	NR	<0.0001	<0.0001	<0.0001	REF
<6.5%	N (%)	341 (74) *	377 (82.1) *	404 (87.1) *	305 (66.2) *	215 (66)	244 (76)	271 (81)	310 (32)

Study		SURPASS-2				SURPASS-4			
Arm		TZP 5 mg	TZP 10 mg	TZP 15 mg	SEM 1 mg	TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin Glargine
	OR (95% CI)	1.63 (1.2 to 2.21)	2.75 (1.98 to 3.82)	3.95 (2.78 to 5.61)	REF	4.86 (3.66 to 6.45)	8.93 (6.53 to 12.21)	11.84 (8.52 to 16.45)	REF
	P value	NR	NR	NR	NR	<0.0001	<0.0001	<0.0001	REF
<5.7%	N (%)	135 (29.3) *	205 (44.7) *	236 (50.9) *	91 (19.7) *	75 (23)	105 (33)	144 (43)	33 (3)
	OR (95% CI)	1.86 (1.35 to 2.57)	3.94 (2.88 to 5.39)	5.1 (3.73 to 6.97)	REF	9.57 (6.16 to 14.86)	17.11 (11.12 to 26.35)	26.53 (17.35 to 40.56)	REF
	P value	NR	NR	NR	NR	<0.0001	<0.0001	<0.0001	REF
Achieving bodyweight targets									
≥5%	N (%)	316 (68.6)*	378 (82.4) *	400 (86.2) *	270 (58.4) *	205 (63)	249 (78)	285 (85)	78 (8)
	OR (95% CI)	1.58 (1.2 to 2.08)	3.49 (2.57, 4.75)	4.6 (3.32, 6.38)	REF	21.42 (15.53 to 29.89)	46.14 (32.05 to 66.42)	76.93 (51.76 to 114.35)	REF
	P value	NR	NR	NR	NR	<0.0001	<0.0001	<0.0001	REF
≥10 %	N (%)	165 (35.8)*	243 (52.9)*	301 (64.9)*	117 (25.3)*	117 (36)	170 (53)	219 (66)	15 (2)
	OR (95% CI)	1.68 (1.26, 2.25)	3.58 (2.69, 4.77)	5.85 (4.37, 7.82)	REF	20.6 to 61.5)	76.79 (44.2 to 132.7)	127.5 (73.5 to 221.1)	REF
	P value	NR	NR	NR	NR	<0.0001	<0.0001	<0.0001	REF
≥15 %	N (%)	70 (15.2)*	127 (27.7)*	185 (39.9)*	40 (8.7)*	45 (14)	77 (24)	122 (37)	5 (<1)
	OR (95% CI)	1.92 (1.27, 2.90)	4.27 (2.9, 6.29)	7.44 (5.09, 10.87)	NR	28.58 (11.88 to 68.75)	59.14 (25 to 139.86)	105.74 (45.1 to 247.87)	REF
	P value	NR	NR	NR	NR	<0.0001	<0.0001	<0.0001	REF

Frias 2020 has two 15-mg arms following two different dosing schedules. TZP: tirzepatide, PBO: placebo, N: number, NR: not reported, SD: standard deviation, ETD: estimated treatment difference, REF: reference, OR: odds ratio, CI: confidence interval, BL: baseline, DBP: diastolic blood pressure, SBP: systolic blood pressure

*Efficacy estimand

†Digitized and calculated by ICER staff

Table D4.6. Safety – Tirzepatide[8,9,32,34]

Study	Frias 2018					Frias 2020				SURPASS-2		SURPASS-4			
Arm	PBO	TZP 5 mg	TZP 10 mg	TZP 15 mg	DUA 1.5 mg	PBO	TZP 12 mg	TZP 15 mg-1	TZP 15 mg-2	TZP 15 mg	SEM 1 mg	TZP 5 mg	TZP 10 mg	TZP 15 mg	Insulin Glargine
N	51	55	51	53	54	26	29	28	28	470	469	328	326	337	998
Timepoint	26 wks					12 wks						104 wks			
Any AE	NR	NR	NR	NR	NR	NR	NR	NR	NR	324 (68.9)	301 (64.2)	NR	NR	NR	NR
Any TEAE, n (%)	27 (52.9)	40 (72.7)	40 (78.4)	45 (84.9)	40 (74.1)	13 (50)	23 (79.3)	19 (67.9)	24 (85.7)	NR	NR	232 (71)	241 (74)	259 (77)	679 (68)
D/C Due to AE, n (%)	1 (2.0)	0	1 (2.0)	2 (3.8)	2 (3.7)	0	0	0	0	40 (8.5)	19 (4.1)	37 (11)	28 (9)	36 (11)	54 (5)
D/C from Study Drug	2 (3.9)	5 (9.1)	3 (5.9)	13 (24.5)	6 (11.1)	1 (3.8)	1 (3.4)	1 (3.6)	0	NR	NR	8%	7%	9%	3%
Serious AE	2 (3.9)	1 (1.8)	3 (5.9)	2 (3.8)	3 (5.6)	0	1 (3.4)	0	0	27 (5.7)	13 (2.8)	48 (15)	54 (17)	41 (12)	193 (19)
Death	1 (2.0)*	0	0	0	0	0	0	0	0	4 (0.9)	1 (0.2)	15 (5)	2 (<1)	8 (2)	25 (4)
Diarrhea	2 (3.9)	13 (23.6)	12 (23.5)	17 (32.1)	9 (16.7)	2 (7.7)	9 (31.0)	10 35.7)	9 (32.1)	65 (13.8)	54 (11.5)	12.2	19.5	20.4	3.2
Nausea	3 (5.9)	11 (20)	11 (21.6)	21 (39.6)	16 (29.6)	2 (7.7)	7 (24.1)	11 (39.3)	10 (35.7)	104 (22.1)	84 (17.9)	11.9	15.9	22.2	1.6
Decreased Appetite	1 (2.0)	11 (20)	13 (25.5)	10 (18.9)	3 (5.6)	0	4 (13.8)	6 (21.4)	8 (28.6)	42 (8.9)	25 (5.3)	29 (9)	36 (11)	35 (10)	5 (<1)
Vomiting	1 (2)	4 (7.3)	8 (15.7)	14 (26.4)	5 (9.3)	1 (3.8)	5 (17.2)	5 (17.9)	5 (17.9)	46 (9.8)	39 (8.3)	4.9	8.2	8.3	1.1
Headache	2 (3.9)	2 (3.6)	1 (2)	5 (9.4)	1 (1.9)	2 (7.7)	2 (6.9)	6 (21.4)	5 (17.9)	NR	NR	NR	NR	NR	NR
Dyspepsia	0	1 (1.8)	6 (11.8)	2 (3.8)	2 (3.7)	0	5 (17.2)	3 (10.7)	3 (10.7)	43 (9.1)	31 (6.6)	18 (6)	27 (8)	26 (8)	13 (1)
Abdominal Pain	1 (2.0)	1 (1.8)	0	3 (5.7)	1 (1.9)	1 (3.8)	1 (3.4)	5 (17.9)	1 (3.6)	24 (5.1)	24 (5.1)	NR	NR	NR	NR
Dizziness	2 (3.9)	2 (3.6)	2 (3.9)	5 (9.4)	1 (1.9)	2 (7.7)	0	1 (3.6)	3 (10.7)	NR	NR	NR	NR	NR	NR
Hypoglycemia (≤70 mg/dL)	2 (3.9)	4 (7.3)	5 (9.8)	4 (7.5)	2 (3.7)	0	2 (6.9)	5 (17.9)	5 (17.9)	NR	NR	NR	NR	NR	NR
Hypoglycemia (≤54 mg/dL)	NR	NR	NR	NR	NR	0	0	0	0*	8 (1.7)	2 (0.4)	6.7	5.5	6.5	15.0
Severe hypoglycemia	0	0	0	0	0	0	0	0	0	1 (0.2)	0	NR	NR	NR	NR

Cholecystitis	0	0	1 (2.0)	0	1 (1.9)	0	0	0	0	4 (0.9)	2 (0.4)	3 (<1)	1 (<1)	1 (<1)	4 (<1)
Acute pancreatitis	0	2 (3.6)	0	0	0	0	0	0	0	2 (0.4)	3 (0.6)	NR	NR	NR	NR
Injection site reaction	2 (3.9)	3 (5.5)	4 (7.8)	1 (1.9)	6 (11.1)	0	2 (6.9)	2 (7.1)	0	21 (4.5)	1 (0.2)	1 (<1)	2 (<1)	1 (<1)	4 (<1)
Hypersensitivity	5 (9.8)	2 (3.6)	2 (3.9)	2 (3.8)	0	1 (3.8)	0	0	0	8 (1.7)	11 (2.3)	NR	NR	NR	NR
Diabetic Retinopathy	0	0	0	0	0	NR	NR	NR	NR	0	0	5 (2) †	5 (2) †	4(1) †	15 (2) †

Frias 2020 has two 15-mg arms following two different dosing schedules. AE: adverse event, BL: baseline, CI: confidence interval, D/C: discontinuation, ETD: estimated treatment difference, N: number, NR: not reported, OR: odds ratio, PBO: placebo, REF: reference, SD: standard deviation, TEAE: treatment emergent adverse event, TZP: tirzepatide

*Fatal TEAE

†Diabetic retinopathy complications

Safety Outcomes for Injectable Semaglutide and Empagliflozin

Injectable Semaglutide

In the SUSTAIN-6 CVOT, there was a greater incidence of AEs that led to study discontinuation in the pooled semaglutide versus pooled placebo group (13% vs 6.7%, respectively; p=NR)(Table D4.10). The rates of gastrointestinal AEs (nausea, vomiting, diarrhea) were greater in the semaglutide arm than placebo, in line with expectations of the GLP-1 RA class. Semaglutide carries an FDA warning label for pancreatitis; less than one percent of participants in either pooled arm experienced adjudicated acute pancreatitis (p=NR). Semaglutide is contraindicated in patients with medullary thyroid carcinoma; neither treatment arm experienced this adverse event. There was little difference between arms in occurrence of malignant neoplasms.

Empagliflozin

In the EMPA REG OUTCOME CVOT, there was a significantly lower incidence of AEs that led to study discontinuation in the pooled empagliflozin versus placebo group (17.3% vs 19.4%, respectively; p<.01)(Table D4.10). The most frequent adverse events in the trial were urinary tract infection and genital infection (Table D4.10). Among female study participants, those treated with empagliflozin experienced fewer rates of urinary tract infection than placebo (36.4% vs 40.6%, respectively; p<.05). Empagliflozin significantly increased the rate of genital infection versus placebo (6.4% vs 1.8%). Within the empagliflozin treatment arm, female participants had twice the rate of genital infection versus male participants (10.0% vs 5.0%).

Table D4.7. Baseline Characteristics– NMA Linkage Studies[38,96-98]

Study		SUSTAIN-2		PIONEER 2			PIONEER 3		HARMONY 3	
Arm		SEM 1.0 mg	SITA 100 mg	OSEM 14 mg	EMPA 25 mg	Total	SEM 14 mg	SITA 100 mg	PBO	SITA 100mg
N		409	407	411	410	821	465	467	101	302
Age, y	Mean (SD)	56.0 (9.4)	54.6 (10.4)	57 (10)	58 (10)	58 (10)	57 (10)	58 (10)	56.1 (10.0)	54.3 (9.8)
Sex, n (%)	Men	205 (50)	208 (51)	206 (50.1%)	209 (51.0%)	415 (50.6%)	247 (53.1%)	238 (51.0%)	50 (49.5)	139 (46.0)
	Women	204 (50)	199 (49)	205 (49.9)	201 (49.0)	406 (49.5)	218 (46.9)	229 (49.0)	NR	NR
Diabetes Duration, y	Mean	6.7	6.6	7.2	7.7	7.4	8.7	8.8	6.7	5.8
	SD	5.6	5.1	5.8	6.3	6.1	6.1	6	6.6	4.8
HbA1c, mean (SD)	%	8.0 (0.9)	8.2 (0.9)	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)	8.3 (0.9)	8.3 (0.9)	8.2 (0.9)	8.1 (0.8)
Weight, kg	Mean	89.2	89.3	91.9	91.3	91.6	91.2	90.9	91.6	90.3
	SD	20.7	19.7	20.5	20.1	20.3	21.7	21	19.3	19.1
BMI, kg/ m^2	mean (SD)	32.5 (6.6)	32.5 (5.8)	32.9 (6.3)	32.8 (5.9)	32.8 (6.1)	32.3 (6.3)	32.5 (6.2)	32.8 (5.4)	32.5 (5.4)
Waist Circumference, cm	Mean (SD)	NR	NR	NR	NR	NR	NR	NR	NR	NR
eGFR	Mean (SD)	97 (55-171)	98 (53-194)	96 (15)	95 (15)	95 (15)	95 (16)	96 (15)	NR	NR
Metformin use, N (%)	Yes	407 (100)	405 (100)	411 (100)	410 (100)	821 (100)	465 (100)	467 (100)	NR	NR
Ethnicity, N (%)	Hispanic	67 (16)	73 (18)	91 (22.1)	108 (26.3)	199 (24.2)	75 (16.1)	93 (19.9)	32 (31.7)	111 (36.8)
	Non-Hispanic	342 (84)	334 (82)	320 (77.9)	302 (73.7)	622 (75.8)	390 (83.9)	374 (80.1)	NR	NR
Race, N (%)										
American Indian/Alaska Native		NR	NR	NR	NR	NR	5 (1.1)	6 (1.3)	NR	NR
Black		24 (6)	17 (4)	26 (6.3)	33 (8.0)	59 (7.2)	45 (9.7)	39 (8.4)	23 (22.8)	35 (11.6)

Asian	99 (24)	102 (25)	28 (6.8)	21 (5.1)	49 (6.0)	61 (13.1)	59 (12.6)	5 (5.0)	20 (6.6)
White	279 (68)	281 (69)	355 (86.4)	353 (86.1)	708 (86.2)	317 (68.2)	333 (71.3)	64 (63.4)	225 (74.5)

EMPA: empagliflozin, N: number, NR: not reported, OSEM: oral semaglutide, REF: reference, SD: standard deviation, SEM: semaglutide, y: years

Table D4.8. Outcomes– NMA Linkage Studies[38,96-98]

Study		SUSTAIN-2			PIONEER-2		PIONEER-3		HARMONY 3	
Arm		SEM 0.5 mg	SEM 1.0 mg	SITA 100 mg	OSEM 14 mg	EMPA 25 mg	OSEM 14 mg	SITA 100 mg	PBO	SITA 100 mg
N		409	409	407	411	410	465	467	101	302
Timepoint		56 wks			52 wks				104 wks	
Glycaemia Endpoints										
HbA1c, %	Mean, Change from BL	-1.3	-1.6*	-0.5*	-1.3	-0.9	-1.2	-0.7	NR	NR
	ETD	-0.77	-1.06	NA	-0.4	REF	-0.5	REF	NR	NR
	95% CI (ETD)	-0.92 to -0.62	-1.21 to -0.91	NA	-0.5 to -0.3	REF	-0.6 to -0.3	REF	NR	NR
	P-Value (ETD)	<0.0001	<0.0001	REF	<0.0001	REF	<0.001	REF	NR	NR
Lipid Levels										
Triglycerides, mg/dL	Change from BL	NR	NR	NR	-16.8	-15.9	-10.9	-1.6	-3.5*	-13.2*
Total Cholesterol, mg/dL	Change from BL	NR	NR	NR	-5.4	3.9	-1.7	1.7	-1.9*	-3.5*
HDL Cholesterol, mg/dL	Change from BL	NR	NR	NR	0.4	2.7	0.4	0	1.2*	1.2*
LDL Cholesterol, mg/dL	Change from BL	NR	NR	NR	-3.9	2.7	0	2.8	-1.2*	-1.9*
Body Weight Endpoints										
Weight, kg	Change from BL	-4.3	-6.1	-1.9	-3.8	-3.6	-3.4	-0.8	-1.0*	-0.86*

	ETD	-2.35	-4.20	NA	-0.2	REF	-2.7	REF	NR	NR
	95% CI	-3.06 to -1.63	-4.91 to -3.49	NA	-0.9 to 0.5	REF	-3.3 to -2.1	REF	NR	NR
	P-Value	<0.0001	<0.0001	REF	0.6231	REF	<0.001	REF	NR	NR
Mean Waist Circumference, cm	Change from BL	-4.3	-5.9	-2.2	-3.5	-2.9	-2.6	-0.4	NR	NR
	ETD	-2.10	-3.67	NA	-0.6	REF	-2.2	REF	NR	NR
	95% CI	-2.91 to -1.29	-4.48 to -2.87	NA	-1.4 to 0.2	REF	-3.0 to -1.4	REF	NR	NR
	P-Value	<0.0001	<0.0001	REF	0.1488	REF	<0.001	REF	NR	NR
Blood Pressure and Pulse Rate										
DBP, mmHg	Change from BL	-2.0	-1.9	-1.1	-2	-2	-2	-1	0*	0.2*
	ETD	-0.90	-0.80	NA	0	REF	-1	REF	NR	NR
	95% CI	-2.10 to 0.30	-2.00 to 0.40	NA	-1 to 2	REF	-2 to 0	REF	NR	NR
	P-Value	0.14	0.19	REF	0.6551	REF	0.28	REF	NR	NR
SBP, mmHg	Change from BL	-5.1	-5.6	-2.3	-4	-4	-3	-1	2.2*	0.2*
	ETD	-2.78	-3.32	NA	0	REF	-2	REF	NR	NR
	95% CI	-4.59 to -0.97	-5.13 to -1.52	NA	-2 to 2	REF	-4 to -1	REF	NR	NR
	P-Value	0.0026	0.0003	REF	0.9371	REF	0.01	REF	NR	NR
Achieving HbA1C Targets										
<7%	N (%)	282 (69) *	321 (78) *	148 (36) *	214 (55.7)	149 (39)	53	31	15.5*	31.6*
	OR (95% CI)	4.16 (3.02 to 5.74)	7.92 (5.59 to 11.22)	REF	2.03 (1.50 to 2.74)	REF	22 (16 to 28)	REF	NR	NR
	P value	<0.0001	<0.0001	REF	<0.0001	REF	<0.001	REF	NR	NR
<6.5%	N (%)	215 (53) *	270 (66) *	83 (20) *	182 (47.4)	83 (21.7)	32	14	7.2*	15.2 *

	OR (95% CI)	4.39 (3.15 to 6.12)	8.99 (6.36 to 12.72)	REF	3.36 (2.43 to 4.66)	REF	18 (13 to 24)	REF	NR	NR
	P value	<0.0001	<0.0001	REF	<0.0001	REF	<0.001	REF	NR	NR
<5.7%	N (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	OR (95% CI)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P value	NR	NR	NR	NR	NR	NR	NR	NR	NR
Achieving bodyweight reduction Targets										
≥5%	N (%)	188 (46)	254 (62)	75 (18)	NR	NR	34	12	NR	NR
	OR (95% CI)	3.76 (2.72 to 5.19)	7.47 (5.38 to 10.37)	REF	NR	NR	22 (16 to 27)	REF	NR	NR
	P value	<0.0001	<0.0001	REF	NR	NR	<0.001	REF	NR	NR
≥10 %	N (%)	52 (13)	97 (24)	14 (3)	58 (15)	30 (7.8)	11	3	NR	NR
	OR (95% CI)	4.09 (2.26 to 7.40)	8.85 (5.01 to 15.61)	REF	2.05 (1.28 to 3.28)	REF	8 (5 to 12)	REF	NR	NR
	P value	<0.0001	<0.0001	REF	0.0028	REF	<0.001	REF	NR	NR
≥15 %	N (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	OR (95% CI)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P value	NR	NR	NR	NR	NR	NR	NR	NR	NR

BL: baseline, CI: confidence interval, DBP: diastolic blood pressure, EMPA: empagliflozin, ETD: estimated treatment difference, N: number, NA: not applicable, NR: not reported, OR: odds ratio, OSEM: oral semaglutide, REF: reference, SBP: systolic blood pressure, SD: standard deviation, SEM: semaglutide, y: years, Lipid levels are NR, HbA1c target of <5.7% is NR, bodyweight target of >15% is NR.

*Efficacy estimand

Table D4.9. Safety– NMA Linkage Studies[38,96-98]

Study	SUSTAIN-2		PIONEER 2		PIONEER 3		HARMONY 3	
Arm	SEM 1.0 mg	SITA 100 mg	OSEM 14 mg	EMPA 25 mg	OSEM 14 mg	SITA 100 mg	PBO	SITA 100 mg
N	409	407	411	410	465	467	101	302
Timepoint	40 wks		52 wks		56 wks		104 wks	
Any AE	NR	NR	289 (70.5)	283 (69.2)	370 (79.6)	388 (83.3)	79.2	79.1
Any TEAE, n (%)	292 (71)	292 (72)	NR	NR	NR	NR	20.8	17.9
D/C Due to AE, n (%)	39 (10)	12 (3)	44 (10.7)	18 (4.4)	54 (11.6)	24 (52.)	5	3.6
D/C from Study Drug	NR	NR	NR	NR	NR	NR	NR	NR
Serious AE	30 (7)	29 (7)	27 (6.6)	37 (9.0)	44 (9.5)	58 (12.4)	12.9	17.9
Death	1 (1)	3 (1)	0	1 (0.2)	1 (0.2)	3 (0.6)	NR	NR
Diarrhea	53 (13)	29 (7)	38 (9.3)	13 (3.2)	57 (12.3)	37 (7.9)	10.9	8.6
Nausea	72 (18)	30 (7)	81 (19.8)	10 (2.4)	70 (15.1)	32 (6.9)	10.9	6.6
Decreased Appetite	27 (7)	11 (3)	21 (5.1)	2 (0.5)	32 (6.9)	14 (3.0)	NR	NR
Vomiting	41 (10)	11 (3)	30 (7.3)	7 (1.7)	42 (9.0)	19 (4.1)	NR	NR
Headache	29 (7)	17 (4)	NR	NR	37 (8.0)	36 (7.7)	NR	NR
Dyspepsia	20 (5)	9 (2)	NR	NR	0	0	NR	NR
Abdominal Pain	NR	NR	5 (1.2)	0	2 (0.4)	2 (0.4)	NR	NR
Dizziness	NR	NR	NR	NR	1 (0.2)	0	NR	NR
Hypoglycemia (plasma glucose ≤70 mg/dL)	NR	NR	45	39	131 (28.2)	112 (24.0)	NR	NR
Hypoglycemia (plasma glucose ≤54 mg/dL)	NR	NR	7 (1.7)	8 (2.0)	36 (7.7)	39 (8.4)	4 (4.0)	5 (1.7)
Severe hypoglycemia	NR	NR	1 (0.2)	1 (0.2)	1 (0.2)	4 (0.9)	0	0
Cholecystitis	1 (1)	0 (0)	NR	NR	NR	NR	NR	NR
Acute pancreatitis	--	--	1 (0.2)	1 (0.2)	3 (0.6)	1 (0.2)	NR	NR
Injection site reaction	NR	NR	NA	NA	NA	NA	2	1.7
Hypersensitivity	NR	NR	NR	NR	NR	NR	NR	NR
Diabetic Retinopathy	0	3 (1)	13 (3.2)	4 (1.0)	17 (3.7)	29 (6.2)	NR	NR

AE: adverse event, CI: confidence interval, D/C: discontinuation, EMPA: empagliflozin, N: number, NA: not applicable, NR: not reported, OR: odds ratio, OSEM: oral semaglutide, REF: reference, SD: standard deviation, SEM: semaglutide, TEAE: treatment emergent adverse event, y: years

Table D4.10. CVOT Studies[10,11]

Study		SUSTAIN-6		EMPA-REG-OUTCOME	
	Arms	SEM 1mg	PBO 1mg	PBO	EMPA (10/25mg)
N		822	825	2333	4687
	Timepoint	109 wks		156 wks	
Baseline Characteristics					
Age, yr		64.7 (7.1)	64.4 (7.5)	63.2 (8.8)	63.1 (8.6)
Male sex, N (%)		518 (63)	507 (61.5)	1680 (72.0)	3336 (71.2)
Weight, kg (SD)		92.9 (21.1)	91.9 (20.8)	86.6 (19.1)	86.2 (18.9)
BMI, kg/m^2 (SD)		32.9 (6.2)	32.7 (6)	30.7 (5.2)	30.6 (5.3)
Type 2 Diabetes					
Diabetes Duration, yr (SD)		14.1 (8.2)	13.2 (7.4)	NR	NR
Hemoglobin, % (SD)		8.7 (1.5)	8.7 (1.5)	8.08 (0.84)	8.07 (0.85)
Race					
White, n (%)		691 (84.1)	676 (81.9)	1678 (71.9)	3403 (72.6)
Asian, n (%)		58 (7.1)	72 (8.7)	511 (21.9)	1006 (21.5)
Black, n (%)		54 (6.6)	59 (7.2)	120 (5.1)	237 (5.1)
Ethnicity					
Hispanic or Latino, n (%)		124 (15.1)	137 (16.6)	418 (17.9)	847 (18.1)
Antihyperglycemic Medication at Baseline					
Metformin, n (%)		594 (72.3)	617 (74.8)	1734 (74.3)	3459 (73.8)
Insulin, n (%)		477 (58.0)	479 (58.1)	1135 (48.6)	2252 (48.0)
Sulfonylurea, n (%)		349 (42.5)	349 (42.3)	992 (42.5)	2014 (43.0)
Cardiovascular Risk Factors					
Systolic Blood Pressure (mmHg)		135.8 (17)	134.8 (17.5)	135.8 (17.2)	135.3 (16.9)
Diastolic Blood Pressure (mmHg)		76.9 (10.2)	76.7 (10.2)	76.8 (10.1)	76.6 (9.7)
LDL Cholesterol		83.3 (41.2)	83.6 (45.9)	84.9 (35.3)	85.9 (36.0)
Never Smoked, n (%)		364 (44.3)	348 (42.2)	957 (41.0)	1925 (41.1)
History of cardiovascular disease, N (%)					

Ischemic Heart Disease		495 (60.2)	496 (60.1)	1763 (75.6)	3545 (75.6)
Myocardial Infarction		264 (32.1)	275 (33.3)	1083 (46.4)	2190 (46.7)
Heart Failure		180 (21.9)	206 (25)	244 (10.5)	462 (9.9)
Ischemic Stroke		89 (10.8)	109 (13.2)	553 (23.7)	1084 (23.1)
Hemorrhagic Stroke		24 (2.9)	29 (3.5)		
Hypertension		771 (93.8)	760 (92.1)	NR	NR
Renal Function (Estimated glomerular filtration rate)					
≥90 mL/min/1.73m^2 (normal)		246 (29.9)	252 (30.5)	488 (20.9)	1050 (22.4)
60 to <90 mL/min/1.73m^2 (mild)		357 (43.4)	346 (41.9)	1238 (53.1)	2423 (51.7)
<60 mL/min/1.73m^2 (moderate to end stage)		219 (26.6)	227 (27.5)	607 (26.0)	1212 (25.9)
Outcomes					
Composite Outcome (CV Causes, Non-fatal MI, or Non-fatal stroke)	n (%)	108 (6.6)	146 (8.9)	282 (12.1)	490 (10.5)
	HR (95%CI)	0.74 (0.58 to 0.95)		0.86 (0.74 to 0.99)	
	p-value, NON	<0.001	REF	<.001	REF
	p-value, SUP	0.02	REF	0.04	REF
Expanded Composite Outcome (Death from CV Causes, Non-fatal MI, Non-fatal Stroke, Revascularization, Hospitalization, HF)	n (%)	199 (12.1)	264 (16.0)	333 (14.3)	599 (12.8)
	HR (95%CI)	0.74 (0.62 to 0.89)		0.89 (0.78 to 1.01)	
	p-value, NON	0.002	REF	<.001	REF
	p-value, SUP	NA	NA	0.08	REF
All Cause Death, Non-fatal MI, or Non-fatal Stroke	n (%)	122 (7.4)	158 (9.6)	NR	NR
	HR (95%CI)	0.77 (0.61 to 0.97)		NR	NR
	p-value	0.03	REF	NR	NR
From Any Cause	n (%)	62 (3.8)	60 (3.6)	194 (8.3)	269 (5.7)
	HR (95%CI)	1.05 (0.74 to 1.50)		0.68 (0.57 to 0.82)	
	p-value	0.79	REF	<.001	REF
From Cardiovascular Cause	n (%)	44 (2.7)	46 (2.8)	137 (5.9)	172 (3.7)
	HR (95%CI)	0.98 (0.65 to 1.48)		0.62 (0.49 to 0.77)	
	p-value	0.92	REF	<.001	REF
Non-fatal MI	n (%)	47 (2.9)	64 (3.9)	121 (5.2)*	213 (4.5)

	HR (95%CI)	0.74 (0.51 to 1.08)		0.87 (0.70-1.09)	
	p-value	0.12	REF	0.22	REF
Non-fatal Stroke	n (%)	27 (1.6)	44 (2.7)	60 (2.6)	150 (3.2)
	HR (95%CI)	0.61 (0.38 to 0.99)		1.24 (0.92 to 1.67)	
	p-value	0.04	REF	0.16	REF
Hospitalization for Unstable Angina	n (%)	22 (1.3)	27 (1.6)	66 (2.8)	133 (2.8)
	HR (95%CI)	0.82 (0.47 to 1.44)		0.99 (0.74 to 1.34)	
	p-value	0.49	REF	0.97	REF
Revascularization	n (%)	83 (5.0)	126 (7.6)	186 (8.0)	329 (7.0)
	HR (95%CI)	0.65 (0.50 to 0.86)		0.86 (0.72 to 1.04)	
	p-value	0.003	REF	0.11	REF
Hospitalization for Heart Failure	n (%)	59 (3.6)	54 (3.3)	95 (4.1)	126 (2.7)
	HR (95%CI)	1.11 (0.77 to 1.61)		0.65 (0.50 to 0.85)	
	p-value	0.57	REF	0.002	REF
Retinopathy Complications	n (%)	50 (3.0)	29 (1.8)	29 (1.2)	41 (0.9)
	HR (95%CI)	1.76 (1.11 to 2.78)		0.69 (0.43 to 1.12)	
	p-value	0.02	REF	0.134	REF
New or worsening nephropathy	n (%)	62 (3.8)	100 (6.1)	388 (18.8)	525 (12.7)
	HR (95%CI)	0.64 (0.46 to 0.88)		0.61 (0.53 to 0.70)	
	p-value	0.005	REF	<0.001	REF
Adverse Events, n (%)					
Adverse Events		732 (89.1)	736 (89.2)	2139 (91.7)	4230 (90.2)
Serious Adverse Event		276 (33.6)	298 (36.1)	592 (25.4)	1100 (23.5)
Severe Adverse Events		207 (25.2)	194 (23.5)	988 (42.3)	1789 (38.2)
Leading to D/C		119 (14.5)	63 (7.6)	453 (19.4)	813 (17.3)
Gastrointestinal Disorder		430 (52.3)	290 (35.2)	NR	NR
Nausea		151 (18.4)	87 (10.5)	NR	NR
Vomiting		122 (14.8)	34 (4.1)	NR	NR
Diarrhea		151 (18.4)	87 (10.5)	NR	NR

Gallbladder Disorder		26 (3.2)	23 (2.8)	NR	NR
Cholelithiasis		17 (2.1)	12 (1.5)	NR	NR
Acute Cholecystitis		0	2 (0.2)	NR	NR
Neoplasm		89 (10.8)	69 (8.4)	NR	NR
Benign		54 (6.6)	34 (4.1)	NR	NR
Malignancy, any		40 (4.9)	35 (4.2)	NR	NR
Malignancy, pancreatic		1 (0.1)	2 (0.2)	NR	NR
Other					
Severe or symptomatic hypoglycemic event		178 (21.7)	173 (21.0)	NR	NR
Acute renal failure		23 (2.8)	35 (4.2)	155 (6.6)	256 (5.2)
Allergic reaction		49 (6.0)	57 (6.9)	NR	NR
Injection Site Reaction		9 (1.1)	12 (1.5)	NR	NR
Cardiac disorder		150 (18.2)	173 (21.0)	NR	NR
Atrial Fibrillation		23 (2.8)	26 (3.2)	NR	NR
Acute Pancreatitis		3 (0.4)	9 (1.1)	NR	NR
Event Consistent with Urinary Tract Infection	Total	NR	NR	423 (18.1)	842 (18)
	Male Patients	NR	NR	158 (9.4)	350 (10.5)
	Female Patients	NR	NR	265 (40.6)	492 (36.4)
Complicated Urinary Tract Infection		NR	NR	41 (1.8)	82 (1.7)
Event Consistent with Genital Infection	Total	NR	NR	42 (1.8)	301 (6.4)
	Male Patients	NR	NR	25 (1.5)	166 (5.0)
	Female Patients	NR	NR	17 (2.6)	135 (10.0)
Acute Kidney Failure		23 (2.8)	35 (4.2)	155 (6.6)	246 (5.2)
Acute Kidney Injury		NR	NR	37 (1.6)	45 (1.0)
Diabetic Ketoacidosis		NR	NR	1 (<0.1)	4 (0.1)
Intermediate Outcomes at Week 104					
HbA1c Change from baseline, %		-1.4	-0.4	-0.1	-0.6†
Body Weight CFB, kg		-4.9	-0.5	-0.8	-3†
SBP CFB, mmHg		-5.37	-2.78	-0.8	-4.1

DBP CFB, mmHg	-1.57	-1.71	-1.5‡	-2.2‡
Total Cholesterol, Ratio to Baseline	0.97	0.99	NR	NR
LDL Cholesterol, Ratio to Baseline	0.97	0.99	1.03	1.05
HDL Cholesterol, Ratio to Baseline	1.01	0.97	1.01	1.05
Triglycerides, Ratio to Baseline	0.92	0.98	NR	NR

CI: confidence interval, CFB: change from baseline, CV: cardiovascular, DBP: diastolic blood pressure, HF: heart failure, HR: hazard ration, N: number, NR: not reported, REF: reference, SBP: systolic blood pressure, SD: standard deviation, y: years

*Nonfatal myocardial infarction excluding silent myocardial infarction

†Outcomes for EMPA 25 mg

‡Digitized and calculated by ICER staff

Table D4.11. CVOT Subgroups[10,11]

CVOT Subgroups					
Study		SUSTAIN-6		EMPA-REG-OUTCOME	
Arm		SEM 1mg	PBO 1mg	PBO	EMPA
N		822	825	2333	4687
Timepoint		109 wks		156 wks	
Composite Outcome					
BMI (kg/m^2)	<30	6.2	8.3	7.57	10.13
	HR: 95% CI; p-value	0.58 (0.39 to 0.87); 0.16		0.74 (0.60 to 0.90)); 0.06	
	>30	6.6	7.7	9.05	9.08
	HR: 95% CI; p-value	0.84 (0.61 to 1.16); 0.16		0.98 (0.80 to 1.21); 0.06	
Race	Asian	6.6	11.2	0.11	0.07
	HR: 95% CI; p-value	0.58 (0.25 to 1.34); 0.88		0.66 (0.48 to 0.95); 0.09	
	Black/AA	4.6	6.2	0.12	0.16
	HR: 95% CI; p-value	0.72 (0.23 to 2.28); 0.88		1.48 (0.80 to 2.72)); 0.09	
	White	6.7	8.7	0.12	0.10
	HR: 95% CI; p-value	0.76 (0.58 to 1.00); 0.88		0.88 (0.74 to 1.04); 0.09	
Ethnicity	Hispanic	5.1	7.5	8.03	12.1
	HR: 95% CI; p-value	0.67 (0.33 to 1.36); 0.80		0.63 (0.44 to 0.90); 0.07	
	Non	6.8	8.7	8.31	9.13
	HR: 95% CI; p-value	0.74 (0.57 to 0.96); 0.80		0.91 (0.77 to 1.07); 0.07	
Chronic HF	No	5.4	8.2	NR	NR
	HR: 95% CI; p-value	0.64 (0.48 to 0.86); 0.09		NR	NR
	Yes	12.3	11.8	NR	NR
	HR: 95% CI; p-value	1.03 (0.64 to 1.66); 0.09		NR	NR
CVD Status	Established	5.4	9.9	NR	NR
	HR: 95% CI; p-value	0.72 (0.55 to 0.93); 0.49		NR	NR
	Risk	3.4	3.4	NR	NR
	HR: 95% CI; p-value	1.00 (0.41 to 2.46); 0.49		NR	NR

eGFR <60 mL/min/1.73m^2	No	5.3	7.9	NR	NR
	HR: 95% CI; p-value	0.67 (0.48 to 0.92)); 0.98		NR	NR
	Yes	9.6	11.3	6.13	6.89
	HR: 95% CI; p-value	0.84 (0.57 to 1.25)); 0.37		0.88 (0.69 to 1.13); 0.20	
CVD Death					
BMI (kg/m^2)	<30	NR	NR	14.36	28.49
	HR: 95% CI; p-value	NR	NR	0.50 (0.37 to 0.68)*; 0.05	
	>30	NR	NR	20.6	26.17
	HR: 95% CI; p-value	NR	NR	0.78 (0.56 to 1.08)*; 0.05	
Ethnicity	Hispanic	NR	NR	14.93	22.32
	HR: 95% CI; p-value	NR	NR	0.53 (0.32 to 0.88)); 0.49	
	Non	NR	NR	17.54	27.2
	HR: 95% CI; p-value	NR	NR	0.64 (0.50 to 0.83); 0.49	
eGFR <60 mL/min/1.73m^2	No	NR	NR	NR	NR
	HR: 95% CI; p-value	NR	NR	NR	NR
	Yes	NR	NR	12.64	16.16
	HR: 95% CI; p-value	NR	NR	0.78 (0.54 to 1.12)2); 0.15	

AA: African American, BL: baseline, CI: confidence interval, DBP: diastolic blood pressure, EMPA: empagliflozin, ETD: estimated treatment difference, N: number, NR: not reported, OR: odds ratio, PBO: placebo, REF: reference, SBP: systolic blood pressure, SD: standard deviation, SEM: semaglutide

*p=0.05 for interaction. All other tests for interaction were non-significant.

†Efficacy estimand

Table D4.12. SURPASS-4 CV and Death Outcomes[34]

Study	**SURPASS-4 CV Outcomes**				
Arms	TZP 5 mg	TZP 10 mg	TZP 15 mg	All TZP	Insulin Glargine
N	329	328	338	995	1000
Timepoint	104 weeks				
MACE-4	19 (6)	17 (5)	11 (3)	47 (5)	62 (6)
HR; 95% CI	--	--	--	0.74 (0.51 to 1.08)*	
CV Death	10 (3)	1 (<1)	5 (2)	16 (2)	21 (2)
MI	7 (2)	9 (3)	3 (<1)	19 (2)	21 (2)
Hospitalization for unstable angina	0	2 (<1)	2 (<1)	4 (<1)	8 (<1)
Stroke	5 (2)	5 (2)	1 (<1)	11 (<1)	13 (<1)
Other MACE					
Coronary Interventions	10 (3)	11 (3)	8 (2)	29 (3)	37 (4)
Transient Ischemic Attack	0	2 (<1)	1 (<1)	3 (<1)	0
Hospitalization for HF	1 (<1)	1 (<1)	2 (<1)	4 (<1)	0
HR; 95% CI	--	--	--	--	--
Death	15 (5)	2 (<1)	8 (2)	25 (3)	35 (4)
HR; 95% CI	--	--	--	0.70 (0.42 to 1.17)*	
CV Death	4 (1)	0	2 (<1)	6 (<1)	9 (<1)
Undetermined	6 (2)	1 <1)	3 (<1)	10 (1)	12 (1)
Non-CV	5 (2)	1 <1)	3 (<1)	9 (<1)	14 (1)

CI: confidence interval, CV: cardiovascular, HF: heart failure, HR: hazard ration, MI: myocardial infarction, TZP: tirzepatide

*Point estimate and 95%CI of hazard ratio comparing pooled TZP versus insulin

D5. Ongoing Studies

Figure D5.1. Ongoing Studies

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
A Study of Tirzepatide (LY3298176) Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes (SURPASS-CVOT)	Phase III, double-blind, randomized N= 12,500	Arm 1: tirzepatide (SC) Arm 2: Dulaglutide (SC)	Inclusion: Have a diagnosis of type 2 diabetesT2DM Have confirmed atherosclerotic cardiovascular disease HbA1c ≥7.0% to ≤10.5% Body mass index (BMI) ≥25 kilograms per meter squared (kg/m^2) Exclusion: Type 1 diabetes MACE in the last 60 days History of severe hypoglycemia History of pancreatitis	Time to fist occurrence of death from CV causes, MI, or stroke (MACE-3)	October 2024
A Study of Tirzepatide (LY3298176) in Participants with Type 2 Diabetes on Metformin with or Without Sulfonylurea (SURPASS-AP-Combo)	Phase III, open-label N= 917	Arm 1: Tirzepatide 5 mg SC Arm 2: Tirzepatide 10 mg SC Arm 3: Tirzepatide 15 mg SC Arm 4: Insulin glargine (SC)	Inclusion: Type 2 diabetes mellitusT2DM Stable metformin with or without a sulfonylurea for at least 2 months Are insulin-naive (except for the use of insulin for treatment of gestational diabetes or short-term use [≤14 consecutive days] for acute conditions)	Mean change from baseline in HbA1c (10 mg and 15 mg)	November 2021

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			HbA1c ≥7.5% to ≤11.0% at screening Stable weight (±5%) ≥3 months Body mass Index (BMI) ≥23 kilograms per meter squared <u>Exclusion:</u> Type 1 diabetes mellitus Have history of chronic or acute pancreatitis Have history of proliferative diabetic retinopathy; or diabetic maculopathy; or non-proliferative diabetic retinopathy that requires acute treatment Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months		
A Study of Tirzepatide (LY3298176) Versus Insulin Lispro (U100) in Participants with Type 2 Diabetes Inadequately Controlled on Insulin Glargine (U100) With or Without Metformin (SURPASS-6)	Phase III, randomized, open-label N= 1182	Arm 1: Tirzepatide 5 mg SC + insulin (u100U100) Arm 2: Tirzepatide 10 mg SC + insulin (Uu100) Arm 3: Tirzepatide 15 mg SC + insulin (Uu100) Arm 4: Insulin glargine (SC) + insulin (u100U100)	<u>Inclusion:</u> Have been diagnosed with type 2 diabetes mellitus (T2DM2) Have HbA1c between ≥7.5% and ≤11% Have been treated for at least 90 days prior to day of screening with once or twice daily basal insulin with or without stable dose of metformin ≥1500 mg/day and up to maximum approved dose per country specific	Change from baseline in HBA1C (pooled doses) at week 52	September 2022

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			approved label, sulfonylureas or dipeptidyl peptidase 4 inhibitors Be of stable weight (± 5%) for at least 90 days Have a BMI ≥23 kilograms per meter squared (kg/m²) and ≤45 kg/m² at screening <u>Exclusion:</u> Type 1 diabetes mellitus Chronic or acute pancreatitis any time prior to study entry Proliferative diabetic retinopathy or diabetic macular edema or non-proliferative diabetic retinopathy requiring immediate or urgent treatment Disorders associated with slowed emptying of the stomach, have had any stomach surgeries for the purpose of weight loss, or are chronically taking drugs that directly affect gastrointestinal motility Heart attack, stroke, or hospitalization for congestive heart failure in the past 2 months		
A Study of Tirzepatide (LY3298176) in Participants with Type	Phase III randomized, double-blind, placebo controlled	Arm 1: Tirzepatide 10 mg SC + insulin (Uu100)	<u>Inclusion</u> Have Type 2 Diabetes (T2DM) with HbA1c ≥7% to ≤10% at screening, on	Percent change from randomization in	June 19, 2023

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
2 Diabetes Who Have Obesity or Are Overweight (SURMOUNT-2)	N= 900	Arm 2: Tirzepatide 15 mg SC Arm 3: placebo	stable therapy for the last 3 months prior to screening Have a BMI of ≥27 kg/m² Are overweight or have obesity Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight Are at least 18 years of age and age of majority per local laws and regulations <u>Exclusion</u> Have Type 1 diabetes mellitus, history of ketoacidosis or hyperosmolar state/coma or any other types of diabetes except T2DM Have at least 2 confirmed fasting self-monitoring blood glucose (SMBG) values >270 mg/dL (on 2 nonconsecutive days) prior to Visit 3 Have proliferative diabetic retinopathy OR diabetic macular edema OR non-proliferative diabetic retinopathy that requires acute treatment Have self-reported change in body weight >5 kg within 3 months prior to screening Have had a history of chronic or acute pancreatitis	boy weight and percentage of patients who achieve >5% body weight reduction from randomization.	

BMI: body mass index, CV: cardiovascular, HbA1c: hemoglobin A1c, kg: kilogram, MACE-3: 3-point MACE, mg: milligram, MI: myocardial infarction, N: number, SC: subcutaneous, T2DM: type 2 diabetes mellitus

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

D6. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessments conducted by the National Institute for Health and Care Excellence (NICE) on tirzepatide summarized below. We also identified two meta-analyses that include empagliflozin and subcutaneous injectable semaglutide in its analyses. All reports are summarized below.

NICE Technology Assessments

Tirzepatide for Treating Type 2 Diabetes

NICE is currently conducting an appraisal of the clinical and cost- effectiveness of tirzepatide for treating type 2 diabetes. The expected publication date is to be confirmed.

Salsali, A. (2016). "Cardiovascular safety of empagliflozin in patients with type 2 diabetes: a meta‐analysis of data from randomized placebo‐controlled trials"[99]

This meta-analysis assessed the effect on empagliflozin on cardiovascular risk in patients with type 2 diabetes across eight placebo-controlled trials. Using data from all available empagliflozin (EMPA) trials greater than 12 weeks duration, the primary endpoint of this analysis was a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina (MACE-4). The secondary endpoint was a composite of CV death, non-fatal MI and non-fatal stroke (MACE-3). Across all trials, 3835 patients were assigned to placebo, 3629 to EMPA 10mg and 3828 to EMPA 25mg with an average age of 61 and 65% of patients identifying as male. Baseline characteristics were generally similar across all arms. For pooled EMPA, patients had a reduced risk in MACE-4 versus placebo (HR 0.86; CI: 0.76 to 0.98) and MACE-3 (HR: 0.84; CI: 0.73 to 0.96). Similar results were seen for EMPA 10mg alone and 25mg alone.

Shi, F. (2018) Efficacy and Safety of Once-Weekly Semaglutide for the Treatment of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials[100]

A systematic review and meta-analysis were conducted to assess the efficacy and safety of once weekly injectable semaglutide in adult patients with type 2 diabetes. Of the 457 initial studies, 9 studies met the inclusion criteria, evaluating a total of 9,773 patients. The outcomes of interest in this evaluation included glycemic control, weight control, blood pressure, pulse rate, and safety. Patients assigned to semaglutide had a significant decrease in HbA1c levels compared to other therapies (weight mean difference[WMD]: -0.93; CI: -1.24 to -0.62; P<0.001) although there was significant heterogeneity (I^2: 92.6%). Semaglutide also significantly reduced body weight (WMD: -3.47; CI: -3.96 to -2.98; P <0.001; I^2: 17.6) and systolic blood pressure (WMD: -0.29 mmHg; CI: -0.65 to 0.07; P=0.0113). Semaglutide significantly increased pulse rate compared to other therapies (WMD: 2.21 bpm; CI: 1.54 to 2.88; P<0.0001; I^2: 67.6). The safety profile was generally well

tolerated with no increased safety risk for semaglutide for adverse events (RR:1.04), serious AEs (RR: 0.93), or fatal AEs (RR: 0.90). There was a significant increase in premature treatment discontinuation associated with semaglutide (RR: 2.07; CI: 1.58 to 2.73; P <0.001). The most common AEs were gastrointestinal events (42.9%) followed by nausea (18.1%) and diarrhea (14.0%).

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	

Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[101]

Target Population

The target population of the model was patients with diabetes that were not controlled with first-line anti-hypoglycemic medication who were eligible for an add-on therapy such as tirzepatide, injectable semaglutide, or empagliflozin. Description of the included patient population, derived from the NHANES is included in the main report.

We assume our patient population is eligible for add-on therapy to help control their diabetes. The three add-on (to background therapy) therapies we consider are: tirzepatide, 15 milligrams once weekly via injectable injection; semaglutide (Ozempic®), 1 milligram once weekly via injectable injection, and empagliflozin (Jardiance®), 25 milligrams daily, orally. We additionally consider background therapy alone, consisting of metformin (with or without sulfonylureas).

E2. Model Inputs and Assumptions

Key model inputs and assumptions are listed in the main text in section 4.2.

Model Inputs

Clinical Inputs

We used the point estimates and 95% credible ranges from the fixed effects model output of the network meta-analysis described above as the treatment effects in the model for the following outcomes: decrease in HbA1c level, decrease in weight, decrease in systolic blood pressure (SBP), and decrease in low-density lipids (LDL). These values can be found in the section reporting NMA output. We will consider using the random effects (assuming evidence-based priors) NMA 95% credible ranges within the revised report if the point estimates remain consistent with the fixed effects NMA.

Response to Treatment

Clinical inputs regarding the efficacy of tirzepatide, injectable semaglutide, and empagliflozin as compared to placebo on intermediate outcomes such as changes in HbA1c, lipid levels, blood pressure, and body weight were derived from the NMA described above.

We applied hazard ratios to estimated outcomes, including major adverse cardiac events, congestive heart failure, and nephropathy. Hazard ratios were derived from clinical outcome trials SUSTAIN-6 for injectable semaglutide and from EMPA-REG-OUTCOME for empagliflozin.[10,35] No adjustment was made to tirzepatide in the base case, reflected by setting the hazard ratios equal to one. The decision to not modify the risk equation estimates for tirzepatide in the base case was based primarily on two factors: a lack of available cardiovascular and renal outcome data to reference and the lack of reliable proxy data due to tirzepatide's novel dual mechanism of action. To understand the impact of this assumption, a scenario analysis examined the impact of applying semaglutide's hazard ratios to tirzepatide as a proxy, but the confidence intervals for the hazard ratios applied to tirzepatide were increased by 20% on both sides to account for the increased uncertainty.

Table E.2. Hazard Ratios Applied in Base Case Analysis

Regimen	Hazard Ratio	Source
Composite MACE HR		
Tirzepatide HR vs. Background Tx	1.00	Immature evidence and assumption
Semaglutide HR vs. Background Tx	0.74	SUSTAIN-6.[10]
Empagliflozin HR vs. Background Tx	0.86	EMPA-REG-OUTCOME[35]
Congestive Heart Failure HR		
Tirzepatide HR vs. Background Tx	1.00	Assumption
Semaglutide HR vs. Background Tx	1.11	SUSTAIN-6.[10]
Empagliflozin HR vs. Background Tx	0.65	EMPA-REG-OUTCOME[35]
Nephropathy HR		
Tirzepatide HR vs. Background Tx	1.00	Assumption
Semaglutide HR vs. Background Tx	0.64	SUSTAIN-6.[10]
Empagliflozin HR vs. Background Tx	0.61	EMPA-REG-OUTCOME[35]

HR: hazard ratio, Tx: treatment

Treatment Discontinuation

The only therapy with extension trial data beyond initial clinical trials was empagliflozin (EMPA-REG Extend), with discontinuation data for patients for 52 weeks assuming they continued the therapy for at least the initial 24 weeks. We derived the probability of discontinuation during the first year after the initial trial period (9.1% per year) from patients who discontinued for any reason; the rationale for choosing discontinuation for any reason was to accurately reflect the number of patients no longer benefiting from the drug regardless of reason. This rate was applied to all included active therapies pending long term trial data availability. Discontinuation of background therapy was derived from the placebo arms of trials for the three active comparators: SURPASS 1, EMPA-REG Extend, and SUSTAIN 2. In addition, patients whose HbA1c levels reach 8.5% or above (with a range from 8.0 to 9.0% used in scenario analyses) were assumed to discontinue therapy. Patients discontinuing their primary modeled treatment transitioned to insulin therapy; this included patients on background therapy. This choice was made to be able to evaluate all

comparators head-to-head as opposed to evaluating differences in different medication treatment pathways. Therefore, all patients who discontinued were assumed to use insulin treatment for the remainder of the model time horizon. Insulin treatment costs were modeled using mean doses from a literature review, applied to unit costs similar to the model comparators.[57] Clinical characteristics for patients on insulin were modeled using the UKPDS-OM2 and Willis equations.[13,57]

Diabetes-related Complications

We modeled diabetes-related complications and mortality based on risk equations from the UKPDS-OM2 risk engine.[13] The UKPDS-OM2 risk equations are widely used in diabetes simulation models, and have been shown to accurately predict results for the population in which it was developed as well as other diabetes populations.[13,102,103] The UKPDS-OM2 complications (13 risk equations) include CHF, ischemic heart disease (IHD), first MI for females, first MI for males, subsequent MI, first stroke, subsequent stroke, blindness, foot ulcer, first amputation without prior ulcer, first amputation with prior ulcer, subsequent amputation, and ESRD.[13] In the microsimulation, patients were able to experience multiple and concurrent complications during each modeled year. The UKPDS-OM2 mortality risk equations predict that previous T2DM-related complications (except foot ulcer and blindness) increase the probability of death. The four mutually exclusive mortality risk equations were death without history of complication(s), death in the year of a clinical event, death in subsequent year of prior event(s), and death with history of clinical event(s).[13]

The effect of included add-on therapies on intermediate outcomes, including several of the time-varying risk factors mentioned above, were applied to the patients and the treatment effect was assumed to persist until patient death or therapy discontinuation. We estimated the effect of included add-on therapies on cardiovascular and renal outcomes in the base case via the reductions in HbA1c, weight, SBP, and LDL, allowing changes in intermediate outcomes to be associated with longer-term outcomes. We also applied hazard ratios from the placebo-controlled cardiovascular outcomes trials for the add-on therapies, and assumed tirzepatide had the same hazard ratios as semaglutide as there was not an applicable trial available.

Treatment Discontinuation and Insulin Uptake

We applied an annual discontinuation rate due to any cause from the empagliflozin extension trial EMPA REG EXTEND to all therapies, as long-term discontinuation data was not available for injectable semaglutide or tirzepatide. Patients discontinuing their primary modeled treatment were assumed to transition to insulin therapy. This choice was made to facilitate head-to-head comparator evaluations as opposed to evaluating differences in multiple potential treatment pathways. All patients who discontinued used insulin in addition to background treatment for the remainder of the model time horizon. After cycle 1, we also assumed that patients discontinued treatment and transition to insulin if their HbA1c reached 8.5 or above. Insulin treatment costs

were based on a multivariate prediction model for estimating long-term HbA1c change, weight change, and hypoglycemic events associated with insulin rescue medication.[57] After cycle 1, clinical characteristics for patients pre- and post-insulin were modeled using the equations for HbA1c and weight change,[57] which then influenced the UKPDS-OM2 complication risk equations for those patients. The hypoglycemia equations from the Willis et al. prediction model were not used due to their substantial uncertainty.

Hypoglycemia

Mild, moderate, and severe hypoglycemia were modeled in cycles 2+ based on the previous UKPDS-OM2 adaptation from Laiteerapong et al.[52] Patients not yet receiving insulin were assumed to have a 5% probability for a severe hypoglycemic event and a 33% probability for a mild or moderate event each year. Patients receiving insulin were assumed to have a 21% probability of a severe hypoglycemic event and a 52% probability of a mild or moderate hypoglycemic event each year. Patients were assumed to have no more than one mild or moderate hypoglycemic event and one severe hypoglycemic event per year but could have multiple hypoglycemic events during their lifetime.

Atrial Fibrillation and Peripheral Artery Disease

The UKPDS-OM2 equations have coefficients for atrial fibrillation and peripheral vascular (artery) disease but the NHANES patient dataset did not provide this information. Therefore, we utilized age-based cumulative incidence estimates from the US population[104,105] and (for atrial fibrillation) relative risk estimates based on patients' HbA1c,[106] to simulate these patient characteristics prior to each microsimulation. Peripheral vascular disease and atrial fibrillation prevalence were modeled independent of existing patient characteristics.

Mortality

The UKPDS-OM2 risk equations predict mortality using four mutually exclusive equations that are stratified based on the person's prior T2DM event history and whether the mortality event is related to a cardiovascular event.

Utilities

We used consistent health state utility values across treatments evaluated in the model. Separate utilities were used for the year in which a complication occurred and for patient history of each complication, where applicable. Health state utilities were derived from publicly available literature and/or manufacturer-submitted data and applied to the modeled events. We used estimates for T2DM complications primarily from Shao et al.[107,108] In Shao et al., the Health Utilities Index Mark 3 (HUI-3) was used to measure heath utility in a sample of 8,713 patients from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of high cardiovascular disease risk T2DM patients.[108]

Lastly, we modeled an annual disutility for daily injection of insulin (for patients who discontinued treatment) based on Boye et al., who used standard gamble interviews of T2DM patients in Scotland to estimate the utility values for injection-related attributes.[109]

Table E.3. Utility Values Used in Model

Health event or history	(Dis)Utility	Source
Baseline T2DM Utility	0.800	Shao et al.[108]
Macrovascular complications		
Congestive heart failure event	-0.089	Shao et al.[108]
Congestive heart failure history	-0.041	Shao et al.[108]
Ischemic heart disease history	-0.016	Shao et al.[108]
Myocardial infarction event	-0.042	Shao et al.[108]
Myocardial infarction history	-0.011	Shao et al.[108]
Stroke event	-0.204	Shao et al.[108]
Stroke history	-0.101	Shao et al.[108]
Microvascular complications		
Blindness history	-0.057	Shao et al.[108]
Foot ulcer event	-0.024	Sullivan et al.[110]
Amputation event	-0.051	Sullivan et al.[110]
Renal disease history	-0.024	Shao et al.[108]
Hypoglycemia		
Hypoglycemia event	-0.036	Shao et al.[108]
Hypoglycemia history	-0.033	Shao et al.[108]
Demographic characteristics		
Age at diagnosis (per year ≥52)	-0.002	Shao et al.[108]
Female	-0.043	Shao et al.[108]
Race (ref = Black)		
Hispanic	-0.045	Shao et al.[108]
Others	-0.010	Shao et al.[108]
White	-0.019	Shao et al.[108]
Current smoker	-0.054	Shao et al.[108]
BMI (per unit ≥32)	-0.007	Shao et al.[108]
Diabetes duration (per year)	-0.005	Shao et al.[108]
Injection-related disutility		
Annual Disutility for Tx Injection	-0.054	Boye et al.[109]

BMI: body mass index, Tx: treatment

Economic Inputs

Drug Acquisition Costs

Because tirzepatide is not approved by the FDA, the drug price is not yet available. Based on the ICER Reference Case, we investigated calculation of a placeholder price based on the average of all available once-weekly injectable GLP-1s. However, we uncovered that discounted pricing for once-weekly injectable Bydureon BCise® (exenatide extended-release) is approximately three times that of Ozempic® (semaglutide), suggesting it may be an unsuitable proxy to inform tirzepatide placeholder pricing. Given this, we used the price of Ozempic® (semaglutide) as a placeholder price for tirzepatide and calculated the threshold prices at the standard cost-effectiveness thresholds: $50,000 through $200,000 per QALY and per evLY gained. We applied the semaglutide drug discount rate to obtain net pricing estimates for tirzepatide.

Health Care Utilization Costs

Table E.4. Cost per T2DM-Related Complication and per Hypoglycemic Event

Incremental Cost in the Year of Event/Diagnosis (per event)	Estimate (2021 USD)*	Source
Year of Event (per event)		Yang[60]
Congestive Heart Failure	$34,898	Yang[60]
Ischemic Heart Disease	$9,962	Yang[60]
Myocardial Infarction	$50,612	Yang[60]
Stroke	$26,597	Yang[60]
Foot Ulcer	$2,691	Ward [59]
Amputation	$11,330	Ward [59]
Hypoglycemia		
Requiring Hospitalization	$8,563	Yang [60]
Requiring ER Visit	$1,643	Yang[60]
Requiring Glucagon Injection	$221	Yang[60]
History of Complication (per year)		
Congestive Heart Failure	$7,899	Yang[60]
Ischemic Heart Disease	$2,386	Ward[59]
Myocardial Infarction	$9,587	Yang[60]
Stroke	$5,289	Yang[60]
Blindness	$14,534	Yang[60]
Renal Disease	$105,394	Yang[60]
Health Care Use Costs		

Outpatient Visit: Non-insulin	$584	Laiteerapong [52]
Outpatient Visit: Insulin	$639	Laiteerapong [52]

ER: emergency room, ESRD: end-stage renal disease, USD: United States dollars

*Costs inflated to USD 2021 using US government Bureau of Labor Statistics Consumer Price Index

Adverse Event Costs and Disutilities

No serious treatment-related adverse events occurring in greater than 5% of the patient population were observed and therefore were not included in the model. We included an annual disutility due to injections in the utility section.

Productivity Costs

We sought to include a modified societal perspective in this analysis. However, we found a paucity of data to inform such modeling. Instead we performed calculations utilizing the model's incremental health gained (QALYs gained) and a measure of the productivity impact of T2DM to approximate the modified societal perspective results. We adjusted Dall et al's estimate of the productivity costs of T2DM from 2017 to 2021 US Dollars using the health care component of the Consumer Price Index, resulting in annual productivity costs of $5842.[111] That annual estimate was assumed to be the potential savings associated with each incremental QALY for an intervention versus a comparator. We multiplied the annual productivity estimate times the incremental QALYs to estimate the assumed societal cost savings and combined these assumed productivity-based savings with the total incremental payer perspective costs in order to calculate cost-effectiveness ratios for the modified societal perspective.

E3. Results

Description evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[112]

2. For each average of model results from a given set of patient simulations where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that set of simulations.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that set of simulations.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms. In this model, each add-on treatment's evLYG was calculated compared to background therapy alone.

E4. Sensitivity Analyses

Additionally, we ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input. In order to efficiently operationalize the one-way sensitivity analysis within the framework of the patient-level microsimulation, we fixed the parameter values for all non-patient-level inputs and then performed a single UKPDS equation simulation for each of 387 NHANES patients for each parameter's low and high value, for each treatment, in order to produce an estimate of uncertainty for each high and low value of each parameter. Therefore, each one-way sensitivity analysis output value represents the average impact over 387 individual patient simulations. Individual one-way sensitivity analyses were performed for incremental costs and incremental QALYs in order to isolate the impact of the inputs on those individual outcomes. The results of these one-way sensitivity analyses are presented as tornado diagrams. Sensitivity analyses will be included in future versions of this report.

E5. Scenario Analyses

We ran the following separate scenario analyses to understand the impact of some of our assumptions within the model: we shortened the time horizon to 10 years; we set tirzepatide's CV and renal event adjustment equal to that of semaglutide; and we set the discontinuation threshold due to advanced HbA1c levels to both 8% and to 9% as opposed to the base case 8.5%. For each of these scenarios, the results presented represent the mean and 95% credible range from probabilistic sensitivity analyses comprised of 500 simulations of each of the 387 people from NHANES with T2DM. We plan to augment these simulations in the revised report, as computing time allows.

Table E.5. Scenario analyses incremental results for tirzepatide added to background therapy versus background therapy alone, mean (95% credible range)*

Scenario Description	Incremental Cost per QALY Gained	Incremental Cost per Life Year Gained	Incremental Cost per evLY Gained
Base Case Scenario	$38,000 (-$33,000 to 91,000)	$41,000 (-$94,000 to 151,000)	$23,000 (-$23,000 to $60,000)
10-year Time Horizon	$40,000 (-$53,000 to $118,000)	$85,000 (-$407,000 to $670,000)	31,000 (-$50,000 to $106,000)
Tirzepatide CV and Renal Benefit Hazard Ratios Set Equal to Semaglutide	$29,000 (-$23,000 to $67,000)	$23,000 (-$20,000 to $50,000)	$17,000 (-$15,000 to $42,000)
Discontinuation When HbA1c=8%	$32,000 (-40,000 to $86,000)	$35,000 (-199,000 to $190,000)	$19,000 (-$28,000 to $56,000)
Discontinuation When HbA1c=9%	$45,000 (-$13,000 to $106,000)	$48,000 (-$34,000 to $280,000)	$28,000 (-$9,000 to $70,000)

CV: cardiovascular, evLYG: equal value life-year gained, HbA1c: hemoglobin levels, QALY: quality-adjusted life-year
*Using a placeholder price for tirzepatide

Modified Societal Perspective Scenario Estimation, using Missing Data Assumptions

We used a placeholder price for tirzepatide and assumed that the incremental QALYs gained by tirzepatide were associated with avoiding productivity losses associated with T2DM. Our calculation of the estimated value of tirzepatide compared to background therapy alone under this modified societal perspective using missing data assumptions, resulted in incremental cost-effectiveness ratios of $32,600 per QALY gained and $34,500 per life year gained, and $21,400 per evLY gained.

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and in supplemental materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

F. Potential Budget Impact: Supplemental Information

F1. Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. These results from the cost-effectiveness analyses include the costs of add-on antidiabetic agent (i.e., tirzepatide, injectable semaglutide, empagliflozin), health care resource utilization offsets, and averted health care event offsets. In patients who discontinued therapy and subsequently progressed to insulin, those insulin costs were attributed to the previously discontinued therapy. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

Comparators in the budget impact model included injectable semaglutide, empagliflozin, each added to background therapy, as well as background therapy alone. Conventional therapy consisted of metformin and/or sulfonylureas. Market shares were derived from analyst projections based on primary market research, company reports, and key opinion leader surveys.[65] We set the initial market shares for injectable semaglutide equal to a calculated market share for the GLP-1 RA class (15.1%), while the market share for empagliflozin was set to a calculated market share for the SGLT-2 inhibitor class (12.7%). The remaining market share (72.2%) was attributed background therapy. Market share was captured in proportion to the comparators' initial market shares at a rate of 20% per year, with all patients having switched to tirzepatide by the end of five-year of the time horizon.

Additionally, we used an estimate of net price (using injectable semaglutide's price as a placeholder), and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) in our estimates of tirzepatide's potential budget impact.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[113,114] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

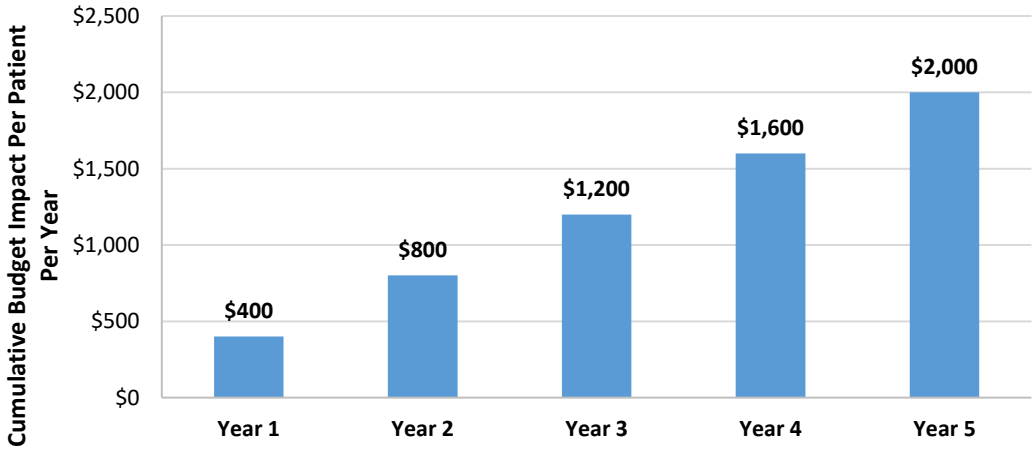
Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods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

For 2021-2022, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $734 million per year for new drugs.

F2. Results

Figure F2.1 illustrates the cumulative per-patient budget impact calculations for tirzepatide added to background therapy compared to a mixed market basket consisting of injectable semaglutide, empagliflozin, and background therapy based on the net price used within the cost-effectiveness analysis. Switching of eligible adult T2D patients to tirzepatide resulted in an average potential budgetary impact of approximately $400 per patient per year when assuming our standard uptake of 20% per year. We suggest caution in interpreting the potential budget impact of tirzepatide due to the placeholder annual net price assumed.

Figure F2.1. Cumulative Annual Per Patient Treated with Tirzepatide at a Placeholder Price of $4,643.50 per Year*



*Placeholder price was assumed. Interpret findings with caution.

Table F2.1 illustrates the average annual per-patient budget impact results in more detail, for tirzepatide's placeholder price ($4,643.50* per year), and the threshold prices to reach $50,000, $100,000, and $150,000 per QALY ($4,774, $5,230, and $5,685, per year, respectively) added to background therapy compared to background therapy alone.

Table F2.1. Average Annual Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

	Average Annual Per-Patient Budget Impact for Each Calculated Price Point			
	Placeholder Price*	**$50,000/QALY**	**$100,000/QALY**	**$150,000/QALY**
Tirzepatide and background therapy vs injectable semaglutide, empagliflozin, and background therapy	$400	$500	$800	$1,100

QALY: quality-adjusted life year

*This is an unvalidated placeholder price that is assumed to be equal to the discounted price for injectable semaglutide; injectable semaglutide price is sourced from Red Book, with corresponding discounts used to derive a net price being sourced from SSR Health, LLC [58]