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Inclisiran and Bempedoic Acid for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value

Modeling Analysis Plan

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Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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1. Approach

This analysis plan details our modeling approach for the economic evaluation of bempedoic acid (in combination with ezetimibe) and inclisiran. Please refer to the Research Protocol for details on the systematic review of the clinical evidence on this topic. Whereas comparative clinical effectiveness evaluation will encompass evidence from a broader set of patient populations, the economic model will focus on evaluating the cost effectiveness of these two agents in patients with established atherosclerotic cardiovascular disease (ASCVD), including analyses in the population as a whole and separate subgroup analyses of individuals with heterozygous familial hypercholesterolemia (HeFH).

The primary aim of this analysis will be to estimate the cost effectiveness of bempedoic acid in combination with ezetimibe and inclisiran using a state-transition Markov decision analytic model. Our analyses of incremental cost effectiveness will compare each of these treatments to maximally tolerated statin therapy and ezetimibe. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), and a lifetime time horizon. Productivity changes and other indirect costs and effects will be considered in a scenario analysis using a modified societal perspective, as data allow. Per ICER's reference case, if we judge the societal costs of care for ASCVD to be large relative to the direct health care costs and the impact of treatment on these costs is substantial, the modified societal perspective will be included as a co-base case, presented directly alongside the health care sector perspective analysis. The model will be developed in TreeAge Pro (TreeAge Software LLC, Williamstown, Massachusetts).

2. Methods: Long-Term Cost Effectiveness

2.1 Overview and Model Structure

We will develop a de novo decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. For this analysis, the inputs for effectiveness will be the percent reduction in LDL cholesterol level. The model will translate LDL cholesterol reduction into changes in major adverse cardiovascular events (MACE, defined as a composite of myocardial infarction [MI], stroke, and cardiovascular death) and mortality. To do so, it will assume that the relationship between LDL cholesterol reduction with bempedoic acid and MACE rates would be identical to that observed with statins, and the relationship between LDL cholesterol reduction with inclisiran and MACE rates would be identical to that observed in trials of currently approved PCSK9 inhibitors. Costs and outcomes will be discounted at 3% per year.

The state-transition Markov model will focus on an intention-to-treat analysis, with a hypothetical cohort of patients with established ASCVD being treated with maximally tolerated lipid-lowering therapy (statin, if tolerated, plus ezetimibe) entering the model and following one of three treatment pathways: the addition of bempedoic acid + ezetimibe combination, addition of inclisiran, or continuation of prior maximally tolerated lipid-lowering therapy alone (Figure 2.1A). Model cycle length will be one year.

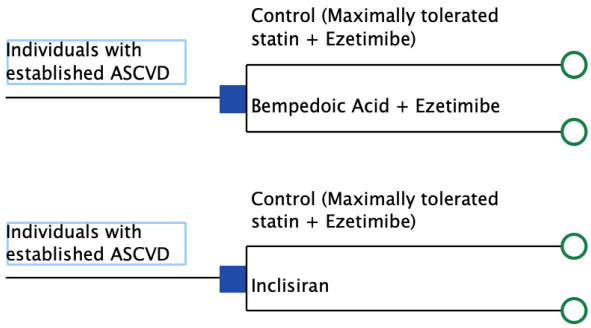
The Markov model will contain the following states (Figure 2.1B):

- History of MI
- History of stroke
- History of MI and stroke
- History of other ASCVD
- Dead from cardiovascular (CV) causes
- Dead from non-CV causes

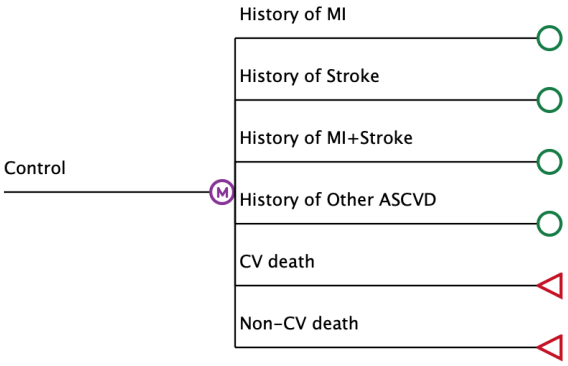
In each annual cycle, a subset of the cohort may experience an MI (fatal or non-fatal), a stroke (fatal or non-fatal), or die from other CV or non-CV causes. They may also undergo elective percutaneous or surgical revascularization (Figure 2.1C). The cohort is followed until all members are dead.

Figure 2.1. Model Schematic

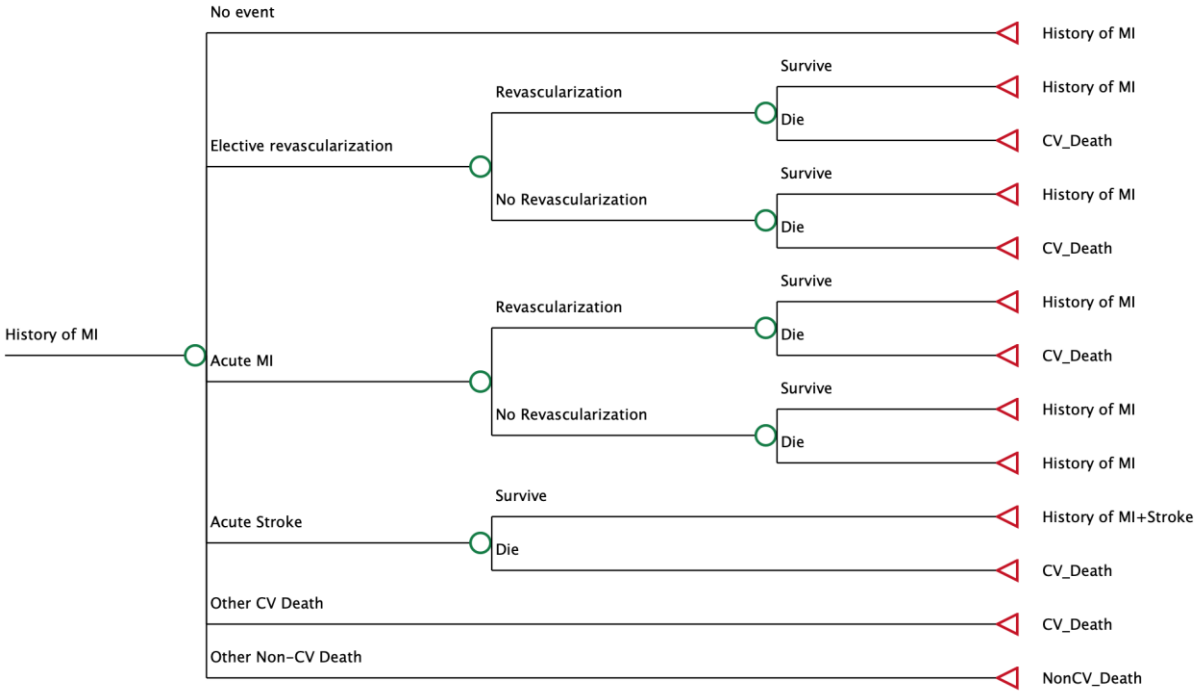
A:



B (Replicated for each arm above):



C (Replicated for each non-death arm above):



ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, MI: myocardial infarction

2.2 Key Model Choices and Assumptions

Our model includes several key assumptions, stated below. Information about specific parameter inputs are described in Section 2.5 below.

Table 2.1. Key Assumptions

Assumption	Rationale
The cohort with pre-existing ASCVD will include individuals with a history of MI, stroke, MI and stroke, or other forms of ASCVD (e.g., angina).	Clinical history determines baseline health-related quality-of-life, risk of future events, and health care costs.
Observed major cardiovascular adverse events (MACE) will be apportioned across the subgroups of the cohort based on prior clinical history.	For instance, patients with a history of MI are at increased risk of recurrent MI.
Patients with established ASCVD who are statin intolerant have a higher baseline LDL cholesterol level and are at increased risk of MACE compared with patients with established ASCVD receiving statin therapy.	Statin use in patients with established ASCVD reduces LDL cholesterol levels and the risk of MACE by 22% per 1 mmol/L reduction in LDL cholesterol levels.[1]
Patients with HeFH with established ASCVD have higher event rates than the general population with established ASCVD.	Lifetime exposure to high levels of LDL cholesterol result in an elevated risk of ASCVD events in individuals with HeFH compared with the general population. This difference has not been shown in individuals with established ASCVD (since this represents a very high-risk subgroup within the general population). In the base case, we will assume a 2x increased risk in individuals with HeFH and ASCVD but will vary this in sensitivity analyses.
Addition of bempedoic acid (as a part of the combination pill) or inclisiran will achieve the same relative reduction in LDL cholesterol levels in the study cohort as in the trial population.	We will assume that relative reductions in LDL cholesterol observed in the clinical trials can be replicated in the real world, though absolute reductions will vary based on baseline LDL cholesterol levels. Of note, we will examine whether the effect of bempedoic acid is modified by concurrent treatment with statins (i.e., whether the relative reduction in LDL cholesterol is different among individuals receiving statin therapy and those deemed statin intolerant and therefore not receiving statins).
Lowering LDL cholesterol levels with bempedoic acid/ezetimibe or inclisiran in patients with established ASCVD will lower the rates of MACE. In the model, LDL cholesterol reductions due to statins and ezetimibe will be translated into MACE reductions based on prior trial data; LDL cholesterol reduction due to the bempedoic acid component of the combination pill will be assumed to produce the equivalent MACE reduction (per mmol/L reduction in LDL cholesterol) as statins; LDL cholesterol reduction due to inclisiran will be assumed to produce the equivalent MACE reduction (per mmol/L reduction in LDL cholesterol) as PCSK9 inhibitors.	This has not been shown in clinical trials for bempedoic acid and inclisiran, as trials powered to examine cardiovascular outcomes are ongoing. Nevertheless, this assumption underpins the regulatory approval of bempedoic acid, and ongoing trials of inclisiran. To estimate the effectiveness of the intervention drugs, we will rely on their mechanistic similarity with other lipid-lowering drugs for which outcomes data are available (bempedoic acid and statins both inhibit key steps in the cholesterol synthesis pathway, whereas inclisiran, evolocumab, and alirocumab inhibit the PCSK9 enzyme).

ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, LDL: low-density lipoprotein, MACE: major adverse cardiovascular events, MI: myocardial infarction, PCSK9: proprotein coverstase subtilisin/kexin type 9.

2.3 Populations

The population of focus for the economic evaluation will include patients with established ASCVD who need additional lipid lowering despite maximally tolerated lipid-lowering therapy (typically statins and ezetimibe). If feasible, to explore higher value subpopulations and to facilitate qualitative comparison with subpopulations in prior ICER reviews of the PCSK9 inhibitors, the model will further explore important "high-risk" subgroups of ASCVD patients:

- Patients with HeFH and established ASCVD
- Patients intolerant to statins
- Patients with an acute MI in the past year

Population characteristics will be derived from the clinical review and will be broadly representative of the US population with established ASCVD.

Baseline characteristics will reflect a real-world population eligible for the therapies being evaluated.

Table 2.2. Baseline Population Characteristics

	Total
Starting Age	65 years
Percent Women	~40%
Statin Intolerance*	5%
Baseline LDL Cholesterol Level	Estimated from epidemiologic data to reflect the control arm of relevant clinical trials (and HeFH status)

HeFH: heterozygous familial hypercholesterolemia, LDL: low-density lipoprotein

* Although statin-related myalgias are common, estimates of the prevalence of statin intolerance vary depending on the extent to which alternative statin regimens (including drug and dosing) are tried before establishing a diagnosis of statin intolerance, and vary from 1%-20%.[2]

2.4 Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Bempedoic acid/ezetimibe combination pill (Nexlizet™, Esperion Therapeutics, Inc.)
- Inclisiran (Novartis)

Because the combination pill of bempedoic acid and ezetimibe is available at the same price (net of discounts) as bempedoic acid alone, the combination pill would be expected to dominate the bempedoic acid pill in any economic evaluation (assuming that ezetimibe is clinically beneficial).

We therefore chose to evaluate the value-based price of the combination pill rather than bempedoic acid in this analysis.

Comparator

Each intervention drug will be compared with:

- Maximally tolerated lipid-lowering therapy (typically statin and ezetimibe). For the portion of the cohort that is statin intolerant, the comparator will be ezetimibe alone. This was chosen to reflect the control arm of the pivotal trials for each drug as well as the likely real-world use of these medications.

Note that previously approved PCSK9 inhibitors (evolocumab and alirocumab) have not been incorporated into the model, but the results of the inclisiran evaluation will be qualitatively compared with the results of prior cost-effectiveness analyses of PCSK9 inhibitors.[3-5]

2.5 Input Parameters

Clinical Inputs

Transition Probabilities

Transition probabilities across the various health states will be estimated from published literature, review of prior models, and systematic review of the relevant trials. When relevant evidence is not directly available in the published literature, we will rely on input from clinical experts and key stakeholders.

Table 2.3. Transition Probabilities

Parameter	Base-Case Value	Range for Sensitivity Analyses	Distribution	Source, Comment
Base-Case Inputs				
Proportion of Entry Cohort (adults with Established ASCVD) in Each State	TBD	-	Beta	Clinical trials and NHANES analysis
Rate of MACE, per 100 Person-Years	4.1	4.0-6.0	Log normal	Review of contemporary trials (e.g., of PCSK9 inhibitors)[6]
Proportion of MACE that is an MI, Stroke, or other CV Death	TBD, will vary by state	-	-	Review of contemporary clinical trials
Accelerator for Increase in MACE Rates per Decade of Advancing Age	TBD	TBD	Normal	Review of contemporary epidemiologic data
Rate of Elective Coronary Revascularization	TBD	TBD	Log normal	Review of contemporary epidemiologic and registry data
Proportion of Elective Revascularization that is Percutaneous (Rather than Surgical)	TBD	TBD	Beta	Review of contemporary clinical trials, registries
Rate of Non-CV Death	Age-specific estimate	0.8x – 2x base-case value	Log normal	US vital statistics[7]
Baseline Mean LDL-C in the Control Arm (mg/dL)	TBD during clinical review	TBD during clinical review	Normal	Estimated from epidemiologic data to estimate nationally representative values of patients who meet eligibility criteria for each intervention (see Table 2 in Kazi, et al. JAMA 2016)[8]

Parameter	Base-Case Value	Range for Sensitivity Analyses	Distribution	Source, Comment
Effectiveness of Interventions				
Relative Reduction in LDL Cholesterol Level with Bempedoic Acid+Ezetimibe, %	TBD during clinical review	TBD during clinical review	Beta	Randomized trials of bempedoic acid compared with placebo, or the combination pill compared with ezetimibe[9-13]
Relative Reduction in LDL Cholesterol Level with Inclisiran, %	TBD during clinical review	TBD during clinical review	Beta	Randomized trials of inclisiran[14-17]
Rate Ratio for MACE, Bempedoic Acid, per mmol/L Reduction in LDL Cholesterol	0.78*	0.76-0.80	Log normal	Based on published meta-analyses of randomized trials of statin therapy
Rate Ratio for MACE, Inclisiran, per mmol/L Reduction in LDL Cholesterol	TBD*	TBD	Log normal	Based on published meta-analyses of randomized trials of evolocumab and alirocumab[18-20]
Rate Ratio for MACE, Ezetimibe, per mmol/L Reduction in LDL Cholesterol	0.75*	0.61-0.94	Log normal	IMPROVE-IT clinical trial[8,21,22]
Subgroup Analyses				
Rate of MACE in HeFH with Established ASCVD, per 100 Person-Years	2x general population rate	1-3x general population rate	Log normal	Assumed[8]
Rate of MACE in Patients Enrolled in the First Year After an MI, per 100 Person-Years	6.7	6.2-7.2	Beta	Kazi 2019[6]

ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, HeFH: heterozygous familial hypercholesterolemia, LDL: low-density lipoprotein, MACE: major adverse cardiovascular events, MI: myocardial infarction, NHANES: National Health and Nutrition Examination Survey, TBD: to be determined

*The model may use different rate ratios for different subtypes of MACE (e.g., MI, stroke, and cardiovascular death) where available.

Mortality

Age- and sex-specific CV and non-CV mortality for patients with established ASCVD will be estimated from prior work.[8,23]

Adverse Events

The incidence of serious adverse events related to the intervention drugs will be estimated from the clinical review and may include gout (for bempedoic acid) and will include injection site reactions (for inclisiran).

Table 2.4. Select Adverse Events

Parameter	Disutility	Cost	Source
Injection-Site Reactions (Inclisiran)	0.0003 (0.0000-0.0020)	0	Khazeni, et al.

Health-Related Quality-of-Life

Estimates of health-related quality-of-life for each state will be derived from publicly available literature. We will use consistent values for health states across treatments evaluated in the model.

The base case will incorporate health-related quality-of-life estimates from the Global Burden of Disease study as in prior models examining lipid-lowering therapies. We will explore the use of estimates from the Medical Expenditure Panel Survey.[24]

Table 2.5. Health State Utilities

Input Parameter	Base-Case Value	Range for Sensitivity Analyses	Distribution for Monte Carlo Simulations	Source
Utility Weights				
History of Angina	0.9064	(0.8710-0.9360)	β	Moran et al. (2014)[25,26] Murray et al. (2012)[27]
History of MI	0.9648	(0.9513-0.9764)	β	Moran et al. (2014)[25,26] Murray et al. (2012)[27]
History of Stroke	0.8835	(0.8456-0.9133)	β	Moran et al. (2014)[25,26] Murray et al. (2012)[27]
History of MI and Stroke	0.8524	(0.8083-0.8987)	β	Moran et al. (2014)[25,26] Murray et al. (2012)[27]
Transient Utility Tolls (Disutilities) for Acute Events				
Percutaneous Revascularization	0.0096	(0.0041-0.0192)	β	Kazi et al. (2014)[28]
Surgical Revascularization	0.0192	(0.0096-0.0396)	β	Kazi et al. (2014)[28]
Acute MI	0.0079	(0.0051-0.0112)	β	Moran et al. (2014)[25,26] Murray et al. (2012)[27]
Acute Stroke	0.0113	(0.0084-0.0154)	β	Moran et al. (2014)[25,26] Murray et al. (2012)[27]

MI: myocardial infarction

Drug Utilization

In the base case, the model will assume the same adherence to the interventions as observed in the clinical trials, to reflect the use of efficacy estimates from the trials. We will assume that patients will continue the therapy throughout their lifetimes.

Table 2.6. Treatment Regimen Recommended Dosage

Generic Name	Bempedoic Acid/Ezetimibe	Inclisiran
Brand Name	Nexlizet™	-
Manufacturer	Esperion Therapeutics, Inc.	Novartis
Route of Administration	Oral	Subcutaneous
Dosing	180 mg/10 mg daily	300 mg on days 1 and 90, and then every 180 days

Cost Inputs

All costs used in the model will be updated to 2020 US dollars.

Drug Costs

As bempedoic acid/ezetimibe was recently approved (in February 2020), net price data from SSR Health is not yet available; therefore, the Federal Supply Schedule (FSS) price will be used as the net pricing estimate (we will switch to estimated net prices from SSR Health should they become available before the final report). For inclisiran, which is not yet approved for use in the US, the base case will assume a placeholder price that is equal to the average of FSS prices for currently approved PCSK9 inhibitors. An additional administration cost will be added for inclisiran if the drug's regulatory approval requires administration by a health care professional.

Table 2.7. Annual Drug Costs

Drug	WAC per Dose	Discount from WAC	Net Price per Dose	Net Price per Year
Bempedoic Acid/ Ezetimibe (Nexlizet)	$11.00	29%	$7.82*	$2,856
Inclisiran	NA	NA	$2,822†	$5,644†

WAC: wholesale acquisition cost, NA: not available

*Federal Supply Schedule price as of September 1, 2020.

†Placeholder price per maintenance year estimated using average annual net cost of alirocumab and evolocumab (from Federal Supply Schedule as of September 1, 2020) and assuming 2 doses per year. Initial treatment year requires 3 doses.

We will assume that patients initiating a lipid-lowering treatment will receive a follow-up lipid panel (at 12 weeks for bempedoic acid/ezetimibe and at 6 months for inclisiran). As patients with established ASCVD are likely to have regular clinic visits, we will not assume any additional monitoring costs specific to the intervention.

Serious adverse events appear to be rare with bempedoic acid/ezetimibe or inclisiran, but we will model costs and quality-of-life penalties associated with any serious adverse events identified during the clinical review.

Non-Drug Costs

In annual cycles, patients accrue background health care costs (estimated from the Medical Expenditure Panel Survey as a part of prior analyses) as well as costs related to any acute events or revascularization procedures (estimated from the published literature, based on the National Inpatient Sample).

Table 2.8. Other Costs

Input Parameter	Base-Case Values	Range for Sensitivity Analyses	Distribution for Monte Carlo Simulations	Source
Costs of CHD Care, USD				
Acute Fatal MI Hospitalization	$64,995	($61,176 - $68,772)	Log normal	National Inpatient Sample, Peterson et al. (2015)[29,30]
Acute Non-Fatal MI Hospitalization	$41,136	($40,691 - $41,594)	Log normal	National Inpatient Sample, Peterson et al. (2015)[29,30]
Acute MI Post-Hospitalization Year 1 Costs	$11,909	($10,406 - 14,192)	Log normal	Medical Expenditure Panel Survey[31]
CHD Costs, Subsequent Years	$2,485	($2,108 - $2,901)	Log normal	Medical Expenditure Panel Survey[31]
Costs of Stroke Care, USD				
Fatal Stroke Hospitalization	$34,525	($32,581 - $36,563)	Log normal	National Inpatient Sample, Peterson et al. (2015)[29,30]
Non-Fatal Stroke Hospitalization	$21,284	($20884 - $21,682)	Log normal	National Inpatient Sample, Peterson et al. (2015)[29,30]
Post-Stroke Cost, Months 2-11	$18,824	($15,717 - $22,153)	Log normal	Medical Expenditure Panel Survey[31]
Post-Stroke Cost, Annual, Subsequent Years	$5,231	($4,347 - $6,205)	Log normal	Medical Expenditure Panel Survey[31]

CHD: coronary heart disease, MI: myocardial infarction, USD: US dollars

For the modified societal perspective, we will attempt to identify productivity losses and other indirect costs related to MACE per ICER's reference case.

2.6 Model Outcomes

Model outcomes will include MACE (major adverse CV events, defined as non-fatal MI, non-fatal stroke, or CV death), total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years gained (evLYG), and total costs for each intervention over a lifetime time horizon. Total costs, LYs, QALYs, and evLYG will be reported as discounted values, using a discount rate of 3% per annum (undiscounted results will be presented in an appendix).

2.7 Model Analysis

Cost effectiveness will be estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing:

1. Bempedoic acid/ezetimibe with optimal lipid-lowering therapy (maximally tolerated statin + ezetimibe), and
2. Inclisiran with optimal lipid-lowering therapy (maximally tolerated statin + ezetimibe).

The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Productivity impacts and other indirect costs (as data permit) will be considered in a separate analysis to the extent feasible. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses thresholds of $100,000-$150,000 per QALY gained. Additionally, we will perform a cost-consequence analysis to examine the incremental cost per MACE averted (for each intervention relative to its control).

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 over 1000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY and evLYG).

Scenario Analyses

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

1. Modified societal perspective that includes components such as productivity losses, and other indirect costs as applicable.

Model Validation

We will use several approaches to validate the model. First, we will provide this Model Analysis Plan with preliminary model structure, methods and assumptions 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 relevant manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results with other cost-effectiveness models in this therapy area. To the extent possible, outputs from the model will be validated against the trial/study data of the interventions and any relevant observational datasets.

Health Benefit Price Benchmarks

We will determine the price for each intervention at which its incremental cost-effectiveness ratio relative to its comparator would be equal to commonly used thresholds (from a US health care sector perspective and a lifetime analytic horizon). To ascertain the cost-effective price of the combination pill of bempedoic acid and ezetimibe, we will determine the value-based price of its bempedoic acid component by comparing the combination pill with the control arm (optimal lipid-lowering with maximally tolerated statin and ezetimibe), and then adding the price of generic ezetimibe.

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 bempedoic acid (in combination with ezetimibe) and inclisiran for the adult population with established ASCVD or HeFH in need of further lipid lowering. We will use the WAC (where available), estimated net or placeholder prices, and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for each drug in our estimates of budget impact.

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 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 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. All costs will be undiscounted 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 eligible prevalent population with established ASCVD in US adults 21 years old or older, we will use a baseline estimate from the AHA Center for Health Metrics and Evaluation (based on National Health and Nutrition Examination Survey [NHANES] 2013-2014 data) of just over 18 million individuals,[32] or 7.93% of the 2014 US population. The same source reported that 64.6% of these patients were currently taking statins. Applying these proportions to the projected average US population from 2020-2024,[33] we arrive at an estimate of approximately 19.8 million individuals with established ASCVD, with approximately 12.8 million taking statins. Wong et al. used NHANES 2011-2012 data to estimate that 79.7% of ASCVD patients on statins were not at LDL-C goal.[34] Applying this proportion to the 2020-2024 average population results in an estimate of approximately 10.2 million individuals with ASCVD not at LDL-C goal despite statin treatment. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or approximately 2,042,000 patients per year.

To estimate the size of the eligible prevalent population with HeFH in US adults age 21 years or older, we will use an estimate from an analysis of NHANES 1999-2012 data of 0.40% of the US population,[35] or approximately one million individuals when applied to the average 2020-2024 US population. We will assume that the entire HeFH population will be eligible for these treatments (i.e., not at LDL-C goal regardless of treatment). For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or approximately 200,000 patients per year.

We will evaluate whether a new drug would take market share from one or more existing treatments and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, we will assume that each drug is added on to optimal lipid-lowering therapy (i.e., maximally tolerated statin + ezetimibe).

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 decision-makers 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 each intervention, 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 five 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 (WAC if known, discounted WAC or assumed 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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