NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Tirzepatide for Type 2 Diabetes: Effectiveness and Value

Modeling Analysis Plan

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Institute for Clinical and Economic Review

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1. Approach

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of tirzepatide added to current antihyperglycemic treatment for type 2 diabetes mellitus (T2D). Elements of this model analysis plan are subject to change as the project progresses. Refer to the Research Protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of this analysis will be to estimate the lifetime cost-effectiveness of tirzepatide added to current antihyperglycemic treatment for T2D using a decision analytic model. Tirzepatide added to current antihyperglycemic treatment will be separately compared to three modeled comparators including: (1) injectable semaglutide, (2) empagliflozin, and (3) ongoing background antihyperglycemic treatment (e.g., metformin with or without sulfonylureas); semaglutide and empagliflozin are also assumed to be added to current antihyperglycemic treatment. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), and a lifetime horizon. Productivity impacts and other indirect costs will be considered in a scenario analysis using a societal perspective if data allow. The model will be developed in Microsoft® Excel® for Office 365 (Version 2108).

2. Methods

2.1 Overview and Model Structure

We will develop a patient-level microsimulation using the Building, Relating, Assessing and Validating Outcomes (BRAVO) risk equations for this evaluation,[1] informed by clinical trials, a network meta-analysis (NMA) of relevant clinical trials, quality of life literature, and validation versus other prior economic models.[2-4] The base case analysis will take a health care sector perspective and thus focus on direct medical care costs only. Costs and outcomes will be discounted at 3% per year.[5] This review will differ from the 2019 T2D review in that no long-term cardiovascular outcomes trial data exist for the primary intervention under examination in this review – tirzepatide. Notions of cardiovascular and renal benefit will instead be informed by intermediate outcomes such as hemoglobin A1c (HbA1c) and body weight derived from the NMA that are predictors that feed into the BRAVO risk engine, an exercise for which there is evidence in published literature.[6] Modeled cardiovascular outcomes (CVO) for therapies with existing long-run CVO trials will be compared against the trial data and calibration exercises will be considered if necessary.

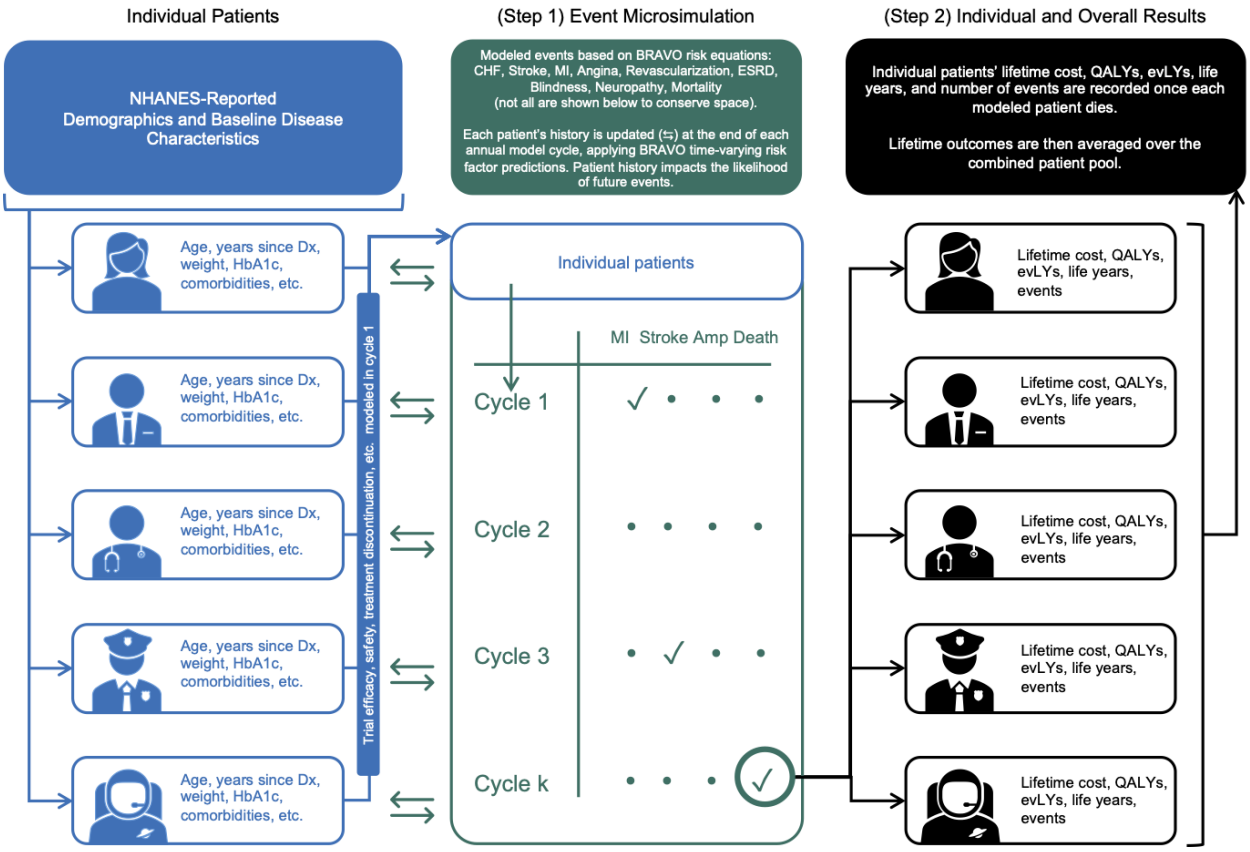
The model (Figure 2.1) will be an individual patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2D among United States (US) adults with the disease. Two modeling steps will be used: (1) event microsimulation and (2) calculation of mean results from the pool of simulated patients' lifetime outcomes. Patients, with data from multiple National Health and Nutrition Examination Survey (NHANES) surveys, will be run through the modeling steps for each comparator versus tirzepatide that are both added to current ongoing background antihyperglycemic treatment. The two model steps are explained below:

(1) Event microsimulation. Each NHANES patient will be sequentially run through the event microsimulation. Each model cycle will be one year in duration. The BRAVO risk equations will be used to calculate the incidence of any clinical event(s) and/or mortality in each year until the simulated patient dies. Effects of each included therapy, such as change in HbA1c after the first cycle, will be included depending on data availability from the NMA. All event and/or mortality associated costs and health state utility weights will be applied concurrently. The BRAVO risk equations account for patient history upon entering the model as well as new clinical events that occur during the microsimulation; for example, a patient who experiences a first myocardial infarction (MI) in a given year of the microsimulation will have the history of MI covariate turned on in each subsequent year.

(2) Calculation of mean results. After each simulated patient dies, the model will record the patient's lifetime cost, quality-adjusted life years (QALYs), equal-value of life years (evLYs), life

years, and clinical events. Each outcome is then averaged over the entire pool of patients to derive overall model results.

Figure 2.1. Model Schematic



T2D = type 2 diabetes mellitus; Dx = diagnosis; HbA1c = glycated hemoglobin; CHF = congestive heart failure; MI = myocardial infarction; QALY = quality-adjusted life year; evLY = equal-value of life years

2.2 Key Model Choices and Assumptions

Below is a list of key model choices:

- Long-term survival and the incidence of diabetes-related clinical events will be modeled using an adaptation of the BRAVO risk equations.[1]
- Survival will be weighted by disutilities for each diabetes-related complication to model quality of life.[1] If available, we will also employ disutilities for individual adverse events.
- The model will include all treatment costs associated with each individual drug regimen, including drug acquisition costs and supportive care costs (e.g., clinician visits and self-monitoring).
- All model outcomes will be calculated over a lifetime time horizon.[5]
- Life-years, QALYs, evLYs, and health care cost outcomes will be discounted at 3% per year.[5]

Our model includes several assumptions stated below.

Table 2.1. Key Model Assumptions

Assumption	Rationale
HbA1c treatment effect remains stable after end of trial and throughout patient lifetime for patients who remain on treatment.	Long-term effectiveness is currently unknown. We will consider modeling changes in long-term HbA1c in scenario analyses.
Weight/BMI remains stable after end of trial and throughout lifetime for patients who remain on treatment.	Long-term effectiveness is currently unknown. We will consider modeling changes in long-term BMI in scenario analyses.
Any calibration of BRAVO for CV and renal outcomes for active comparators with CVO trial data will be maintained over patient lifetime.	Active treatment comparators (injectable semaglutide and empagliflozin) have trial data with CVOs. We will consider model calibration depending on how the BRAVO risk equations compare to those trial outcomes, either in the main analysis or as a scenario analysis.
Any calibration of BRAVO for CV and renal outcomes for tirzepatide will be maintained over patient lifetime.	Long-term effectiveness of tirzepatide is currently unknown. We will potentially model relative changes in long-term CV and renal outcome effectiveness in scenario analyses.
Ongoing background antihyperglycemic medications are assumed the same for all comparators.	The goal is to evaluate direct comparisons among the treatments of interest and not multiple possible treatment sequences.

2.3 Populations

The population of interest for this review is adults with T2D with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). A cohort of individual patients who are U.S. adults with self-reported diabetes will be drawn from NHANES (Table 2.2).

Table 2.2. Characteristics of US Adults with Self-Reported Diabetes, NHANES 2013–2018[7]

Description	Value
Patient characteristics	
Age at time of survey (years), mean (SD)	63.7 (12.48)
Female, % (N)	47.4% (558)
Duration of disease (years), mean (SD)	12.3 (10.15)
Black race, % (N)	43.2% (508)
Weight (kg), mean (SD)	95.2 (24.48)
Height (cm), mean (SD)	168.1 (10.00)
BMI (kg/m^2), mean (SD)	33.6 (7.98)
eGFR (mL/min), mean (SD)	77.1 (28.92)
HbA1c, mean (SD)	7.3 (1.72)
HDL (mg/dL), mean (SD)	1.3 (0.39)
Heart rate (beats/min), mean (SD)	73.8 (12.62)
LDL (mg/dL), mean (SD)	2.5 (0.91)
SBP (mmHg), mean (SD)	133.6 (20.23)
Current Smokers, % (N)	31.4% (370)
White blood cell count (per µL, mean (SD)	7.7 (2.29)
On Metformin, % (N)	57.9% (681)
On Sulfonylurea, % (N)	27.3% (321)
Age at time of survey (years), mean (SD)	63.7 (12.48)
Female, % (N)	47.4% (558)
T2D Medication Treatment History	
TZD, % (N)	6.6% (78)
DPP-4, % (N)	6.0% (71)
GLP-1, % (N)	2.5% (30)
Meglitinide, % (N)	0.6% (7)
Alpha Glucosidase, % (N)	0.3% (3)
Insulin (medium), % (N)	1.2% (14)
Insulin (Basal), % (N)	8.9% (105)
Insulin (Bolus), % (N)	14.2% (167)
Insulin (SGLT-2), % (N)	6.6% (78)
Other antidiabetic drugs, % (N)	0.2% (2)
Disease History	
Myocardial infarction, % (N)	13.4% (158)
Stroke, % (N)	11.8% (139)
Heart failure, % (N)	12.7% (149)
Ischemic heart disease, % (N)	12.8% (151)
Angina, % (N)	8.0% (94)
Renal disease, % (N)	19.4% (228)

HbA1c: glycated hemoglobin, kg: kilogram, cm: centimeter, SD: standard deviation, BMI: body mass index, eGFR: estimated glomerular filtration rate, TZD: thiazolidinedione, DPP-4: dipeptidyl peptidase 4 inhibitors, GLP-1: Glucagon like peptide-1 agonist, SGLT-2: Sodium glucose co-transporter 2 inhibitors.

2.4 Interventions

Our intervention of interest for this review is tirzepatide (Eli Lilly) added to current ongoing background antihyperglycemic treatment.

Comparators

We plan to compare to each of the following treatments:

- Semaglutide (Ozempic®, Novo Nordisk), a GLP-1 agonist, added to ongoing background treatment
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), a SGLT-2 inhibitor, added to ongoing background treatment
- Ongoing background antihyperglycemic treatment alone

The two add-on agents were chosen in part because: they are common existing add-on treatments; they are representative of the two main classes recommended by guidelines for similar populations to those studied with tirzepatide, and semaglutide shares one of two mechanisms with tirzepatide.

2.5 Input Parameters

Clinical Inputs

Clinical inputs regarding the efficacy of tirzepatide compared to injectable semaglutide and empagliflozin on intermediate outcomes such as changes in HbA1c, lipid levels, blood pressure, and body weight will be derived from trials used in the NMA, tentatively including SURPASS-2, SUSTAIN-2, PIONEER-2, and PIONEER-3.[8-11] Other intermediate or surrogate outcomes that may be captured in the NMA and economic model include those listed within the *Diabetes-Related Complication and Mortality Probabilities* section below. While oral semaglutide and sitagliptin are not currently planned to be a part of this modeling exercise, the corresponding SUSTAIN-2, PIONEER-2, and PIONEER-3 trials may be included to facilitate potential network meta-analytic comparison between tirzepatide and empagliflozin, and injectable semaglutide and empagliflozin.[12-14] Given that this network does not include background therapy alone, separate clinical trials will tentatively be used to inform benefits of these therapies on intermediate outcomes.

Diabetes-Related Complication and Mortality Probabilities

We will model diabetes-related complications and mortality based on risk equations from the BRAVO risk engine.[1] The BRAVO risk equations were developed based on the ACCORD trials to predict the onset of diabetes complications over an individual's life span, have been externally validated against over 18 international trials, and have been used in recent economic modeling as alternative to prior diabetes risk models.[6,15]

The BRAVO risk engine accounts for time-varying risk factors (7 risk equations), including HbA1c, systolic blood pressure (SBP), low-density lipids (LDL), weight, severe and symptomatic hypoglycemia, and smoking. The risk engine also predicts diabetes complications (8 risk equations), which include congestive heart failure (CHF), stroke, myocardial infarction (MI), angina, revascularization, end-stage renal disease (ESRD), blindness, and neuropathy.[1] Patients will be able to experience multiple and concurrent complications during each modeled year.

The effect of included add-on therapies on intermediate outcomes, including several of the time-varying risk factors mentioned above, will be applied to the patient cohort after an initial cycle and the treatment effect will be assumed to persist until patient death or therapy discontinuation. We plan to estimate the effect of included add-on therapies on cardiovascular and renal outcomes in the base-case via the BRAVO risk equations, assuming changes in intermediate outcomes will predict lifetime cardiovascular and renal outcomes. Modeled outcomes will be compared against available cardiovascular and renal outcome data for injectable semaglutide and empagliflozin, and model calibration may be considered to ensure reasonable estimates. Standard errors of model coefficients will also be increased to reflect the much higher uncertainty around cardiovascular and renal outcomes for tirzepatide than for the other active comparators given the novelty of tirzepatide's dual mechanisms of action and their unknown long-term effects when combined.[16,17]

Discontinuation

We will apply pooled estimates of treatment discontinuation for any reason, along with assumptions for long-term treatment discontinuation, as applicable for tirzepatide and each comparator. Discontinuation rates will be derived from extension trials for patients who successfully completed the first year of therapy. In addition, patients whose HbA1c levels reach 8.5 or above will be assumed to discontinue therapy. Patients discontinuing their primary modeled treatment will be assumed to transition to insulin therapy. This choice was made to be able to evaluate the three medications head-to-head as opposed to evaluating differences in different medication treatment pathways. Therefore, all patients who discontinue will be assumed to use insulin treatment for the remainder of the model time horizon. Insulin treatment costs will be modeled using mean doses from a literature review, applied to unit costs similar to the model comparators.[18] Clinical characteristics for patients on insulin will be modeled using the BRAVO equations, which will then drive the event risk equations for those patients.[18]

Mortality

The BRAVO risk equations predict mortality in two equations: all-cause and cardiovascular-related. Cardiovascular-related death risk derives from hemoglobin levels, blood pressure, body mass index (BMI), and cardiovascular disease history. All-cause mortality factors in gender, education level, and smoking status in addition to disease history, hemoglobin level, blood pressure and BMI. Stroke or congestive heart failure both substantially increase mortality risk the year in which they occur.[1]

Health State Utilities

We will use consistent health state utility values across treatments evaluated in the model. Separate utilities will be used for the year in which a complication occurs and for patient history of each complication, if applicable. Health state utilities will be derived from publicly available literature and/or manufacturer-submitted data and applied to the modeled events. We plan to utilize estimates for T2D complications primarily from Shao et al. and Neuwahl et al.[19,20] 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 T2D patients.[20] Neuwahl et al. also used the HUI-3 to measure health utility in 15,252 patients from the ACCORD trial and the Look AHEAD (Action for Health in Diabetes) model of patients with T2D.[19] Lastly, we will model an annual disutility for daily injection of insulin (for patients who discontinue treatment) based on Boye et al., who used standard gamble interviews of T2D patients in Scotland to estimate the utility values for injection-related attributes.[21]

Table 2.3. Health State Utilities/Disutilities

	Estimate	SE	Source
Baseline Utility	0.800	0.023	Shao[20]
Macrovascular Complications			
Congestive heart failure event	-0.089	0.022	Shao[20]
Congestive heart failure history	-0.041	0.010	Shao[20]
Ischemic heart disease history*	-0.016	0.005	Shao[20]
Myocardial infarction event	-0.042	0.016	Shao[20], Neuwahl[19]
Myocardial infarction history	-0.011	0.006	Shao[20], Neuwahl[19]
Stroke event	-0.204	0.035	Shao[20], Neuwahl[19]
Stroke history	-0.101	0.008	Shao[20], Neuwahl[19]
Microvascular Complications			
Blindness history	-0.057	0.009	Shao[20]
Renal disease history	-0.024	0.016	Shao[20]
Hypoglycemia Event	-0.036	0.010	Shao[20], Neuwahl[19]
Hypoglycemia History	-0.033	0.011	Shao[20]
Patient Characteristics			
Current smoker	-0.054	0.006	Shao[20], Neuwahl[19]
BMI (per unit ≥32)	-0.007	0.000	Shao[20], Neuwahl[19]
Diabetes duration (per year)	-0.005	0.000	Shao[20], Neuwahl[19]

SE: standard error

*Disutility for ischemic heart disease is based on "revascularization history" from Shao et al.[1]

Drug Utilization

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

- Duration of treatment
- Schedule of doses for each drug in each add-on regimen
- Protocol dosage for the indication
- Treatment adherence (base case assumption = 100% since modeling treatment efficacy and safety based on randomized controlled trial data)

Table 2.4. Treatment Regimen Recommended Dosage

	Tirzepatide	Semaglutide	Empagliflozin
Brand Name	**N/A**	**Ozempic®**	**Jardiance®**
Manufacturer	Eli Lilly	Novo Nordisk	Boehringer Ingelheim & Eli Lilly
Route of Administration	Subcutaneous injection	Subcutaneous injection	Oral
Dosing	15 mg once weekly	1 mg once weekly	10 or 25 mg daily

mg: milligram

Cost Inputs

Drug 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, if the drug cost or an analyst estimate is not available at the time of the report, we will use the price of Ozempic® (semaglutide) as a placeholder price for tirzepatide, as well as calculate the threshold prices at the standard cost-effectiveness thresholds: $50,000 through $200,000 per QALY and per evLY gained. If the Wholesale Acquisition Cost is available at the time of the report but no information is available related to the net price, we will use manufacturer supplied estimates of net price or if not available, then apply estimated branded drug discount rates based on an average for GLP-1s to obtain net pricing estimates for tirzepatide.

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.[22] 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.

Table 2.5. Drug Costs

Drug	WAC per 30-Pill Bottle/Pen	Net Price Per 30-Pill Bottle/Pen	Discount From WAC	Net Price per Year‡
Tirzepatide*	Placeholder $851.60 (4 weekly doses)	Placeholder $355.97 (4 weekly doses)	Placeholder 58.20%	Placeholder $4,627.59
Semaglutide (Ozempic®) 4 mg/3 mL pen†	$851.60 (4 weekly doses)	$355.97 (4 weekly doses)	58.20%	$4,627.59
Empagliflozin (Jardiance®) 30-tablet bottle§	$548.54	$107.51	80.40%	$1,308.98
Metformin#	$1.65	-	-	$20.09
Sulfonylureas¤	$5.05	-	-	$61.51

WAC: wholesale acquisition cost

*As a placeholder, we will use Ozempic® (semaglutide) prices and discounts, 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.

Please refer to the ICER Reference Case for more details on drug pricing.

Non-Drug Costs

We plan to use costs for T2D-related complications and hypoglycemia from available published literature such as Ward et al., who estimated direct medical costs from data sources including inpatient and emergency department databases, national physician and laboratory fee schedules, government reports, and published literature.[23] Complication costs in the year of the event reflect acute care and any subsequent care provided in the first year; history state costs reflect annual resource use for the ongoing management of complications in subsequent years.[23] Costs were assessed from the perspective of a comprehensive US healthcare payer and were originally reported in 2012 US dollars (USD); the costs in Table 2.6. reflect inflation to first half of 2021. Data permitting, updated health care costs related to diabetes monitoring may be included in the model.

Table 2.6. Cost per T2D-Related Complication and per Hypoglycemic Event

	Estimate (2021 USD)
Incremental Cost in the Year of Event/Diagnosis (per event)[23,24]	
Heart Failure	$29,774
Ischemic Heart Disease	$26,827
Myocardial Infarction	$70,738
Stroke	$52,785
Hypoglycemia	
Episode Requiring Hospitalization	$20,651
Episode Requiring ED visit	$1,643
Episode Requiring Glucagon Injection	$221
Incremental Cost of Living with History of Complication (per year)[23,24]	
Heart Failure*	$2,386
Ischemic Heart Disease*	$2,386
Myocardial Infarction*	$2,386
Stroke	$19,475
Blindness	$3,587
Renal Disease	$89,874

*Annual state costs for cardiovascular complications were obtained from a Medical Expenditure Panel Survey report on heart condition-associated office visits and medications.

2.6 Model Outcomes

Model outcomes will include life years (LYs) gained, equal value life years (evLYs) gained, QALYs gained, clinical events, and total costs for each intervention over a lifetime time horizon. Costs will also be reported by the clinical event in order to understand the contribution of different cost elements. All costs and outcomes will be reported as discounted values, using a discount rate of 3% per annum.[5]

2.7 Model Analysis

Cost-effectiveness will be estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing tirzepatide to each comparator, from a health care sector perspective in the base case analyses. Additionally, we will present a cost per consequence outcomes including cost per MACE avoided and cost per renal disease avoided.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters and BRAVO risk engine equation coefficients over 1,000 simulations (or the minimum number necessary to achieve statistical convergence), then calculating 95% credible range estimates for each model outcome based on the results. This probabilistic analysis

incorporates uncertainty in the model input parameters and BRAVO risk engine patient-level predictions simultaneously. When modeling the BRAVO equation uncertainty for tirzepatide, we plan to double the uncertainty estimates due to a lack of long-term cardiovascular outcomes data against which to calibrate. For any of the BRAVO equation coefficients with unavailable uncertainty estimates, we plan to use a 10% parameter uncertainty for the comparators and 20% parameter uncertainty for tirzepatide. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1) Modified societal perspective that includes components such as productivity impacts or other indirect costs as applicable
2) Modified time horizon (e.g., 10 years)
3) Sub-groups by cardiovascular event risk and renal impairment as data allow

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other T2D cost-effectiveness models. The outputs from the model will be validated against the available trial data of the interventions and also any relevant observational datasets.

3. Methods: Potential Budget Impact

3.1 Overview

ICER will use results from the cost-effectiveness model to estimate the potential total budgetary impact of tirzepatide in adults with T2D with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We will use a placeholder estimate, and the three benchmark prices (at $50,000, $100,000, and $150,000 per QALY) for tirzepatide in our estimates of budget impact. The pricing estimates will align with those used in the cost-effectiveness model.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices 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.

3.2 Methods

We will use results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events or decreased healthcare utilization. All costs will be undiscounted with regard to time and estimated over a five-year time horizon.

This potential budget impact analysis will include the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate population for treatment, we used inputs for the total US adult population size (~265 million) [25], overall T2D prevalence (14.6%) [26], proportion of patients with diagnosed T2D (76.7%) [26], and the proportion of patients having failed background therapy and thus eligible for treatment (47.2%) [20]. Applying these sources results in estimates of 14,006,143 eligible patients in the US. For the purposes of this analysis, we will assume that 20% of these patients would initiate tirzepatide treatment in each of the five years, or approximately 2,801,229 patients per year. Market shares in the model will be aligned with those comparators selected within the cost-effectiveness analysis. Any market shares attributed to therapies outside the scope of this review will instead be attributed to background therapy. We will evaluate whether tirzepatide would take market share from one or more existing treatments and calculate the blended budget impact associated with displacing use of existing therapies. The analysis will use clinical expert opinion regarding the treatments likely to be displaced and to what extent they are displaced by use of tirzepatide within the eligible population.

3.3 Analyses

The analysis will indicate when the potential budget impact threshold is reached at each combination of price and percent uptake among eligible patients at five years. The goal is to estimate the net cost per patient treated with new interventions so that decisionmakers can use their own assumptions about uptake and pricing to determine estimates of potential budget impact. Results of the analysis will be presented as cumulative per-patient potential budget impact for each year over the five-year time horizon, with results being presented graphically for tirzepatide, and numerical data presented in tabular format in an appendix. The graph will show the average potential budget impact for a single patient over various time horizons from one to five years, and the estimated average net cost of treating a patient with the intervention relative to comparator(s) over the five years of the potential budget impact analysis.

If the potential budget impact threshold is reached, a figure will be presented showing the approximate proportion of eligible patients that could be treated in a given year without crossing the threshold at each price, indicating when the potential budget impact threshold is reached at each combination of price and percent uptake among eligible patients at 5 years. If the potential budget impact threshold is not reached, a table for each treatment and population of interest will present the annual potential budgetary impact of treating the entire eligible populations across all prices (placeholder price, and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY), and the percent of the potential budget impact threshold that this represents.

Access and Affordability

In the final evidence report, ICER will include an "affordability and access alert" if discussion among clinical experts at the public meeting of ICER's independent appraisal committees suggests that full, "clinically optimal" utilization at estimated net pricing (or at the $150,000 per QALY threshold price if estimated net price is not available) would exceed the ICER annual potential budget impact threshold, without active intervention by insurers and others to manage access to the treatment.

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