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

Final Report

March 2, 2021

Prepared for

April 12, 2022: New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to patient and clinical experts and the relevant manufacturers included in this review 12 months after the publication of this report, giving them an opportunity to submit public comments regarding new relevant evidence or information on coverage that they wish to highlight. No stakeholders submitted public comments. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

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Grace Lin served as the lead author for the report and wrote the background, other benefits, and contextual considerations sections of the report, with Jane Jih serving as a co-author. Foluso Agboola was responsible for the oversight of the systematic review and authorship of the comparative clinical effectiveness section with the support of Katherine Fazioli and Avery McKenna. Dhruv Kazi developed the cost-effectiveness model and authored the corresponding section of the report. Rick Chapman developed the potential budget impact analysis and authored Section 8. Monica Frederick authored the section on coverage policies and clinical guidelines with support from Maggie O'Grady. Steve Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Grace Fox, Kanya Shah, and Eric Borrelli for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer.org.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 21% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include Merck and Novartis. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. The Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about the Midwest CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.

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 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/assessment/high-cholesterol-2021/#overview.

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List of Acronyms and Abbreviations Used in this Report

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AHA	American Heart Association
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BCBS	Blue Cross Blue Shield
CI	Confidence interval
CTAF	California Technology Assessment Forum
CV	Cardiovascular
CVD	Cardiovascular disease
CTTC	Cholesterol Treatment Trialists Collaboration
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
FSS	Federal Supply Schedule
HCSC	Health Care Service Corporation
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
IndepBC	Independence Blue Cross
ITT	Intention to treat
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MD	Mean difference
N	Total number
No.	Number
NR	Not reported
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, and Settings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RR	Risk ratio
SASE	Statin associated side effects
SE	Standard error
SPEC	Tufts Medical Center Specialty Drug Evidence and Coverage
UHC	UnitedHealthcare
ULN	Upper limit of normal
US	United States
USPSTF	US Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

Background

Atherosclerotic cardiovascular disease (ASCVD) encompasses a set of common, complex, and burdensome conditions with coronary artery disease, peripheral artery disease, and cerebrovascular disease as the three most prevalent types. Almost 1 in 10 people are estimated to have some form of ASCVD, and ASCVD remains the leading cause of death in the United States.[1,2] There are significant disparities in ASCVD burden by race and sex, with Hispanic and non-Hispanic Black men and women at higher risk of death compared with White men.[1] The financial cost of the disease is staggering, with total costs expected to reach $1.1 trillion by 2035.[3]

Risk factors for ASCVD include diabetes mellitus, hypertension, obesity, smoking, and elevated levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-C). A genetic disorder of cholesterol metabolism, familial hypercholesterolemia (FH), can lead to severely elevated plasma concentrations of LDL-C, placing patients at higher risk of major adverse cardiac events (MACE) such as myocardial infarctions and strokes earlier in life. Although heterozygous FH (HeFH) is the most common form of FH, affecting approximately 1 in 250 people in the US, the condition is underdiagnosed and undertreated, particularly amongst women, Blacks, and Asians.[4]

Treatment of patients with FH and established ASCVD includes risk factor modification such as dietary and lifestyle changes and smoking cessation, medical therapy, and when necessary, percutaneous or surgical revascularization. Because of the association between lipid levels and MACE, medical therapy should include intensive lipid-lowering therapy, with a goal LDL-C reduction of at least 50%.[5] Ideally this should be accomplished with a high dose or maximally tolerated statin, but for patients who continue to have LDL-C levels at or above 70 mg/dL, the addition of ezetimibe is recommended as second-line therapy. Finally, for those patients who continue to have LDL-C levels above 70 mg/dL on statin and ezetimibe, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor can be considered. For patients who have statin-associated side effects (SASE) (also known as statin intolerance) -- defined as not able to tolerate moderate to high intensity statin therapy due to side effects -- therapy with ezetimibe, PCSK9 inhibitors, and other lipid-lowering therapies may be considered to reach treatment goals.

Even with the wide range of aforementioned options for risk factor modification and treatment, patients with HeFH and established ASCVD, who are the focus of this review, remain at high residual risk for further MACE, particularly if LDL-C levels are not adequately controlled. Thus, there is an important public health need for additional treatment options to improve outcomes for patients who remain at higher risk for cardiovascular events. One new lipid-lowering treatment has recently been approved by the FDA: bempedoic acid with or without ezetimibe (Nexlizet™ and

Nexletol®, Esperion Therapeutics, Inc.), an inhibitor of adenosine triphosphate (ATP) citrate lyase that lowers LDL-C by reducing cholesterol synthesis and up-regulating LDL receptors. Another agent currently under evaluation at the FDA is inclisiran (Novartis), a double-stranded small interfering RNA agent targeting and inhibiting hepatic PCSK9 synthesis. These therapies are the focus of this review (Table ES1).

Table ES1. Cholesterol-Lowering Drugs Examined in Report

Drug	Brand Name	FDA Approval Date	Route	Dose	Estimated Annual Cost*
Bempedoic acid	Nexletol®	02/21/2020	Oral	180 mg daily	$2,856
Bempedoic acid/ezetimibe	Nexlizet™	02/21/2020	Oral	180 mg/10 mg daily	$2,856
Inclisiran	N/A	Pending	Subcutaneous injection	300 mg on days 1 and 90, then every 6 months	$5,644†

*Based on 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 two doses per year. Initial treatment year requires three doses.

Patient Perspectives

From the beginning of this assessment, we sought input from patients, caregivers, and representatives from patient advocacy organizations on the research design of this review, the patient experience of HeFH and ASCVD and its treatment, including statin intolerance, benefits of treatment that may not be described in the clinical literature, any broader potential other benefits or disadvantages associated with treatments, and contextual consideration related to HeFH and ASCVD. We also built upon the insights that these stakeholders shared with ICER during our initial 2015 review of PCSK9 inhibitors,[6] new evidence update in 2017 of evolocumab[7] and subsequent new evidence update in 2019 of alirocumab.[8]

We heard from patients, caregivers, and advocacy organizations in the open input, draft scope, and draft report phases of the review. As a result, the draft scope and draft report were revised, including new language that: 1) clarifies the subpopulations of interest within the clinical and the economic sections of the review; 2) highlights disparities in cholesterol treatment as a key concern; 3) addresses the real-world low use of ezetimibe; 4) notes that patients with HeFH who do not have established ASCVD are also a high-risk group for MACE; and 5) provides additional contextual factors that stakeholder groups felt should be considered during the review.

In response to the feedback we received during the preliminary model presentation and draft report, we also made changes to key inputs to the cost effectiveness model, including using

Cholesterol Treatment Trialists Collaboration (CTTC) data for converting LDL-C reduction into MACE rates for both drugs.

Impact on Patients

Patient groups highlighted that diagnosis of FH is often missed or delayed, and that patients with FH are often undertreated despite their very high risk of ASCVD events. Additionally, patients with FH often have events earlier in life and during years of prime productivity and their lives may be impacted by the disease for a longer time horizon than other ASCVD patients; therefore, earlier treatment may be particularly beneficial for this population.

Accessibility, affordability, side effects of continued therapy during the life course, impact of therapies on health care utilization, long-term ASCVD events, and outcomes were other concerns brought forth by patient groups. Access to new therapies was of particular concern to patients, given that the often-cumbersome insurance prior authorization process for newer cholesterol-lowering drugs like PCSK9-inhibitors has resulted in delayed or denial of access to therapy for some patients.[9,10] Furthermore, inability to access prescribed PCSK9 inhibitor therapy has been associated with an increased risk of having a cardiovascular event.[11]

Patient groups and clinical experts were concerned about longstanding health care disparities in high cholesterol treatment and outcomes across race/ethnicity, gender, and insurance type. For example, women and racial/ethnic minorities are less likely to receive statin therapy, PCSK9 inhibitors, or achieve LDL goals.[11,12] The reasons for health inequities are likely multifactorial, including patient and provider factors, structural racism in the health care system, and inequities in social determinants of health. In addition, the lack of adequate inclusion of racial/ethnic minorities in clinical trials of new therapies was identified as a barrier to being able to evaluate whether there may be differential effects of therapies in these subpopulations.

Clinical experts were largely of the view that bempedoic acid and the bempedoic acid/ezetimibe combination therapy would be most helpful in patients with statin intolerance and those who are close to their LDL goal but do not wish to take an injectable drug. Experts also cautioned that side effects such as increased uric acid levels and risk of gout would likely affect patient and clinician consideration of the role of bempedoic acid in therapy. For inclisiran, clinical experts suggested that the clinical community would be likely to view the evidence on its LDL-lowering as equivalent to that of PCSK9 inhibitors, but that there would be some degree of skepticism on its clinical equivalence until clinical outcome studies are completed and their results published. On the other hand, clinical experts and patient groups both highlighted inclisiran's potential benefits for patient adherence to treatment given its twice-yearly dosing compared to every two-week dosing for PCSK9 inhibitors.

Manufacturers highlighted that consideration in value assessment should be given to the impact of potential differences between treatments beyond LDL-C lowering, including mode of delivery, drug administration considerations (e.g., in a physician's office or self-administered), dosing interval, adherence, and effects on other disease parameters (e.g., hemoglobin A1c, high-sensitivity CRP) which could impact patient experience, treatment burden and patient-important outcomes.

Impact on Caregivers and Families

The impact of cardiovascular events such as myocardial infarction and stroke may range from mild to severe, with severe events leading to major disabilities affecting activities of daily living and independence. Prevention of cardiovascular events could benefit caregivers and families by maintaining patient independence and decreasing the need for caregiving. In addition, prevention of cardiovascular events could increase the productivity of patients, which may be particularly important for younger patients in the workforce and those with dependent children (e.g., FH patients, women).

Comparative Clinical Effectiveness

We systematically identified and synthesized the existing evidence from available clinical studies to assess the comparative clinical effectiveness of treatment of patients with HeFH and established ASCVD with bempedoic acid (with or without ezetimibe) and inclisiran. We compared the efficacy, safety, and effectiveness of these treatments to maximally tolerated lipid-lowering therapy (i.e., the placebo arms of their respective clinical trials). We conducted pairwise meta-analysis for primary and secondary outcomes of each drug separately, but we did not attempt to compare these treatments to each other because of key differences across trials in patient characteristics and trial design. Change in LDL-C was the primary outcome assessed in the trials of these interventions. Additionally, because trials evaluating the impact of treatment on clinical outcomes have not been completed, we did not pursue a quantitative comparison of inclisiran with PCSK9 inhibitors.

We assessed the benefits and harms of each drug in three subgroups where sufficient data were available: patients with HeFH, both with and without ASCVD (primary and secondary prevention), patients with established ASCVD at relatively higher risk (e.g., patients with myocardial infarction), and patients with statin intolerance.

Bempedoic Acid With or Without Ezetimibe

A total of five pivotal Phase III randomized clinical trials (RCTs) informed our review of bempedoic acid with or without ezetimibe. Four studies examined bempedoic acid compared with maximally tolerated lipid lowering therapy, including two RCTs in patients with ASCVD, HeFH, or both in (CLEAR Wisdom and CLEAR Harmony) and two RCTS in patients with statin intolerance (CLEAR Serenity and CLEAR Tranquility). There was one study examining the combination of bempedoic

acid with ezetimibe, a four-arm RCT in patients with ASCVD, HeFH, or multiple CVD risk factors (Ballantyne 2020). Since we found no data to suggest that ezetimibe modifies the effect of bempedoic acid, we considered bempedoic acid versus placebo to be equivalent to bempedoic acid/ezetimibe versus ezetimibe in our discussion of the clinical benefits of bempedoic acid.

Clinical Benefits

LDL-C and Other Lipid Parameters

Meta-analysis of existing data found that bempedoic acid in addition to maximally tolerated lipid-lowering therapy provided an overall 19.5% decrease in LDL-C after 12 weeks of treatment (Table ES2). However, heterogeneity among the studies was high and statistically significant (I^2=69%, p<0.01). Bempedoic acid also improved other lipid parameters, including significant reductions versus placebo in total cholesterol (9% -18%), non-HDL-C (11% -23%), apolipoprotein B (7% -25%), and hsCRP (9% -31%).

Table ES2. Bempedoic Acid: Percentage Change in LDL-C from Baseline to Week 12

Trials	Population	Baseline LDL-C	Percent Reduction		
			Control	Bempedoic Acid	Between-Arm Difference
Bempedoic Acid vs. Placebo					
CLEAR Wisdom	ASCVD, HeFH, or both on maximally tolerated statin therapy	120.4 mg/dL	2.4 (NR)	-15.1 (NR)	-17.4 (-21.0, -13.9)
CLEAR Harmony	ASCVD, HeFH, or both on maximally tolerated statin therapy	103.2 mg/dL	1.6 (0.9)	-16.5 (0.5)	-18.1 (-20.0, -16.1)
Ballantyne 2020*	ASCVD, HeFH, or both on maximally tolerated statin therapy	149.2 mg/dL	1.8 (3.4)	-17.2 (2.6)	-19.0 (-27.8, -10.2)
CLEAR Serenity	Patients with statin intolerance	157.6 mg/dL	-1.3 (1.4)	-23.6 (1.4)	-21.4 (-25.1, -17.7)
CLEAR Tranquility	Patients with statin intolerance	127.6 mg/dL	5 (2.2)	-23.5 (2.0)	-28.5 (-34.4, -22.5)
Bempedoic Acid/Ezetimibe Combination Pill vs. Ezetimibe					
Ballantyne 2020*	ASCVD, HeFH, or both on maximally tolerated statin therapy	151.4 mg/dL	-23.2 (2.2)	-36.2 (2.6)	-13.0 (-19.7, -6.5)
Summary Estimate: Random Effect Meta-Analysis Bempedoic Acid vs. Placebo					-19.5 (-22.7, -16.4); p<0.0001; I^2 =69%

ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, I^2: I-squared, LDL-C: low-density lipoprotein cholesterol, SE: standard error

*Ballantyne 2020 is a four-arm trial (bempedoic acid/ezetimibe combination pill, ezetimibe, bempedoic acid, and placebo) that provided separate data for the combination pill versus ezetimibe & bempedoic acid versus placebo in the meta-analysis

Subgroup Analysis

HeFH (primary and secondary prevention): We did not identify any bempedoic acid trials conducted exclusively in the HeFH population, and the included studies enrolled very few patients with HeFH (1-5%). A subgroup analysis by HeFH status was conducted using two of the pivotal trials (CLEAR Wisdom and CLEAR Harmony). The results showed a marginally higher LDL-C reduction (MD: –22.3, 95% CI: –33.3 to –11.4) in the HeFH patients compared to the other patients (MD: –18.3, 95% CI: –20.1 to –16.6); however, the difference was not statistically significant (p-value for interaction =0.65).

Established ASCVD (secondary prevention): The three pivotal trials (CLEAR Wisdom, CLEAR Harmony, and Ballantyne 2020) primarily enrolled patients with established ASCVD. Our meta-analysis, including only these three studies, showed a 17.7% LDL-C reduction with bempedoic acid compared to control.

Statin intolerance: The percentage reduction in LDL-C appears to be greater in CLEAR Serenity and CLEAR Tranquility, which exclusively enrolled statin-intolerant patients, than the other studies where patients were on background statin therapy (21% to 28% vs. 13% to 19%) (Table ES2). We conducted a subgroup analysis across all trials to further evaluate these potential differences. The results showed there was a 24.6% LDL-C reduction (95% CI: -31.5 to -17.6, $p<0.0001$, $I^2=75\%$) with bempedoic acid treatment compared to placebo for statin-intolerant patients. This was larger than the 17.7% LDL-C reduction with bempedoic acid found in the other studies that included patients on maximally tolerated statin therapy. The test for subgroup difference just reached statistical significance (Q=3.87, p=0.05). Bempedoic acid with ezetimibe combination pill

In the single trial that included an arm with the bempedoic acid/ezetimibe fixed-dose combination pill, the combination pill produced greater reductions in LDL-C at 12 weeks compared to the ezetimibe, bempedoic acid, and placebo arms. Although the combination pill showed a 38.3% reduction in LDL-C compared with placebo, this value was slightly less than the additive effect of bempedoic acid (25%) and ezetimibe (19%) arms in the same trial. Compared with the bempedoic acid monotherapy arm, the combination pill reduced LDL-C by 19%, and compared with the ezetimibe monotherapy arm, the combination pill reduced LDL-C by 13%.

Clinical Outcomes

Although LDL-C was the primary outcome for the included trials, all-cause mortality and CV outcome events (CV mortality, non-fatal stroke, non-fatal MI, and MACE) at 52 weeks were recorded and reported as part of the safety evaluation in two trials, CLEAR Wisdom and CLEAR Harmony. Meta-analysis of the data found a higher incidence of all-cause mortality (RR: 2.25; 95% CI: 0.76-6.67) and CV mortality (RR: 1.52; 95% CI: 0.41-5.70) in the bempedoic acid group compared with the placebo group, though numbers of events were small, and 95% confidence intervals were

non-significant (Table ES5). Findings also included a non-significant lower event rate on MACE with bempedoic acid compared to placebo (RR: 0.79; 95% CI: 0.58, 1.07). No studies assessed the impact of bempedoic acid on health-related quality of life.

Harms

Overall, there were more adverse events (AEs) associated with taking bempedoic acid compared with placebo (24.1% versus 20.3%, p=0.01). The majority of the adverse events (AEs) observed were mild or moderate, and included muscle pain and spasm, hyperuricemia, gout, elevated liver enzymes, and changes in blood creatinine level. Eleven patients (0.5%) in the bempedoic acid group were reported to have tendon rupture, compared with none in the placebo group. The incidence of increased uric acid was 4 times higher in the treatment group than placebo (2.1% vs. 0.5%, p < 0.001), and there was a three-fold higher occurrence of gout reported in the bempedoic acid group compared with placebo, although the absolute rates of occurrence were relatively small (1.4% vs. 0.4%, p=0.008). These AEs caused bempedoic acid to receive a label warning for hyperuricemia and tendon rupture. Discontinuation due to AEs occurred in 11% of patients on bempedoic acid compared to 8% of patients on placebo (p=0.001). Serious AEs reported included all-cause mortality and CV events. Overall, a similar pattern of adverse events was observed in the bempedoic acid/ezetimibe combination pill trial.

Inclisiran

We identified four pivotal trials of inclisiran that met our inclusion criteria and informed our review. The ORION 9, 10 and 11 trials were Phase III RCTs that included patients with HeFH (ORION 9), established ASCVD or ASCVD risk equivalent (ORION 10 and 11) who had elevated LDL-C levels despite maximally tolerated statin therapy with or without additional lipid-lowering therapy such as ezetimibe. The ORION 1 trial was a Phase II RCT conducted in patients with ASCVD or an ASCVD risk equivalent who were on stable, maximally tolerated doses of statin therapy with or without additional lipid-lowering therapy.

Clinical Benefits

LDL-C and Other Lipid Parameters

Overall, inclisiran therapy decreased LDL cholesterol levels by 51% from baseline (MD: -50.5, 95% CI: -45.5 to -55.5) compared to placebo (Table ES3). There was no between-trial heterogeneity for this outcome (I^2 = 0%, p=0.37). Similarly, the summary estimate for the time-adjusted change in LDL-C after day 90 and up to day 540 was 50.5% (95% CI: -46.9 to -54.1). Inclisiran also improved other lipid parameters compared to placebo (all p<0.0001), including HDL cholesterol (increase to 6.1%), and reductions in PCSK9 (83%), total cholesterol (32.4%), non-HDL-C (46.4%), apolipoprotein B (41.9%), and lipoprotein(a) (20%).

Overall, inclisiran therapy decreased LDL cholesterol levels by 51% from baseline (MD: -50.5, 95% CI: -45.5 to -55.5) compared to placebo (Table ES3). There was no between-trial heterogeneity for this outcome (I^2 = 0%, p=0.37). Similarly, the summary estimate for the time-adjusted change in LDL-C after day 90 and up to day 540 was 50.5% (95% CI: -46.9 to -54.1). Inclisiran also improved other lipid parameters compared to placebo (all p<0.0001), including HDL cholesterol (increase to 6.1%), and reductions in PCSK9 (83%), total cholesterol (32.4%), non-HDL-C (46.4%), apolipoprotein B (41.9%), and lipoprotein(a) (20%).

Table ES3. Inclisiran: Percentage Change in LDL-C from Baseline to Day 510

Trials (Population Enrolled)	Baseline LDL-C	Percent Reduction (95% CI)		
		Placebo Group	Inclisiran Group	Between-Arm Difference
ORION 9 (HeFH)	153 mg/dL	8.2 (4.3, 12.2)	-39.7 (-43.7, -35.7)	-47.9 (-53.5, -42.3)
ORION 10 (ASCVD)	105 mg/dL	1 (NR)	-51.3 (NR)	-52.3 (-55.7, -48.8)
ORION 11 (ASCVD + ASCVD risk equivalent)	106 mg/dL	4 (NR)	-45.8 (NR)	-49.9 (-53.1, -46.6)
Summary Estimate	Random Effect Meta-Analysis of Inclisiran vs. Placebo			-50.5 (-55.5, -45.5); p<0.001; I^2=0.00

95% CI: 95% confidence interval, ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, mg/dL: milligram per deciliter, NR: not reported

Subgroup Analyses

HeFH (primary and secondary prevention): Treatment with inclisiran was associated with 47.9% (95% CI: 42.3% to -53.5%) reduction in LDL-C compared to placebo at day 510. These results are similar to what was observed in the overall population.

Established ASCVD (secondary prevention): Treatment with inclisiran decreased LDL-C levels by 52.3% from baseline (95% CI: -48.8 to -55.7) compared to placebo in the ORION 10 trial, whose participants all had established ASCVD, and by 53.3% at day 510 (95% CI: -50.1 to -56.6) compared with placebo in ORION 11, where almost 90% of participants had established ASCVD. This finding was consistent with the finding in the overall population.

Statin intolerant: Between 5.3%-10.8% of patients in the ORION trials were not on statins at baseline and were assumed to be statin intolerant. We conducted a subgroup analysis of the ORION trials in which we found a 47.2% LDL-C reduction at day 510 with inclisiran treatment compared to placebo in the statin-intolerant group, and a 53.9% LDL-C reduction in those on statins. This difference was not statistically significant (Q=1.9, p=0.2).

Clinical Outcomes

The included Phase III trials (ORION 9, 10 & 11) were designed with LDL-C lowering as the primary outcome. However, all-cause mortality and cardiovascular outcomes were reported as safety events in these trials, and we conducted a meta-analysis on these outcomes. Our results suggest that inclisiran did not reduce the risk of all-cause mortality or CV mortality, and there was no statistically significant difference in the occurrence of stroke and MI compared with placebo. However, the meta-analysis results showed a relative risk of 0.76 (0.60-0.96) on the pre-specified exploratory composite CV outcome (CV mortality, cardiac arrest, non-fatal MI, or stroke) with inclisiran compared to placebo. Finally, no studies reported data on the impact of inclisiran on health-related quality of life.

Harms

Our meta-analysis of safety events showed no difference overall in the incidence of AEs, serious AEs, and AEs leading to discontinuation of the drug in patients receiving inclisiran compared with those on placebo. The majority of AEs observed were mild or moderate. The most common treatment-related AE was injection site reaction, which occurred in 5.4% of patients in the inclisiran group versus 0.8% in the placebo group. Other AEs occurring more commonly in the inclisiran group include myalgias, elevated liver enzymes, and increase in serum creatinine levels. Serious AEs other than mortality and CV events included cancer-related deaths and new, worsening, or recurrent cancers, incidences of which were low and were similar among patients in both arms of the trials.

Controversies and Uncertainties

For bempedoic acid, data are limited to short-term LDL-lowering in selected populations (trials included very few patients with HeFH or from minority populations). Impact of the drug on reduction of CV events has not been demonstrated, as outcomes trials are ongoing. Evidence suggests that bempedoic acid may offer modestly greater relative effectiveness in patients who are not on statins. This finding receives conceptual support from a plausible argument that bempedoic acid acts on the same cholesterol synthesis pathway as statins and therefore statins may "block" the full effectiveness of bempedoic acid. However, even if one assumes an increased reduction of LDL-C in statin-intolerant patients, it remains unknown whether that reduction is substantial enough to translate into a greater reduction in cardiovascular outcomes compared with other populations.

The combination bempedoic acid/ezetimibe pill represents a potential increase in convenience for those needing to take both drugs to reach their LDL-C goal, and a method of increasing the use of a currently underutilized drug – ezetimibe. However, bempedoic acid's safety profile raises

important questions about whether the increased risk seen in early trials of hyperuricemia and gout, as well as a risk of tendon rupture, will be important real-world problems.

For inclisiran, the degree of LDL-C lowering compared with placebo appears to be substantial and in the same general range as found for PCSK9 inhibitors. However, long-term data on MACE and safety are lacking, and thus there remains some uncertainty regarding whether treatment with inclisiran will translate into reduction in MACE rates comparable to those seen with statins or those with PCSK9 inhibitors. Furthermore, trials did not include many patients with statin intolerance or from minority populations, so we are unable to determine if there may be differential effects of treatment or on safety events in these populations. Finally, inclisiran's twice-yearly dosing schedule delivered in the clinical setting may have implications for patient willingness to take the drug and longer-term adherence, but this is yet an untested assumption, and uncertainty also remains about how patients and clinicians will weigh this feature of inclisiran during the time of the COVID pandemic.

Summary and Comment on Comparative Clinical Effectiveness

For bempedoic acid, the available data demonstrates the drug's efficacy in lowering LDL-C over twelve weeks, and the relative effects may be somewhat greater for patients who are not taking statins due to statin intolerance. However, longer-term efficacy on LDL-C lowering and reduction in cardiovascular events remain to be demonstrated, and there are limited data on efficacy in the HeFH population. Furthermore, bempedoic acid is associated with moderate to severe adverse events such as gout and tendon rupture. Given these safety concerns, the pending results of clinical outcome studies, and the relatively modest degree of LDL-lowering, we judge the evidence provides moderate certainty of a comparable or small net health benefit compared to usual care with maximally tolerated statins ("C+").

For inclisiran, all available data suggest that it substantially lowers LDL-C compared with placebo, with very few safety concerns. Whether the dosing schedule is advantageous for improving adherence compared with PCSK9 inhibitors is currently unknown; real-world data are required to confirm this benefit. The longer-term trials underway to examine the impact of inclisiran on cardiovascular events and overall mortality are also needed because history has shown that reductions in LDL-C do not always translate into improved overall clinical outcomes (e.g., clofibrate). Nonetheless, inclisiran has a mechanism of action linked closely to the mechanism of PCSK9 inhibitors, which have demonstrated longer-term positive outcomes, and the magnitude of the LDL-C reduction seen with inclisiran, in combination with nearly two years of data showing no significant adverse events, lends confidence to the likelihood that the drug will also produce a long-term net health benefit for most patients. Uncertainty remains regarding the magnitude of that overall benefit, and how it compares to that of PCSK9 inhibitors, but we believe the current evidence offers high certainty of at least a small net health benefit for inclisiran when used for patients who have

need of significant reduction in LDL-C despite maximally tolerated oral lipid-lowering therapy. This equates to an ICER evidence rating of "Incremental or Better" (B+).

Long-Term Cost Effectiveness

The economic model focuses on evaluating the cost effectiveness of bempedoic acid in combination with ezetimibe and of inclisiran in patients with established ASCVD, including separate evaluations of subgroups of patients with HeFH, those intolerant to statins, and "high-risk" patients who have had an acute coronary syndrome (ACS) in the past year. For bempedoic acid, we estimate the cost effectiveness of the combination pill only, as it is priced the same as bempedoic acid monotherapy and so would be expected to dominate the bempedoic acid pill in any economic evaluation. Our analyses of incremental cost effectiveness compare each treatment with ezetimibe and maximally tolerated statin therapy, assuming that the efficacy observed in clinical trials would be replicated and sustained in clinical practice. The base-case analysis assumes a health care sector perspective (i.e., focusing on direct medical care costs only), and a lifetime time horizon.

The analysis is based upon a *de novo* state-transition Markov decision analytic model, informed by key clinical trials, registries, health care claims data, and prior relevant economic models. We created a hypothetical cohort of patients with established ASCVD being treated with maximally tolerated lipid-lowering therapy (statin, if tolerated, plus ezetimibe). In the control arm, patients continued to receive the prior maximally tolerated lipid-lowering therapy (of maximally tolerated statin and ezetimibe). In the intervention arm, the patients received additional lipid-lowering therapy in the form of either 1) bempedoic acid/ezetimibe combination (with the ezetimibe in the combination pill replacing the ezetimibe the patients were previously receiving) or 2) inclisiran. Each of the interventions (addition of bempedoic acid/ezetimibe or inclisiran) was compared with the control arm. Of note, while step therapy through ezetimibe may not be the right option for all patients, we believe that the cost-effectiveness and related value-based price of novel lipid-lowering therapies should be measured against the backdrop of maximally tolerated statin and ezetimibe given that both are endorsed by clinical guidelines as effective at lowering LDL-C levels at low cost. Model cycle length was one year. In each annual cycle, a subset of the cohort may experience ACS (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. The cohort is followed until all members turn 95 years of age or die.

Key population characteristics were estimated from the National Health and Nutrition Examination Survey (NHANES) of US adults 35 and older who have prior ASCVD and an LDL-C level of ≥70 mg/dL on statin therapy.[13] The key input for effectiveness of each drug was the percent reduction in LDL-C achieved among individuals receiving the therapy based on results from ICER's meta-analyses of RCTs of bempedoic acid/ezetimibe and inclisiran. The model then translated LDL-C reduction into changes in MACE, defined in this economic section as a composite of ACS that includes MI and

hospitalizations for unstable angina, stroke, cardiovascular death, and all-cause mortality. The model assumed that the relationship between LDL-C lowering with each drug and the subsequent reduction in MACE rates would be identical to that observed with statins (based on the meta-analysis performed by the Cholesterol Treatment Trialists' Collaboration).[14] In a sensitivity analysis, we assume a different relationship between LDL-C reduction with inclisiran and MACE rates, with resulting risk reduction per unit LDL-C reduction set to match those observed in the completed trials (with 2-3 years of follow-up data) of the currently approved PCSK9 inhibitors evolocumab and alirocumab.

Additionally, in order to explore higher risk subpopulations who may derive a greater benefit from the therapies, and to facilitate qualitative comparison with subpopulations in prior ICER reviews of the PCSK9 inhibitors, the model explores important "high-risk" subgroups of ASCVD patients: patients with HeFH and established ASCVD, patients intolerant to statins (estimated to be 10% of the population), and patients with ACS in the past year.

Estimates of health-related quality of life for each health state were based on publicly available literature and were used consistently across treatments evaluated in the model. The base case incorporated health-related quality-of-life estimates from the Global Burden of Disease study as in prior models examining lipid-lowering therapies. The incidence of serious adverse events related to the intervention drugs was estimated from the clinical review and included gout (for bempedoic acid/ezetimibe) and injection site reactions (for inclisiran). These quality-of-life penalties are only applied to the proportion of the cohort that experience the adverse event.

Drug costs included the annual cost of statin therapy and the annual cost of ezetimibe, the cost of adding bempedoic acid/ezetimibe or inclisiran in the intervention group (Table ES4), and adverse event costs (gout events for bempedoic acid/ezetimibe and injection site reactions for inclisiran). Non-drug costs include background health care costs and costs related to acute events (non-fatal and fatal ACS or stroke) and revascularization procedures (elective percutaneous coronary revascularization or coronary artery bypass graft surgery).

Model outcomes include MACE, total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years gained (evLYGs, which assume that any incremental years of survival would result in perfect health-related quality-of-life), and total costs for each intervention over a lifetime time horizon. Costs and outcomes were discounted at 3% per year.

Table ES4. Annual Drug Costs

Drug	WAC per Dose	Discount from WAC	Net Price per Dose	Net Price per Year
Bempedoic Acid/Ezetimibe	$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 as equal to the average annual net cost of alirocumab and evolocumab (from Federal Supply Schedule as of September 1, 2020) and assuming two doses per year. Initial treatment year requires three doses.

Key Model Characteristics and Assumptions

A full listing of key model assumptions is provided in the report. Among the most important assumptions are the following:

Table ES5. Key Model Assumptions

Assumption	Rationale
Age-specific risk of death from non-cardiovascular causes is similar to that observed in the general population	Similar to prior models. We varied this in sensitivity analyses, as patients with ASCVD typically have an increased burden of risk factors such as diabetes or chronic kidney disease that may also increase their risk of non-cardiovascular death.
Patients with established ASCVD who statin-intolerant have a higher baseline LDL-C 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-C levels by 35% on average and the risk of MACE by 22% per 1 mmol/L reduction in LDL-C levels (the actual proportion differs by specific type of MACE).[14]
Patients with HeFH with established ASCVD have higher event rates than the general population with established ASCVD.	Lifetime exposure to high levels of LDL-C 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 1.5x increased risk in individuals with HeFH and ASCVD but will vary this in sensitivity analyses.
We assumed no interaction between bempedoic acid and ezetimibe for effectiveness.	Bempedoic acid/ezetimibe combination pill is being evaluated against statin + ezetimibe in the economic evaluation, but, since each arm includes ezetimibe, we model effectiveness based on the bempedoic acid vs. placebo meta-analysis presented in the Clinical Effectiveness section.
Lowering LDL-C levels with bempedoic acid/ezetimibe or inclisiran in patients with established ASCVD lowers the rates of future MACE.	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 of future reduction in MACE underpins the regulatory approval of

	bempedoic acid, and ongoing trials of inclisiran. To estimate the effectiveness of the intervention drugs, we use the long-term effectiveness data available for statins. In a sensitivity analysis, we rely on the mechanistic similarity of inclisiran with evolocumab and alirocumab (monoclonal antibodies that inhibit the PCSK9 enzyme) and assume that the LDL-C reduction due to inclisiran produces the equivalent MACE reduction (per mmol/L reduction in LDL-C) as observed in the available Phase III trials of the currently approved PCSK9 inhibitors.
A recurrent ACS or stroke (i.e., an ACS event in a patient with a prior history of one or more ACS events, and a stroke in a patient with one or more prior strokes) is assumed to produce a short-term decrement in quality of life. In the long-term, quality of life returns to that prior to the recurrent event. A different type of MACE – e.g., a stroke in a patient with prior ACS, or an ACS event in a patient with prior stroke, may produce a permanent change in quality-of-life if the subsequent event produces a larger quality-of-life decrement than the prior baseline.	The assumption that recurrent events do not permanently alter the patient's quality of life is consistent with prior models and is driven by the scarcity of empirical data on the effect of recurrent events on quality of life.

ACS: acute coronary syndrome, ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, MACE: major adverse cardiovascular events, PCSK9: proprotein convertase subtilisin/kexin type 9.

Base-Case Results

Total lifetime discounted costs for treatment were $216,000 for bempedoic acid/ezetimibe and $253,000 for inclisiran compared with $185,000 for statin + ezetimibe. Discounted life expectancy was 11.66 life-years for bempedoic acid/ezetimibe and 11.94 for inclisiran compared with 11.48 life-years for statin + ezetimibe. Mean projected QALYs ranged from 10.74 for bempedoic acid/ezetimibe to 11.01 for inclisiran, compared with 10.57 for statin + ezetimibe.

For bempedoic acid/ezetimibe, the incremental cost per QALY and per evLYG was $186,000 and $168,000, respectively. For inclisiran, at its placeholder price, the corresponding incremental cost-effectiveness findings were $157,000 per QALY and $142,000 per evLYG. Both treatments had lower cost-effectiveness ratios in high-risk subgroups. For example, in patients with HeFH with established ASCVD, the incremental cost per QALY was $101,000 for bempedoic acid/ezetimibe and $84,000 for inclisiran. For patients with statin intolerance, we found the incremental cost per QALY to be $92,000 for bempedoic acid/ezetimibe and $103,000 for inclisiran. Finally, patients with recent ACS had slightly improved cost-effectiveness ratios compared to the overall population, with an incremental cost for QALY of $176,000 for bempedoic acid/ezetimibe and $147,000 for inclisiran. All findings, including those using evLYG as the measure of health gain, are shown in the full report.

Table ES6. Base-Case Results

Regimen	Cost	QALYs	Life Years
Bempedoic acid/ezetimibe	$216,000	10.74	11.66
Inclisiran	$253,000	11.01	11.94
Statin + ezetimibe	$185,000	10.57	11.48

QALY: quality adjusted life years

Table ES7. Pairwise Results for Interventions Compared to Statin + Ezetimibe

Regimen	Incr. Cost	Incr. QALY	Incr. LYG	Cost/QALY vs. statin + ezetimibe	Cost/evLYG vs. statin + ezetimibe
Bempedoic acid/ezetimibe	$31,000	0.17	0.18	$186,000	$168,000
Inclisiran	$68,000	0.44	0.46	$157,000	$142,000

QALY: quality adjusted life years; LYG: life-years gained; evLYG: equal value of life years gained

Sensitivity Analyses

To examine the effect of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in the incremental cost-effectiveness ratio (in dollars per QALY).

The incremental cost-effectiveness ratio was most sensitive to the cost of the drug, the relationship between LDL-C lowering and reduction in CV death, the rate of MACE, and baseline LDL-C level (which was varied ±20% from base-case value) (Figures ES1 and ES2). In contrast, it was not very sensitive to assumptions about the magnitude of quality-of-life decrements from prior ASCVD events.

Figure ES1. Tornado Diagram for One-Way Sensitivity Analyses of Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin vs. Ezetimibe + Maximally Tolerated Statin

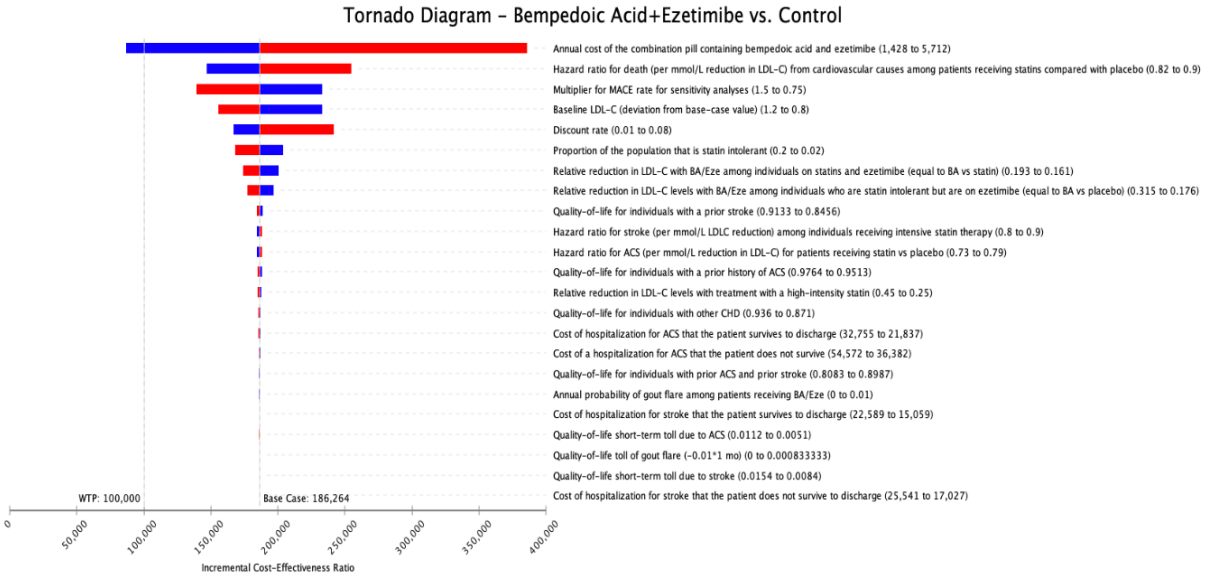
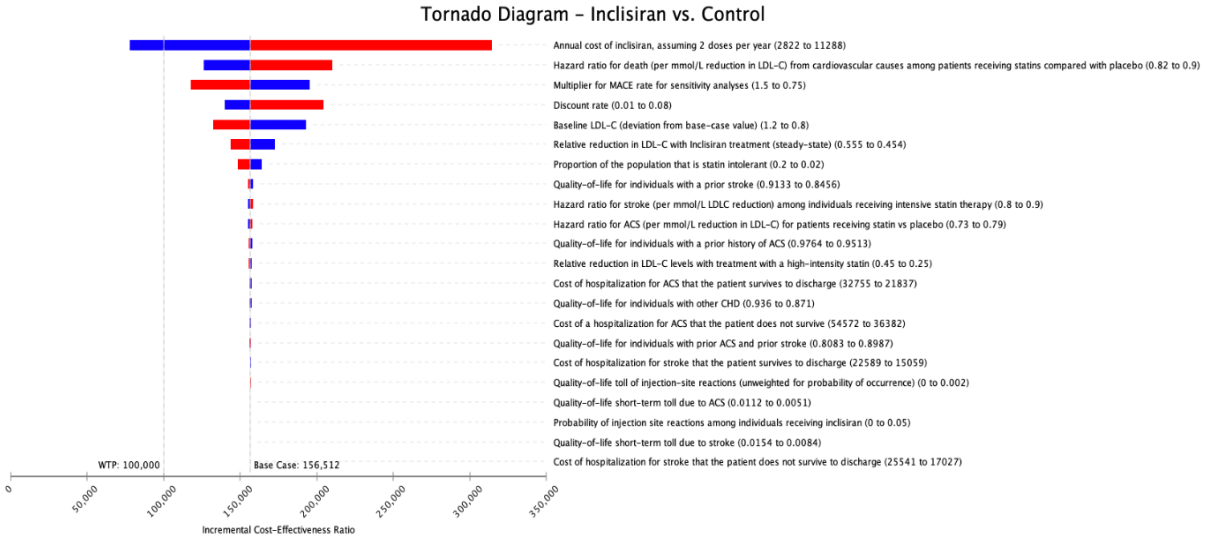


Figure ES2. Tornado Diagram for One-Way Sensitivity Analyses of Inclisiran + Ezetimibe + Maximally Tolerated Statin vs. Ezetimibe + Maximally Tolerated Statin



In probabilistic sensitivity analyses, we drew 1,000 samples of key input parameters from pre-specified statistical distributions (with replacement). Each combination was then used in the model to produce 95% credible intervals of key outcomes. We also used the results of these 1,000 simulations to estimate the proportion of simulations in which a particular therapy is the optimal choice at various cost-effectiveness thresholds.

The use of bempedoic acid/ezetimibe was cost-effective relative to the control arm in none of the simulations at a threshold of $100,000 per QALY gained and only 6.3% of the simulations at a threshold of $150,000 per QALY gained (Table ES8). The use of inclisiran was cost-effective relative to the control arm in 0% of the simulations at a threshold of $100,000 per QALY gained and 35.9% of the simulations at a threshold of $150,000 per QALY gained (Table ES9).

Table ES8. Probabilistic Sensitivity Analysis Results: Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Bempedoic Acid/Ezetimibe	0%	0%	6.3%	64.8%

QALY: quality-adjusted life years

Table ES9. Probabilistic Sensitivity Analysis Results: Inclisiran + Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Inclisiran	0%	0%	35.9%	90.3%

QALY: quality-adjusted life years

Threshold Analyses

Annual prices necessary for bempedoic acid/ezetimibe and inclisiran to reach cost-effectiveness thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and evLYG are listed in Tables ES10-ES13 below, in both the overall population and in high-risk subgroups.

Table ES10. Annual Prices at Which Bempedoic Acid/Ezetimibe Reaches Cost per QALY Thresholds

Subgroup	Base-Case Annual Cost	$50,000/QALY	$100,000/QALY	$150,000/QALY
Overall	$2,856	$910	$1,600	$2,300
HeFH	$2,856	$1,500	$2,800	$4,100
Statin intolerance	$2,856	$1,700	$3,100	$4,500
Recent ACS	$2,856	$990	$1,700	$2,500

QALY: quality-adjusted life-year

Table ES11. Annual Prices at Which Bempedoic Acid/Ezetimibe Reaches Cost per evLYG Thresholds

Subgroup	Base-Case Annual Cost	$50,000/evLYG	$100,000/evLYG	$150,000/evLYG
Overall	$2,856	$980	$1,800	$2,600
HeFH	$2,856	$1,600	$3,100	$4,500
Statin intolerance	$2,856	$1,800	$3,400	$5,000
Recent ACS	$2,856	$1,100	$1,900	$2,700

evLYG: equal value life years gained

Table ES12. Annual Prices at Which Inclisiran Reaches Cost per QALY Thresholds

Subgroup	Placeholder Base-Case Annual Cost*	$50,000/QALY	$100,000/QALY	$150,000/QALY
Overall	$5,644*	$1,800	$3,600	$5,400
HeFH	$5,644*	$3,400	$6,700	$10,100
Statin intolerance	$5,644*	$2,800	$5,500	$8,200
Recent ACS	$5,644*	$2,000	$3,900	$5,700

QALY: quality-adjusted life-year

*The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Table ES13. Annual Prices at Which Inclisiran Reaches Cost per evLYG Thresholds

Subgroup	Placeholder Base-Case Annual Cost*	$50,000/evLYG	$100,000/evLYG	$150,000/evLYG
Overall	$5,644*	$2,000	$4,000	$6,000
HeFH	$5,644*	$3,700	$7,400	$11,100
Statin intolerance	$5,644*	$3,100	$6,100	$9,000
Recent ACS	$5,644*	$2,200	$4,200	$6,200

evLYG: equal value life years gained

*The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

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. We conducted numerous sensitivity analyses to ensure the model was producing findings consistent with expectations. Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Summary and Comment on Long-Term Cost Effectiveness

Our findings suggest that bempedoic acid/ezetimibe would produce a modest improvement in outcomes among individuals with established ASCVD who need additional lipid-lowering despite treatment with maximally tolerated statin and ezetimibe. However, at current estimated prices net of rebates and other concessions, the drug is unlikely to achieve commonly cited cost-effectiveness thresholds of $100,000-$150,000 per QALY or per evLYG.

For inclisiran, the large reduction in LDL-C is projected to translate to substantial reductions in MACE. At a placeholder price of $5,644 per year – the current average FSS price of PCSK9 inhibitors – inclisiran approaches a cost-effectiveness threshold of $150,000 per QALY (and falls slightly below $150,000 per evLYG) when compared with background therapy of maximally tolerated statin and ezetimibe.

We also found that the cost effectiveness of either agent is improved when used exclusively for higher risk subgroups, such as patients with established ASCVD who are also statin-intolerant or who have HeFH. The incremental cost-effectiveness ratio for bempedoic acid/ezetimibe improves to $101,000 per QALY gained when used among patients with established ASCVD and HeFH, and drops further to $92,000 per QALY gained for patients with established ASCVD who are statin intolerant.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits that treatments may offer to the individual patient, to caregivers, the delivery system, other patients, or the public. In particular, our goal is to highlight factors that would not have been considered or were incompletely captured as part of the evidence on comparative clinical effectiveness and cost effectiveness. These elements are listed in the tables below.

Contextual Considerations	Relevant Information
Acuity of need for treatment of individual patients based on the severity of the condition being treated	These are preventive therapies and although MACE can be fatal or severe there is relatively modest acuity of need for treatment. This is reflected in the relatively small proportional QALY shortfall compared to other conditions (see Table 6.2 in the report).
Magnitude of the lifetime impact on individual patients of the condition being treated	Although early MACE can lead to significant lifetime reductions in quality of life, on average the lifetime impact of ASCVD is relatively low, as reflected in the small absolute QALY shortfalls compared to other conditions (see Table 6.2 in the report). HeFH increases the risk for early MACE and therefore has a higher magnitude of lifetime impact.
Other (as relevant)	N/A

Potential Other Benefits or Disadvantages	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Because cardiovascular events typically occur in older adults, the reduction in MACE estimated from these treatments does not produce striking increases in work productivity – on average -- over the entire population of patients with ASCVD. However, patients with HeFH are at higher risk of events earlier in their life and the prevention of MACE may impact lifetime economic productivity.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Additional lipid-lowering offered by bempedoic acid and inclisiran for patients with established ASCVD and HeFH may translate into fewer CV events, thereby reducing caregiving needs among family members.
Patients' ability to manage and sustain treatment given the complexity of regimen	Among patients already on ezetimibe, the use of the bempedoic acid/ezetimibe combination pill offers an opportunity to escalate lipid-lowering therapy without increasing the pill-burden. Inclisiran offers twice yearly dosing, potentially administered in a health care setting, compared with twice monthly dosing of PCSK9 inhibitors. This may offer greater convenience to patients but whether it will increase long-term adherence is uncertain.
Health inequities	Cardiovascular disease is the most common cause of death across all racial and ethnic groups in the U.S. but is more prevalent among patients from minority communities. For example, deaths from heart disease are higher in Black Americans than in White Americans and other ethnic groups, and heart disease develops at a younger age in African- Americans. Additionally, women and minorities are less likely to be treated with statins and PCSK9 inhibitors and achieve LDL-C goals.
Other (as relevant): New option that may provide particular benefits for patients with statin intolerance	Bempedoic acid represents a new oral option for patients with statin intolerance and may offer a potential benefit to those who do not need the LDL reduction provided by PCSK9 inhibitors or inclisiran or prefer not to have injections. Inclisiran also offers a new treatment option for patients unable to tolerate statins but its role in therapy is likely to be viewed as similar to existing PCSK9 inhibitor drugs.

Health Benefit Price Benchmarks

The ICER health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

The HBPB range for the annual price for bempedoic acid/ezetimibe in the broad population of eligible patients is from approximately $1,600 to $2,600. The corresponding HBPB range for the annual price of inclisiran in the broad population of eligible patients is from $3,600 to $6,000.

Potential 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 reports begun in the years 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.

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of bempedoic acid with ezetimibe and of inclisiran for the adult population with established ASCVD in need of further lipid lowering. We use the WAC (where available), estimated net or placeholder prices, and three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for each drug in our estimates of potential budget impact.

For this analysis, we estimated the number of individuals in the US who would be eligible for treatment. Based on data from the AHA Center for Health Metrics and Evaluation and US Census population projections,[15,16] we estimated the size of the eligible population to be approximately 19.8 million individuals with established ASCVD, with approximately 12.8 million taking statins. Furthermore, we used an estimate from Wong et al. to calculate that approximately 10.2 million individuals with ASCVD are not at their LDL-C goal despite statin treatment.[17] For the purposes of this analysis, we assume that, at whatever level of uptake is assumed over 5 years, 20% of patients would initiate treatment in each of the five years.

We assumed that these drugs will be added on to optimal lipid-lowering therapy (i.e., maximally tolerated statin + ezetimibe) and will not take existing market share from PCSK9 inhibitors. Given that bempedoic acid/ezetimibe is likely to be considered for patients with relatively lower LDL-C as compared to inclisiran, we made a rough assumption that approximately half of the total number of patients with ASCVD needing further lipid lowering would be considered for one drug or the other.

This assumption produces a total eligible population of 1,021,000 patients per year who, at 100% uptake, would use each drug.

Please note that we do not assume 100% uptake. Figure ES3 below illustrates the potential budget impact of bempedoic acid/ezetimibe at different prices (vertical axis) along a horizontal axis that allows the reader to make her own assumption of uptake as a percentage of eligible patients. As shown, approximately 8% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the WAC, and approximately 11% at the current net price. At threshold prices linked to cost-effectiveness results, an increasing proportion of eligible patients could be treated as prices decrease, up to 49% of eligible patients at the price needed to reach the $50,000 per QALY threshold.

Figure ES3. Potential Budgetary Impact of Bempedoic Acid Plus Ezetimibe in Adults with Established ASCVD in Need of Further Lipid Lowering

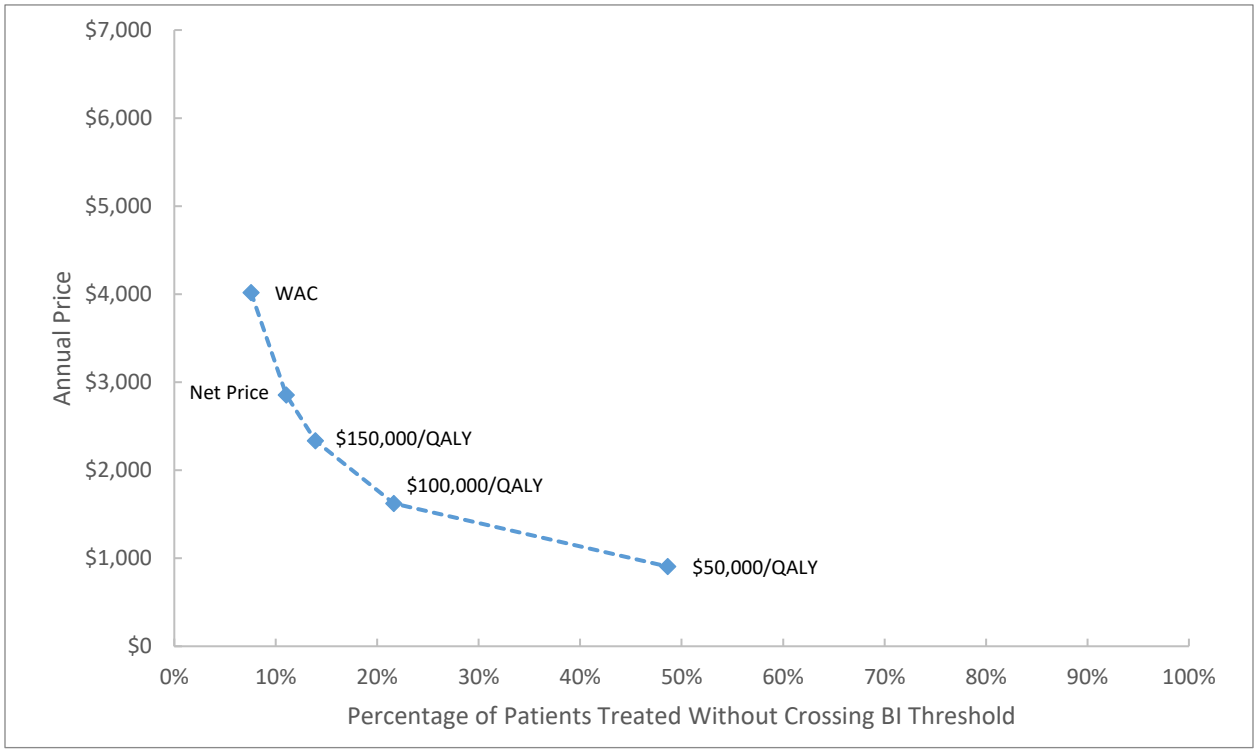
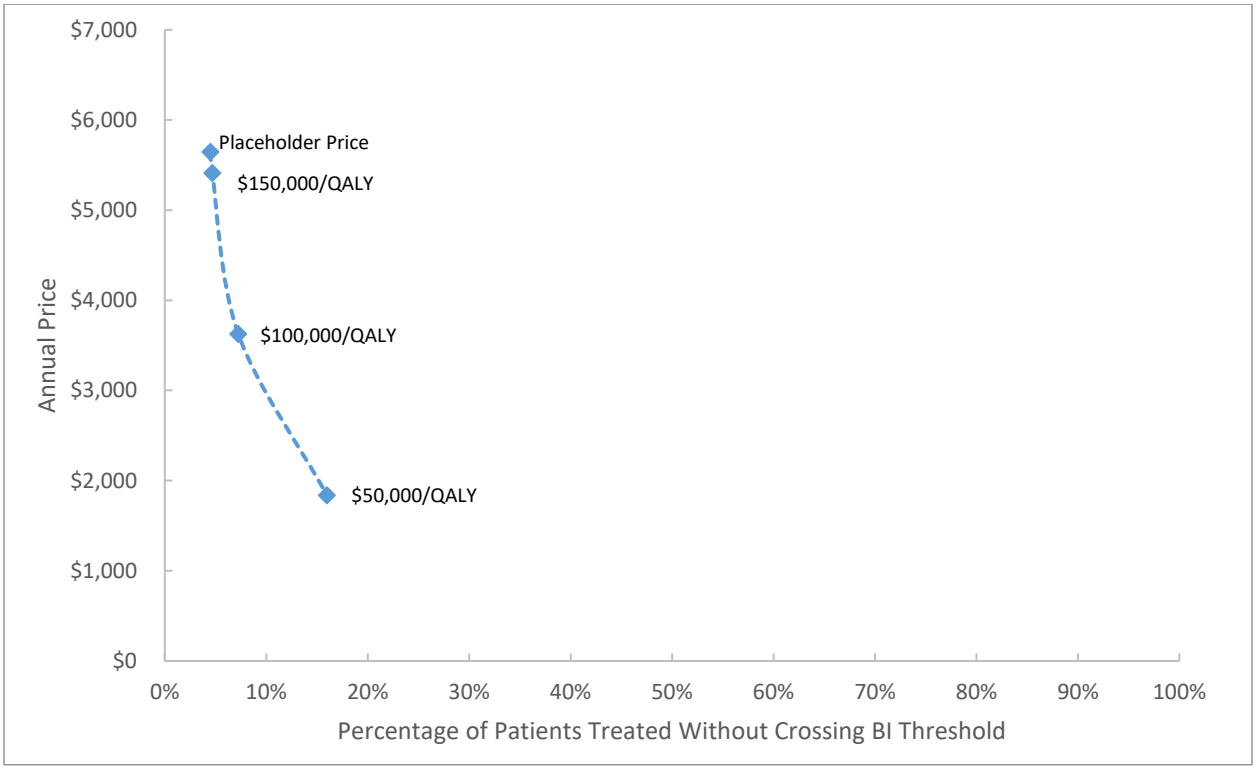


Figure ES4 below illustrates the corresponding potential budget impact of treatment with inclisiran. Given that the placeholder price we are using for inclisiran is higher than the net price of bempedoic acid, the potential short-term budget impact of inclisiran is more substantial. At the placeholder annual price of $5,644, approximately 4.5% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million. At the far lower $50,000 per QALY threshold price, approximately 16% of eligible patients (estimated at 1,021,000) could be treated without exceeding the ICER budget impact threshold.

Figure ES4. Potential Budgetary Impact of Inclisiran in Adults with Established ASCVD in Need of Further Lipid Lowering



Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on February 5, 2021. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

Clinical Evidence

Patient population for questions 1 and 2: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated oral lipid-lowering therapy.

1. Given today's evidence, is the evidence adequate to demonstrate that the net health benefit of adding **bempedoic acid alone** to usual care is superior to that provided by usual care alone?

Yes: 5 votes	***No: 9 votes***

   a. If the answer to question 1 is no, is the evidence adequate to demonstrate the net health benefit of adding **bempedoic acid alone** to usual care is superior to that

provide by usual care alone in patients who have statin-associated side effects ("statin intolerant")?

Yes: 12 votes	No: 2 votes

b. If the answer to question 1 is no, is the evidence adequate to demonstrate the net health benefit of adding **bempedoic acid alone** to usual care is superior to that provide by usual care alone in patients with HeFH?

Yes: 11 votes	No: 3 votes

2. Given today's evidence, is the evidence adequate to demonstrate that the net health benefit of adding **inclisiran** to usual care is superior to that provided by usual care alone?

Yes: 14 votes	No: 0 votes

Contextual Considerations and Potential Other Benefits or Disadvantages

Question: When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* new effective treatment for the SECONDARY PREVENTION OF ASCVD, on the basis of the following contextual considerations:

1= Very low priority; 2 = Low priority; 3 = Average priority; 4 = High priority; 5= Very high priority

1. Acuity of need for treatment of individual patients based on the severity of the condition being treated

Very Low Priority	Low Priority	Average Priority	High Priority	Very High Priority
0 votes	5 votes	7 votes	2 votes	0 votes

2. Magnitude of the lifetime impact on individual patients of the condition being treated

Very Low Priority	Low Priority	Average Priority	High Priority	Very High Priority
0 votes	2 votes	5 votes	5 votes	2 votes

Question: What are the relative effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcomes that inform judgment of the overall long-term value for money of BEMPEDOIC ACID?

1= Major negative effect; 2 = Minor negative effect; 3 = No difference; 4 = Minor positive effect; 5 = Major positive effect

3. Patients' ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 votes	5 votes	9 votes	0 votes

4. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 votes	3 votes	11 votes	0 votes

5. The problem of health inequity

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
1 vote	4 votes	9 votes	0 votes	0 votes

6. Other (as relevant): New treatment option for patients with statin intolerance

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 votes	1 vote	9 votes	4 votes

Question: What are the relative effects of INCLISIRAN versus PCSK9 INHIBITORS on the following outcomes that inform judgment of the overall long-term value for money of INCLISIRAN?

1= Major negative effect; 2 = Minor negative effect; 3 = No difference; 4 = Minor positive effect; 5 = Major positive effect

7. Patients' ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	1 vote	10 votes	2 votes	0 votes

8. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	1 vote	12 votes	1 vote	0 votes

9. Health inequities

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 vote	13 votes	1 vote	0 votes

Long-Term Value for Money

Patient population for question 1: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

1. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **bempedoic acid with ezetimibe** to usual care versus usual care with **ezetimibe**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
13 votes	1 vote	0 votes

Patient population for question 2: All adult patients with established ASCVD – with or without HeFH – who have elevated LDL-C levels and have statin-associated side effects ("statin intolerant").

2. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **bempedoic acid with ezetimibe** to usual care versus usual care with **ezetimibe.**

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
0 votes	12 votes	2 votes

Patient population for question 3: All adult patients with HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

3. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **bempedoic acid with ezetimibe** to usual care versus usual care with **ezetimibe.**

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
1 vote	13 votes	0 votes

Patient population for question 4: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

4. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **inclisiran** to usual care versus **usual care alone**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
10 votes	4 votes	0 votes

Patient population for question 5: All adult patients with established ASCVD – with or without HeFH – who have elevated LDL-C levels and have statin-associated side effects ("statin intolerant").

5. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **inclisiran** to usual care versus **usual care alone**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
1 vote	13 votes	0 votes

Patient population for question 6: All adult patients with HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

6. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **inclisiran** to usual care versus **usual care alone**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
0 votes	10 votes	3 votes

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on bempedoic acid with or without ezetimibe and inclisiran to policy and practice. The policy roundtable members included two patients, two clinical experts, two payers and two pharmaceutical representatives. The

discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

All Stakeholders

- All stakeholders should ensure that the introduction of new therapies for high cholesterol do not exacerbate existing health inequities and should strive to decrease inequity in the health care system by decreasing cost and access barriers for patients to access effective therapies.

- All stakeholders should act to help increase awareness about the diagnosis and treatment of high cholesterol and, in particular, address the underdiagnosis and undertreatment of familial hypercholesterolemia (FH).

- Along with encouraging steps to improve diet and exercise, all stakeholders should seek to increase utilization of effective therapies such as statins and ezetimibe for patients with established ASCVD and HeFH. These therapies are backed by extensive evidence, are safe for the vast majority of patients, and are far less expensive than other treatment options.

Payers

- Payers should develop consistent prior authorization criteria for lipid-lowering drugs and assure that the documentary burden and other administrative elements of prior authorization do not create an unreasonable burden on clinicians and patients.

- Payers should work with clinical experts and patient groups to develop consistent criteria and procedures for demonstrating drug intolerance due to statin associated side effects (SASE).

- Payers should ensure that coverage criteria reflect the status of higher-risk subpopulations for whom therapies may be both more clinically effective and cost effective.

Manufacturers

- Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with independent assessments of the therapeutic value of their treatments. In particular, until cardiovascular outcomes data are available from ongoing trials, Novartis should fulfill its stated intent to set the price of inclisiran at or below the cost-effective range of pricing for PCSK9 inhibitors.

- Manufacturers should include measurement of a broad set patient-important outcomes in clinical trials.

Researchers

- Researchers should seek to standardize definitions of ASCVD, major adverse cardiovascular events (MACE), and SASE (statin intolerance) in clinical trials to facilitate comparison of drugs and assist payers, clinicians, and patients in understanding which groups may benefit from a particular drug therapy.

- Researchers should use real world data to standardize definitions of "adherence to therapy" as part of trials that evaluate adherence and its impact on clinical outcomes.

1. Introduction

1.1 Background

Background

Atherosclerotic cardiovascular disease (ASCVD) encompasses a set of common, complex, and burdensome conditions with coronary artery disease, peripheral artery disease, and cerebrovascular disease as the three most prevalent types. ASCVD results from atherosclerosis, a chronic degenerative process involving fat and cholesterol build-up in the arteries that can obstruct blood flow. Over the life course, ASCVD can result in angina, claudication, myocardial infarction (MI), and stroke, among other problems. Risk factors for ASCVD include diabetes mellitus, hypertension, obesity, smoking, and elevated levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-C).

One important condition that predisposes people to ASCVD is familial hypercholesterolemia (FH). FH is an autosomal-dominant genetic disorder of cholesterol metabolism, which results in very elevated plasma concentrations of LDL-C and premature ASCVD.[18] If both copies of a gene are defective, this results in homozygous FH (HoFH), which occurs in approximately 1 in 300,000 to 1 in 1 million[19] persons worldwide; patients with HoFH typically develop severe atherosclerosis and cardiovascular events during childhood.[20] Heterozygous FH (HeFH), in which one copy of a gene affecting cholesterol metabolism is defective, is the most common form of FH and affects approximately 1 in 250 people in the United States (US). Men and women appear to be equally affected. There are several accepted clinical criteria to diagnose HeFH based on cholesterol levels, physical exam findings, family history, and genetic testing. These criteria include LDL-C ≥ 190 mg/dL, a family history of a first-degree relative with similarly high LDL-C, and a family history of premature ASCVD. Additional criteria may include tendon xanthomas and/or the presence of an LDL-C-raising gene defect (e.g., LDL receptor, apolipoprotein B or PCSK9).[21-24] Because of a lifelong exposure to high cholesterol, patients with FH are at high risk of developing ASCVD and major atherosclerotic cardiovascular events (MACE), often much earlier than the general population. Almost 1 in 10 patients who experience an MI before age 50 meet clinical criteria for FH.[25] However, patients with FH remain an underdiagnosed and undertreated subpopulation; additionally, women, Blacks and Asians with FH are less likely to reach LDL-C treatment goals.[4]

Overall in the US, almost 1 in 10 people are estimated to have some form of ASCVD, and ASCVD remains the leading cause of death.[1,2] The financial burden of ASCVD is also substantial, with total costs expected to reach $1.1 trillion by 2035.[3] Between 2007 and 2013, death rates from ASCVD decreased for all racial/ethnic groups in the US but disparities in the overall burden of ASCVD continue to persist by race/ethnicity and sex. The overall rates of death attributable to ASCVD in

2013 were 356.7 per 100,000 for non-Hispanic Black men, 270.6 per 100,000 for non-Hispanic white men, 197.4 per 100,000 for Hispanic men, 246.6 per 100,000 for non-Hispanic Black women, 183.8 per 100,000 for non-Hispanic white women, and 136.4 per 100,000 for Hispanic women.[1]

Treatment of all patients with FH and patients with established ASCVD includes risk factor modification, medical therapy, and when necessary, percutaneous or surgical revascularization.[26] Risk factor modification is the cornerstone of treatment for ASCVD. This includes education on dietary modifications, encouragement of physical activity, weight reduction, and smoking cessation, all of which can modify cardiovascular risk. In addition, treating chronic conditions that contribute to ASCVD risk such as hypertension and diabetes can modify risk for cardiovascular events. Medications to treat ASCVD include antiplatelet agents such as low-dose aspirin, which has been shown to decrease mortality in patients with established ASCVD,[27] and is recommended in all patients who can tolerate it.[26] Other agents such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors have also demonstrated benefit in reducing the risk of cardiovascular events and mortality, particularly in patients with concomitant diabetes or left ventricular dysfunction.[28,29] Finally, medical therapy includes intensive lipid-lowering therapy, which is recommended for primary prevention in all patients with FH and for the secondary prevention of further events in patients with established ASCVD.

A goal LDL-C reduction of at least 50% is recommended for patients with HeFH or established ASCVD, ideally with high dose or maximally tolerated statin.[5,26] For patients who continue to have LDL-C levels at or above 70 mg/dL despite being on statin therapy, the addition of ezetimibe is recommended as second-line therapy. Finally, for those patients who continue to have LDL-C levels above 70 mg/dL despite the addition of ezetimibe, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor can be considered. For patients who have statin associated side effects (SASE) – defined as not able to tolerate moderate to high intensity statin therapy due to side effects – therapy with ezetimibe, PCSK9 inhibitors, and other lipid-lowering therapies such as bile acid sequestrants and lipoprotein apheresis may be considered to reach treatment goals.[30] Throughout this report, we will use the term “statin intolerance” to describe SASE, consistent with descriptions in the clinical trials reviewed.

Even with the wide range of aforementioned options for risk factor modification and treatment, patients with HeFH and established ASCVD, who are the focus of this review, remain at high residual risk for further MACE, particularly if LDL-C levels are not adequately controlled. It is important to note that we do not address treatment for HoFH patients in this review, as these patients were not included in the relevant clinical trials and treatment for this very high-risk group may differ from patients with HeFH and/or established ASCVD. There is an important public health need for additional treatment options to improve outcomes for patients who remain at higher risk for cardiovascular events. Two new lipid-lowering treatments, bempedoic acid with or without

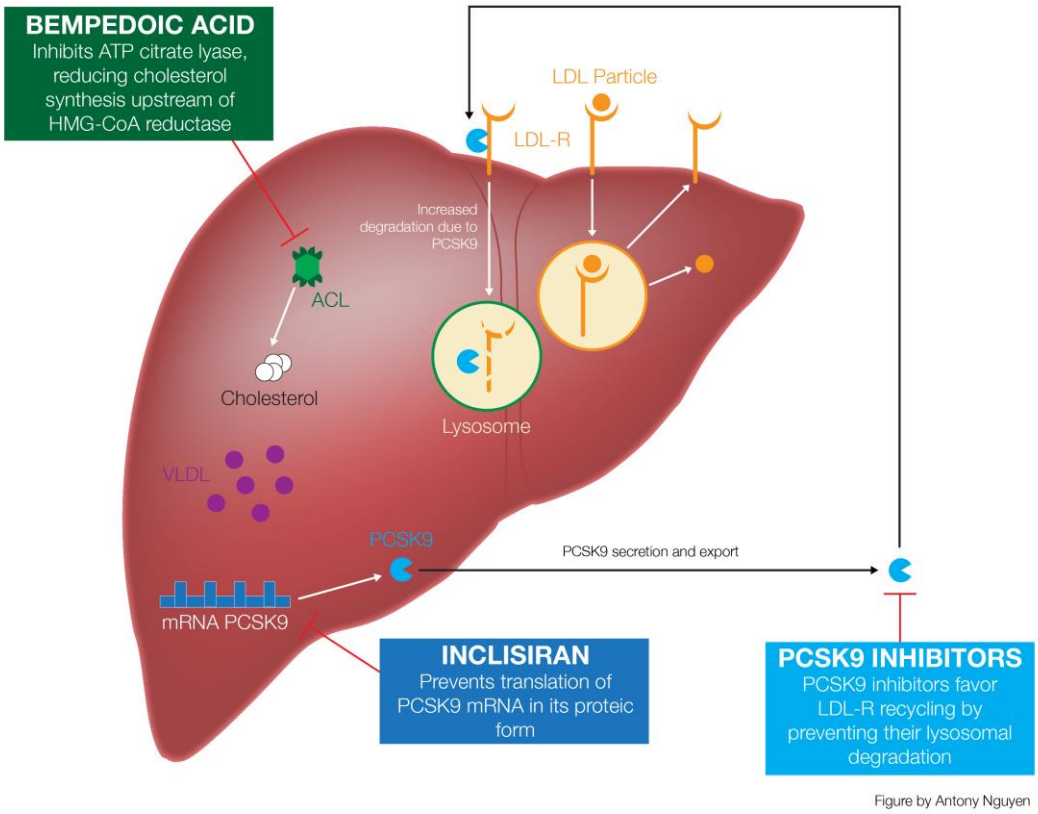
ezetimibe (Nexlizet™ and Nexletol™, Esperion Therapeutics, Inc.), which recently came to market, and inclisiran (Novartis), which is pending regulatory approval, are the focus of this review.

Interventions

Bempedoic acid is a first-in-class orally administered inhibitor of adenosine triphosphate (ATP) citrate lyase that lowers LDL-C by reducing cholesterol synthesis and up-regulating LDL receptors.[31] It works upstream from HMG-CoA, which is the target for statins, to inhibit cholesterol synthesis (Figure 1.1). This reduction in synthesis, along with the upregulation in LDL receptors, leads to decreased levels of LDL-C in the bloodstream. The drug is available as a standalone oral pill or in combination with ezetimibe. The bempedoic acid/ezetimibe combination lowers elevated LDL-C through complementary mechanisms of action by inhibiting cholesterol synthesis in the liver and intestinal absorption.[32] Both treatments received US Food and Drug Administration (FDA) approval in February 2020 as adjuvant oral therapy for adults with either HeFH on maximal statin therapy or with established ASCVD requiring additional LDL-C lowering.

Inclisiran is a double-stranded small interfering RNA agent targeting and inhibiting hepatic PCSK9 synthesis. PCSK9 typically binds to LDL-C receptors and leads to their destruction in hepatic lysosomes, preventing those LDL-C receptors from binding to LDL-C in the circulation, leading to increased LDL-C levels. Unlike PCSK9 inhibitors, which are antibodies that inhibit circulating PCSK9, inclisiran prevents synthesis of the PCSK9 protein through cleaving messenger RNA inside hepatocytes. By decreasing production of PCSK9, inclisiran increases LDL-C receptor recycling and expression on hepatocytes to increase LDL-C uptake, thereby lowering LDL-C levels in the circulation (Figure 1.1).[33] Inclisiran is a subcutaneously administered injection which is given twice yearly (after two initial doses in the first 90 days of treatment). A new drug application was submitted to the FDA in December 2019 for inclisiran to be an adjunct to lifestyle change and maximally tolerated statin therapy among adults with ASCVD or HeFH. The FDA issued a complete response letter with regard to inclisiran on December 18, 2020 deferring approval of the drug due to issues with a European manufacturing site. The letter did not raise any issues related to the efficacy or safety of the drug.[34] Due to COVID-19 travel restrictions, there is currently no timeline for resolution of the manufacturing issue.

Figure 1.1. Mechanism of Action of Bempedoic Acid, Inclisiran, and PCSK9 Inhibitors



The figure depicts the effects of the drugs during the synthesis of cholesterol in the liver.

1.2 Scope of the Assessment

The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.

Populations

The population of interest for this review is adults with elevated LDL-C levels despite treatment with maximally tolerated lipid-lowering therapy. We considered evidence across relevant populations including all patients with HeFH and patients with established ASCVD (secondary prevention).

Where data were available, we evaluated evidence on the following subpopulations:

- Patients with HeFH with and without established ASCVD (primary and secondary prevention)
- Patients with established ASCVD at relatively higher risk (e.g., patients with a recent MI)
- Patients with statin intolerance

As noted below in the description of the scope for the Comparative Value Analysis, not all patient subpopulations will be evaluated in the economic model.

Interventions

The interventions of interest for this review are bempedoic acid with or without ezetimibe (Nexlizet™ and Nexletol™, Esperion Therapeutics, Inc.) and inclisiran (Novartis) added to maximally tolerated lipid-lowering therapies.

Comparators

We compared the use of bempedoic acid without ezetimibe and inclisiran in conjunction with maximally tolerated background lipid-lowering therapy (i.e., placebo arm in clinical trials). We compared the use of the bempedoic acid/ezetimibe combination pill with maximally tolerated statin with ezetimibe.

Outcomes

For bempedoic acid with or without ezetimibe, the primary outcome we considered was the percentage of LDL-C lowering at 12 weeks. For inclisiran, the primary outcomes we considered were the percentage of LDL-C lowering at 510 days and time-averaged percentage of LDL-C lowering between 90 and 540 days.

Additionally, we looked for evidence on the following outcomes of interest:

- Patient-Important Outcomes
    - All-cause mortality
    - Cardiovascular disease mortality
    - MI
    - Stroke
    - Unstable angina
    - Revascularization
    - Health-related quality of life

- Other Outcomes
    - LDL-C
    - High-density lipoprotein cholesterol (HDL-C)
    - Total cholesterol
    - Non-HDL-C
    - Triglycerides
    - Apolipoprotein B
    - Lipoprotein(a)
    - High-sensitivity C-reactive protein (hsCRP)
    - PCSK9 level (for inclisiran and PCSK9 inhibitors)
- Safety
    - Treatment-emergent adverse events (AEs), including:
        - Muscle-related AEs
        - Increase in liver function tests
        - Tendon rupture
        - Uric acid level
        - Gout
        - Injection-site reactions
        - Discontinuation due to AEs
        - Serious AEs, including:
            - Death

Timing

We considered evidence from studies with at least four weeks of follow-up.

Settings

We considered all relevant settings.

1.3 Definitions

Atherosclerotic cardiovascular disease (ASCVD): Disease of the arteries caused by plaque buildup in artery walls. ASCVD includes the clinical conditions of coronary artery disease with stable angina, acute coronary syndromes, stroke, transient ischemic attack, peripheral vascular disease with or without claudication, coronary or other arterial revascularization, and aortic aneurysm.[5]

- Primary prevention of ASCVD: Prevention of a first cardiovascular event such as MI or stroke.
- Secondary prevention of ASCVD: Prevention of subsequent cardiovascular events in patients who have already suffered at least one cardiovascular event such as MI or stroke or have

undergone revascularization procedures in the coronary, cerebral or other peripheral vascular beds.

Familial hypercholesterolemia (FH): A genetic disorder of cholesterol metabolism that results in elevated cholesterol levels, particularly low-density lipoprotein cholesterol.

- Heterozygous FH: A form of the disorder where only one copy of a gene is defective. HeFH is characterized by LDL ≥ 190 in adults or ≥ 160 mg/dL in children and a family history of similarly high LDL and/or early cardiovascular disease.
- Homozygous FH: A form of the disorder where both copies of a gene are defective. HoFH is characterized by LDL ≥ 400 mg/dL and one or both parents having clinically diagnosed FH, positive genetic testing, or aortic valve disease or xanthomata before the age of 20.

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 MI, heart failure, recurrent angina pain, re-hospitalization for cardiovascular-related illness, repeat or unscheduled percutaneous coronary intervention, coronary artery bypass grafting, fatal and non-fatal stroke and all-cause mortality.[35]

Maximally tolerated lipid-lowering therapy: The highest number and highest dosage of cholesterol-lowering medications that a patient can tolerate. This is typically a statin at the maximally tolerated dose, as well as ezetimibe and other cholesterol-lowering drugs if necessary, to achieve LDL-C goals. In this report, this corresponds to the placebo arms in clinical trials.

Statin associated side effects (SASE): See statin intolerance. This report will use the term "statin intolerance" to refer to patients with SASE, to be consistent with the clinical trials reviewed.

Statin intolerance: Any adverse event considered unacceptable by the patient and/or some laboratory abnormalities, temporally related to statin treatment and, in the case of symptoms, reversible upon statin discontinuation that lead to the discontinuation or decrease in dosage of a statin.[36] In clinical trials, this is often defined as the inability to tolerate at least two statins at moderate or high doses.

1.4 Potential Cost-Saving Measures in FH and Established ASCVD

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 HeFH and ASCVD (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 HeFH and secondary prevention of ASCVD 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 HeFH or ASCVD that could be reduced, eliminated, or made more efficient. The FH Foundation suggests that earlier treatment of lipids for patients with FH is potentially cost saving, given their high rates of MACE at early ages.

2. Patient Perspectives

2.1 Methods

From the beginning of this assessment, we sought input from patients, caregivers, and representatives from patient advocacy organizations on the research design of this review (e.g., the PICOTS framework; population, intervention, comparators, outcomes, timing, and setting). We also sought insight on the patient experience of HeFH and ASCVD and their treatment including statin intolerance, benefits of treatment that may not be described in the clinical literature, any broader potential other benefits or disadvantages associated with treatments, and contextual consideration related to HeFH and ASCVD, details of which are reported in this section and Section 6. We also built upon the insights that these stakeholders shared with ICER during its initial 2015 review of PCSK9 inhibitors,[6] new evidence update in 2017 of evolocumab,[7] and subsequent new evidence update in 2019 of alirocumab.[8]

We heard from patients, caregivers, and advocacy organizations in the following ways during this review. Additional details regarding how this input informed ICER's research approach can be found below the list.

- **Open Input**
  - Seven responses to ICER's Patient Input Questionnaire from patients and caregivers
  - One letter from a patient advocacy organization
  - Three discussion calls with patient advocacy organization representatives

- **Draft Scope**
  - One letter from a patient advocacy organization

- **Draft Report**
  - ICER presented the preliminary modeling approach to one patient organization and considered feedback
  - 95 additional responses to ICER's Patient Input Questionnaire from patients and caregivers
  - Six responses from patient advocacy organizations
  - Five responses from clinicians and clinical societies
  - Three responses from manufacturers
  - Two responses from individuals

Input received during the Open Input period informed the draft scoping document containing suggested population, interventions, comparators, and outcome measures. This draft document was open to public comment for three weeks.

We revised the draft scope to reflect feedback from patient advocacy organizations and additional stakeholder groups including clinicians, researchers, payers, and manufacturers of the agents of focus in this review. Among the changes to the scoping document that benefited from stakeholder input were new language clarifying the subpopulations of interest within the clinical and the economic sections of the review; clarification of the basis of clinician concerns about the potential risks of unknown side effects as a result of inclisiran's dosing schedule; and additional language highlighting disparities in cholesterol treatment as a key concern and the addition of more contextual factors that stakeholder groups felt should be considered during the review.

In response to the feedback we received during the preliminary model presentation, we made changes to key inputs to the cost-effectiveness model, including using Cholesterol Treatment Trialists Collaboration (CTTC) data for converting LDL-C reduction into MACE rates for both drugs. Based on feedback from the FH Foundation, we highlight that although we did not include primary prevention in the economic evaluation, patients with HeFH who do not have established ASCVD are also a high-risk group for MACE.

In response to feedback we received to the draft report, we further highlighted the underdiagnosis and undertreatment of the FH population, added more information about the reasons for disparities in treatment in minority populations, clarified the reasons for using statin and ezetimibe as the comparator in the economic model, addressed the low rate of real-world utilization of ezetimibe, and clarified that we did not find any relevant clinical trials that reported health-related quality of life as an outcome.

2.2 Impact on Patients

Patient groups highlighted that there is still a lack of awareness about FH, resulting in missed or delayed diagnoses of FH. If diagnosis only occurs after a cardiovascular event, it represents a missed opportunity for primary prevention. Additionally, patients with FH are often undertreated despite their very high risk of ASCVD events, highlighting the need for both improved access to and utilization of existing treatment options, as well as new effective treatment options. Patients with FH often have events earlier in life and during years of prime productivity, so their lives may be impacted by the disease for a longer time horizon than other ASCVD patients. One patient with FH wrote *"I have not had any cardiovascular events so far…but I do worry every day that I didn't do enough, early enough in life to prevent heart disease. I almost lost my father at age 57 when he had sudden cardiac death in the middle of a tennis tournament (revived with CPR), but we always expected that to happen - not if, but when. My mother prepared to be a widow when we were young, given the family history and the fact that my youngest uncle had bypass at age 28."*

Accessibility, affordability, side effects of continued therapy during the life course, impact of therapies on health care utilization and long-term ASCVD events and outcomes were other

concerns brought forth by patient groups. Access to new therapies was of particular concern to patients, given the possibility of step therapy requirements and the often-cumbersome insurance prior authorization process for newer cholesterol-lowering drugs like PCSK9-inhibitors.[10] These kinds of coverage policies have resulted in delayed or denial of access to therapy for some patients,[9] which could result in underuse of effective therapies and higher cardiovascular event rates if access is limited for high-risk patients.[11] Identified areas warranting further investigation included gaining a full understanding of impact of the new therapies on the patient experience including patient preferences on utilizing new therapies.

Both patient groups and clinicians were concerned about underlying health and health care disparities in high cholesterol treatment by factors including race/ethnicity, gender, and insurance type. For example, women and racial/ethnic minorities are less likely to receive statin therapy, PCSK9 inhibitors or achieve LDL-C goals.[11,12] The reasons for this are likely multifactorial, including patient and provider factors, structural inequalities in the health care system, and other social determinants of health. For example, Black Americans may have more limited interactions with the health care system due to such factors as less ability to take time off work and mistrust of the health care system, leading to fewer opportunities for education and limited or ineffective shared decision-making. Providers may prescribe less potent statins or statins at less than maximal dosages and may perceive minority patients as less compliant. Additionally, more aggressive lipid-lowering therapy such as ensuring use of high potency statins at adequate doses and use of ezetimibe is often delayed until after a cardiovascular event occurs, which may delay achievement of LDL-C goals and lead to additional cardiovascular events. Patient groups and clinicians also noted that insurance type and status may also play a role in uptake of therapy in part due to anticipated insurance challenges for new therapies based on experiences with the prior authorization process with PCSK9 inhibitors. An additional insurance-related barrier mentioned was that uninsured patients and those with governmental sponsored health insurance (Medicaid, Medicare) may be less likely to have access to newer, costlier therapies. For instance, a patient respondent to the patient input questionnaire shared a significant downside to their current lipid-lowering treatment was cost and concern about *"when I get to Medicare will it pay for my treatments that private insurance does now? Husband has to work longer so I have insurance."* Furthermore, the lack of adequate inclusion of racial/ethnic minorities in clinical trials of new therapies was identified as a barrier to being able to evaluate whether there may be differential effects of therapies in these subpopulations.

Clinicians discussed the potential role of bempedoic acid with or without ezetimibe and inclisiran in the context of treatment of HeFH and secondary prevention of ASCVD and the varying risk levels and needs of patients. The patient's level of need for LDL-C reduction and experience with prior therapies were cited as a major factor in choosing additional therapy. Bempedoic acid and the bempedoic acid/ezetimibe combination therapy were viewed as most helpful in patients with statin intolerance and those who are close to their LDL goal but do not wish to take an injectable drug.

Some clinical experts highlighted that side effects of bempedoic acid, such as increased uric acid levels and the risk of gout, would likely affect patient and clinician consideration of the role of bempedoic acid in therapy. Clinicians also reported that with currently available data, inclisiran would be considered as an option having generally similar LDL-lowering ability as the PCSK9 inhibitors and thus they would consider use of inclisiran for patients requiring a large amount of LDL-C lowering. However, they cautioned that some degree of skepticism on inclisiran's clinical equivalence to PCSK9 inhibitors would remain until confirmatory trial data on cardiovascular disease outcomes from ongoing outcomes trials are published. Clinical experts and patient groups both highlighted inclisiran's potential benefits for patient adherence to treatment with its twice-yearly dosing compared to every two-week dosing for PCSK9 inhibitors. Some clinicians said they would be cautious about adoption of inclisiran given its relatively limited safety experience and perception that there may be a risk of prolonged side effects from a drug formulated for an extended dosing interval.

Manufacturers highlighted that consideration in value assessment should be given to the impact of potential differences between treatments beyond LDL-C lowering, including mode of delivery, drug administration considerations (e.g., in a physician's office or self-administered), dosing interval, adherence, and effects on other disease parameters (e.g., hemoglobin A1c, high-sensitivity CRP) which could impact patient experience, treatment burden and patient-important outcomes.

2.3 Impact on Caregivers and Families

The impact of cardiovascular events such as MI and stroke may range from mild to severe, with severe events leading to major disabilities affecting activities of daily living and independence. Prevention of cardiovascular events could benefit caregivers and families by maintaining patient independence and decreasing the need for caregiving. In addition, prevention of cardiovascular events could increase the productivity of patients, which may be particularly important for younger patients in the workforce and those with dependent children (e.g., FH patients, women). Finally, avoiding or minimizing the number of injections may be important for some patients, as some may need assistance with injections and a twice-yearly dosing regimen may be more convenient than once or twice monthly dosing.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

Alirocumab and Evolocumab

Because it has not yet been approved by the FDA, we were unable to find publicly available coverage policies for inclisiran. We anticipate that inclisiran will be covered similarly to the PCSK9 inhibitors, so we reviewed the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database for its US commercial health plans' coverage policies for alirocumab (Praluent®, Regeneron) and evolocumab (Repatha®, Amgen) as of October 2020.[37] Developed by the Center for Evaluation of Value and Risk in Health, the SPEC database features data on more than 290 specialty drugs, more than 175 disease areas, and more than 25,000 decisions from the following 17 largest US national and regional commercial payers: Aetna, Anthem, Blue Cross Blue Shield (BCBS) of Florida (FL), Massachusetts (MA), Michigan (MI), North Carolina (NC), New Jersey (NJ), and Tennessee (TN), CareFirst, Centene, Cigna, Emblem, Health Care Service Corporation (HCSC), Highmark, Humana, Independence Blue Cross (IndepBC), and UnitedHealthcare (UHC).

Table 3.1 and Table 3.2 on the following pages summarize the coverage determinations from representative commercial payers. The SPEC database did not provide information for alirocumab from BCBS New Jersey, BCBS Tennessee, Emblem, or Health Care Service Corporation; or for evolocumab from BCBS New Jersey, BCBS Tennessee, Emblem, Health Care Service Corporation, or Highmark.

In addition, we manually scanned coverage policies for the payers listed in Tables 3.1 and 3.2 to determine whether each requires patients to step through ezetimibe to access alirocumab and evolocumab. Eight (Aetna,[38] Anthem,[39] BCBSMA,[40] Centene,[41] Cigna,[42] Humana,[43] IndepBC,[44] and UnitedHealthcare[45]) of the thirteen payers[46-52] listed require step therapy through ezetimibe for alirocumab, and six (Aetna,[38], Anthem,[39] BCBSMA,[53] Centene,[54] Cigna,[42] and IndepBC[44]) require step therapy through ezetimibe to access evolocumab.

Table 3.1. Coverage Decisions for Alirocumab by Health Plan[37]

Health Plan	Coverage	Step Therapy Protocol	Prescriber Requirement	Patient Subgroup Restriction	Other Restriction
Aetna	More restrictive than FDA label	Yes	No	Yes	Yes
Anthem	More restrictive than FDA label	Yes	No	No	Yes
BCBS Florida	More restrictive than FDA label	Yes	Yes	No	Yes
BCBS Massachusetts	More restrictive than FDA label	Yes	Yes	No	Yes
BCBS Michigan	More restrictive than FDA label	Yes	Yes	No	No
BCBS North Carolina	More restrictive than FDA label	Yes	Yes	No	Yes
CareFirst	More restrictive than FDA label	Yes	No	Yes	No
Centene	More restrictive than FDA label	Yes	Yes	Yes	Yes
Cigna	More restrictive than FDA label	Yes	No	No	No
Highmark	More restrictive than FDA label	Yes	Yes	Yes	Yes
Humana	More restrictive than FDA label	Yes	No	No	Yes
Independence BC	More restrictive than FDA label	Yes	No	No	No
UnitedHealthcare	More restrictive than FDA label	Yes	Yes	Yes	Yes

Table 3.2. Coverage Decisions for Evolocumab by Health Plan[37]

Health Plan	Coverage	Step Therapy Protocol	Prescriber Requirement	Patient Subgroup Restriction	Other Restriction
Aetna	More restrictive than FDA label	Yes	No	No	Yes
Anthem	More restrictive than FDA label	Yes	No	No	Yes
BCBS Florida	More restrictive than FDA label	Yes	Yes	No	Yes
BCBS Massachusetts	More restrictive than FDA label	Yes	Yes	No	Yes
BCBS Michigan	More restrictive than FDA label	Yes	Yes	No	No
BCBS North Carolina	More restrictive than FDA label	Yes	Yes	Yes	No
CareFirst	More restrictive than FDA label	Yes	No	No	No
Centene	More restrictive than FDA label	Yes	Yes	No	No
Cigna	More restrictive than FDA label	Yes	No	No	Yes
Humana	More restrictive than FDA label	No	No	No	Yes
Independence BC	More restrictive than FDA label	Yes	No	No	No
UnitedHealthcare	More restrictive than FDA label	Yes	Yes	No	Yes

Bempedoic Acid

Bempedoic acid and the bempedoic acid/ezetimibe combination (Nexletol® and Nexlizet™) are not available in the SPEC database, so we conducted a manual search through the US commercial health plans' coverage policies. We were unable to locate coverage policies for bempedoic acid or bempedoic acid/ezetimibe from BCBS Florida, CareFirst, Emblem, Health Care Service Corporation, or Independence BC. Of those health plans for which we were able to locate coverage policies, Anthem, Centene, Highmark, and UnitedHealthcare present patient subgroup restrictions. In addition, all plans placed other restrictions on coverage, such as quantity limits or requirements for documented LDL measurement from the past year. None of the health plans, except for BCBS Massachusetts, give prescriber restrictions, but all require individuals to follow step therapy protocol. See Table 3.3 below for more information regarding coverage policies for bempedoic acid and bempedoic acid/ezetimibe.

Table 3.3. Coverage Decisions for Nexletol®/Nexlizet™ by Health Plan

	Step Therapy Protocol	Prescriber Requirement	Patient Subgroup Restriction	Other Restriction
Aetna[55]	Yes	No	No	Yes
Anthem[56]	Yes	No	Yes	Yes
BCBS Massachusetts[57]	Yes	Yes	No	Yes
BCBS Michigan[58]	Yes	No	No	Yes
BCBS New Jersey[59]	Yes	No	No	Yes
BCBS North Carolina*[60]	Yes	NA	NA	NA
Centene[61]	Yes	No	Yes	Yes
Cigna[62]	Yes	No	No	Yes
Highmark[63]	Yes	No	Yes	Yes
Humana[64]	Yes	No	No	Yes
UnitedHealthcare[65]	Yes	No	Yes	Yes

NA: Information not found

The following health plan(s) did not issue a coverage decision for the selected drug and indication: BCBS Florida, CareFirst, Emblem, Health Care Service Corporation, Independence BC

*For Nexletol only; Nexlizet is non-formulary.

3.2 Clinical Guidelines

Below, we summarize guidelines pertaining to secondary prevention of ASCVD and HeFH from the American College of Cardiology (ACC) and American Heart Association (AHA), as well as the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). We focused primarily on guidelines for treatment with lipid lowering agents relevant to this review (statins, ezetimibe, bempedoic acid, and PCSK9 inhibitors).

American College of Cardiology and American Heart Association[66]

The ACC/AHA Task Force on Clinical Practice guidelines released guidelines in 2018 for the management of blood cholesterol.

ASCVD

The guidelines recommend using high-intensity statin therapy to treat patients aged 75 or younger with clinical ASCVD, with an initial goal of 50% LDL-C reduction. Moderate intensity statins may be used in patients who are not very high risk if high-intensity statins cannot be tolerated. For patients over the age of 75, clinicians should weigh potential benefits versus adverse effects of statin therapy before initiating treatment. If LDL-C levels remain above 70 mg/dL on maximally tolerated statin therapy, it is reasonable to add ezetimibe.

For very-high risk patients, the guidelines recommend that it is reasonable to treat patients with ezetimibe as an adjunct to maximally tolerated statin therapy. If LDL-C levels remain above 70 mg/dL following treatment with ezetimibe, adding a PCSK9 inhibitor is reasonable.

HeFH

Patients with HeFH have severe hypercholesterolemia and a high lifetime risk of cardiovascular events. For adults with HeFH, high-intensity statin therapy is recommended. For patients whose LDL-C level remains above 100 mg/dL, the addition of ezetimibe is reasonable. If further LDL-C lowering is needed, clinicians may also consider adding a PCSK9 inhibitor.

European Society of Cardiology and European Atherosclerosis Society[67]

An ESC and EAS Task Force released joint guidelines for the management of dyslipidemias in 2019.

ASCVD

The guidelines recommend treating patients with high-intensity statin to reach the goals set for their risk level. In secondary prevention for patients at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of < 55 mg/dL are recommended. Combination therapy with

ezetimibe is recommended for patients whose goals are not achieved with the maximally tolerated dose of statin. For secondary prevention of ASCVD, patients at very-high risk who have not achieved their goal with maximally tolerated statin and ezetimibe, addition of a PCSK9 inhibitor may be considered.

At the time of publication, bempedoic acid was being tested in Phase III trials and was described as a potential new approach to reduce LDL cholesterol. Though it was not formally incorporated into the clinical guidelines, the guidelines state that bempedoic acid had been found to lower LDL-C levels by around 30% as monotherapy and 50% in combination with ezetimibe, though these estimates were based on Phase II trials, which were the only results available at the time.

HeFH

HeFH patients with ASCVD or another major risk factor should be treated as very-high risk, and those with no prior ASCVD or other risk factors should be treated as high-risk. In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of 55 mg/dL should be considered. Very-high risk patients should be treated to achieve an initial goal of 50% reduction in LDL-C levels and receive a drug combination if this goal is not achieved. Addition of a PCSK9 inhibitor is also recommended in very-high risk patients if the treatment goal is not met with maximally tolerated statin and ezetimibe.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our review of the comparative clinical effectiveness of bempedoic acid and inclisiran for the treatment of adults with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated lipid-lowering therapy, we systematically identified and synthesized the existing evidence from available clinical studies. We considered evidence across relevant populations, including all patients with HeFH (primary and secondary prevention) and patients with established ASCVD (secondary prevention). We sought evidence related to each of these therapies in conjunction with maximally tolerated background lipid-lowering therapy versus ongoing maximally tolerated lipid-lowering therapy. We did not attempt to compare the interventions to each other because of key differences across trials in patient characteristics and trial design. Additionally, since outcomes trials are still ongoing, we did not pursue quantitative comparison of inclisiran with PCSK9 inhibitors. Our review focused on clinical benefits as well as potential harms (treatment-related adverse events). Methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on inclisiran and bempedoic acid followed established best research methods.[68,69] Evidence was sought from randomized controlled trials as well as high-quality systematic reviews and observational studies.

We conducted the systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[70] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

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/.

Study Selection

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all identified publications using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during the full-text review.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies. We used the US Preventive Services Task Force (USPSTF) criteria to assess the quality of clinical trials. For more information on data extraction and quality assessment, see Appendix D.

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms included bempedoic acid, ETC-1002, inclisiran, ALN-PCSsc, and ALN-60212. We searched for studies that would have met our inclusion criteria and for which no findings have been published.

Assessment of Level of Certainty in Evidence

In order to lend transparency to our judgment of the 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 (see Appendix D).[71]

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Table D) and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessments for each outcome of interest. We conducted random effect pairwise meta-analyses separately for bempedoic acid and inclisiran on the following outcomes: LDL-C and the other lipid parameters (in the absence of pooled estimates), cardiovascular outcomes, and safety events (in the absence of pooled estimates). Effect sizes for continuous outcomes, such as LDL-C changes, were expressed as mean difference (MD) and 95% CIs. For binary outcomes (e.g., safety events), we calculated risk ratios (RRs) and their respective 95% CIs using the Mantel–Haenszel method. We assessed heterogeneity using the Cochran q test and the I^2 statistic. To explore heterogeneity across studies, we examined for differences in the distribution of key characteristics across studies, such as enrolled patients, baseline LDL-C, and background lipid-lowering therapy. We performed subgroup analyses where studies differ in these characteristics, and sufficient data existed. We did not conduct network meta-analyses to compare bempedoic acid and inclisiran because of key differences across trials in patient characteristics and trial design.

4.3 Results

Study Selection

Our literature search identified 1,833 potentially relevant references (see Appendix Figure A1), of which 18 references (15 publications, one conference presentation, and two FDA Review Packets) relating to 13 individual studies met our inclusion criteria. The primary reason for study exclusion included the wrong study population (e.g., diabetes), the use of interventions (e.g., ezetimibe alone, statins, PCSK9-inhibitors) or dosing outside of our scope, and conference abstracts with duplicate data as the full-text publications.

Of the 18 included references, eight references represented five Phase III RCTs of bempedoic acid,[72-79] and four represented four Phase II trials.[80-83] The four Phase II trials of bempedoic acid were eventually excluded from our evaluation of the clinical benefit of bempedoic acid because these studies were focused on primary prevention and did not enroll patients with established ASCVD and/or HeFH (see Appendix D).[80-83] The six remaining references present data on four RCTs (three Phase III trials and one Phase II trial) of inclisiran.[84-89] We did not identify any high-quality observational studies. Details of all included studies are summarized in Appendix Table D1 and described in the sections below.

Quality of Individual Studies

We rated three of the bempedoic acid trials (CLEAR Harmony, CLEAR Serenity, and CLEAR Tranquility) and all the inclisiran trials (ORION 9, 10, 11 & 1) to be of good quality using criteria from the USPSTF (Appendix D). These trials had adequate blinding of patients, investigators, and outcome assessors. The groups were comparable at baseline, and there was non-differential follow-up. We rated two bempedoic acid trials (CLEAR Wisdom and Ballantyne 2020) as fair quality trials because of differential loss to follow-up observed in these trials. Furthermore, due to data irregularities observed in the Ballantyne 2020 trial, post-hoc analysis was considered the primary analysis (intention to treat analysis was also presented).

Assessment of Publication Bias

As described in our methods, we searched for studies completed more than two years ago, which would have met our inclusion criteria, and for which no findings have been published. Such studies may have provided qualitative evidence for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for bempedoic acid and inclisiran using the clinicaltrials.gov database of trials. For this review, we identified one Phase II trial of bempedoic acid that was completed more than two years ago and has not yet been published (NCT03193047). However, this study would have been excluded from our review based on the inclusion and exclusion criteria provided on clinicaltrials.gov.

Trials of Bempedoic Acid

We identified five trials of bempedoic acid that met our inclusion criteria (Table 4.1). In two pivotal RCTs (CLEAR Wisdom and CLEAR Harmony), bempedoic acid was compared to placebo in patients with ASCVD or HeFH who required further LDL-C lowering despite being on maximally tolerated statin therapy. One smaller trial (Ballantyne 2020) evaluated the combination pill (bempedoic acid/ezetimibe) versus bempedoic acid alone, ezetimibe alone, and placebo in patients with ASCVD or HeFH on maximally tolerated statin therapy. The other two studies were RCTs enrolling only patients with statin intolerance, with or without established ASCVD, who required LDL-C lowering (CLEAR Serenity and CLEAR Tranquility). The trials are described in detail below (Table 4.1 provides an overview of each trial; additional trial details can be found in Appendix Table D).

Pivotal Trials of Bempedoic Acid and Bempedoic Acid/Ezetimibe

CLEAR Wisdom

The CLEAR Wisdom trial was a Phase III multinational, randomized trial conducted in North America and Europe among 779 patients with ASCVD, HeFH, or both in whom LDL-C levels were elevated

(LDL-C ≥ 100 mg/dl) despite receiving maximally tolerated lipid-lowering therapy (maximally tolerated statin alone or in combination with other approved lipid-lowering therapies).[75] Patients with severe renal impairment and a cardiovascular (CV) event within three months of the trial were excluded. The study participants had a median age of 64 years, 36% were female, and 94% were white. The majority of enrolled patients had established ASCVD (95%), while a small percentage had only underlying HeFH (6%). The baseline LDL-C was 120 mg/dl. Baseline characteristics were well-balanced between treatment arms. The participants were randomized 2:1 to bempedoic acid 180 mg or to an identical placebo once daily for 52 weeks. All patients continued stable background lipid-lowering therapy. After 24 weeks, investigators were permitted to adjust background lipid-lowering therapy, including dose adjustment or addition of other medications. A greater proportion of patients in the bempedoic acid arm discontinued the trial compared to the placebo arm (6.1% vs. 2.7%).[79] The primary endpoint was the percentage change in LDL-C from baseline to week 12 in the intention-to-treat (ITT) population. The key secondary endpoints included percentage change from baseline to week 12 in total cholesterol, apolipoprotein B, non-HDL-C (total cholesterol minus HDL-C), and hsCRP.

CLEAR Harmony

The CLEAR Harmony trial was a Phase III multinational, randomized trial conducted in 2,230 patients with ASCVD, HeFH, or both in whom LDL-C levels were elevated (LDL-C ≥ 70 mg/dl) despite receiving maximally tolerated lipid-lowering therapy (maximally tolerated statins alone or in combination with other lipid-lowering therapies).[77] Patients with severe renal impairment, CV event within three months, and those who received PCSK9-inhibitors within four weeks of the trial were excluded. The study participants had a median age of 66 years, 27% were female, 96% were white, 3% had HeFH, and 98% had established ASCVD. The baseline LDL-C was 103 mg/dl. Baseline characteristics were well-balanced between treatment arms. The participants were randomized 2:1 to receive oral bempedoic acid 180 mg or identical placebo once daily for 52 weeks. All patients continued stable background lipid-lowering therapy. Patients were randomized according to the presence of HeFH and the background use of statin. The primary endpoint was the overall rate of adverse events in the ITT population. The key secondary endpoints included percentage change from baseline to week 12 in LDL-C, total cholesterol, apolipoprotein B, non-HDL-C (total cholesterol minus HDL-C), and hsCRP.

Ballantyne 2020

Ballantyne 2020 was a Phase III multinational, randomized trial conducted in 301 patients with ASCVD, HeFH, or multiple cardiovascular disease (CVD) risk factors in whom LDL-C levels were elevated (≥ 100 mg/dL for HeFH or ASCVD, ≥ 130 mg/dL for multiple risk factors) despite receiving statin therapy at the maximum tolerated dose, with or without additional lipid-lowering therapy.[73] Patients with severe renal impairment or significant CV event within three months of the trial were excluded. The study participants had a median age of 64 years, 50% were female, 81% were white,

and 63% had established ASCVD and/or HeFH. The baseline LDL-C was 150 mg/dl. Baseline characteristics were well-balanced between treatment arms. The study participants were randomized 2:2:2:1 to once-daily treatment with 180 mg bempedoic acid and 10 mg ezetimibe combination pill, 180 mg bempedoic acid, 10 mg ezetimibe, or placebo for 12 weeks. Patients were randomized according to their CVD risk category (ASCVD and/or HeFH vs. multiple CVD risk factors) and background statin use. The primary endpoint was the percentage change in LDL-C from baseline to week 12. The key secondary endpoints included percentage change from baseline to week 12 in total cholesterol, apolipoprotein B, non-HDL-C (total cholesterol minus HDL), and hsCRP. The pre-specified analyses were in the ITT population. However, the investigators reported that three sites had data irregularities (51 patients from these study sites who were reported to be taking the study drugs had no detectable study drug in the blood sample taken at week 12); data from these sites were therefore excluded from the post hoc analyses. The FDA reviewed the data from these sites and ultimately concluded that the exclusion of data from these three sites more accurately represented the efficacy and safety of the bempedoic acid/ezetimibe combination pill. As such, our review of this trial focuses on the post-hoc population.

Other Trials of Bempedoic Acid

CLEAR Serenity

The CLEAR Serenity trial was a Phase III multinational, randomized trial conducted in North America and Europe among 345 patients with statin intolerance.[76] Statin intolerance was defined as the inability to tolerate at least two statins (one at lowest starting dose) due to an AE that started or worsened during statin therapy and resolved or improved upon statin discontinuation. Patients with severe renal impairment, CV event within three months of the trial, and those who received statin therapy with doses greater than those defined as 'low-dose' (average daily dose of 5 mg rosuvastatin, 10 mg atorvastatin, 10 mg simvastatin, 20 mg lovastatin, 40 mg pravastatin, 40 mg fluvastatin, or 2 mg pitavastatin) within four weeks of the trial were excluded. The trial enrolled patients with ASCVD, HeFH, or those who required lipid-lowering therapy for primary prevention of cardiovascular disease. LDL-C level was required to be ≥100 mg/dL for HeFH or ASCVD patients and ≥130 mg/dL for primary prevention. The study participants had a median age of 65, 56% were female, 89% were white, 2% had HeFH, and 39% had established ASCVD. The baseline LDL-C was 158 mg/dl. Baseline characteristics were well-balanced between treatment arms. The study participants were randomized 2:1 to receive oral bempedoic acid 180 mg or identical placebo once daily for 52 weeks. All patients continued stable background lipid-lowering therapy. The primary endpoint was the percentage change in LDL-C from baseline to week 12. The key secondary endpoints included percentage change from baseline to week 12 in total cholesterol, apolipoprotein B, non-HDL (total cholesterol minus HDL), and hsCRP.

Clear Tranquility

The CLEAR Tranquility trial was a Phase III multinational, randomized trial conducted in North America and Europe among 269 patients with statin intolerance on low dose statin or no statin therapy.[72] The trial enrolled patients requiring additional lipid-lowering therapy (LDL-C level ≥ 100 mg/dL). Patients with known New York Heart Association (NYHA) Class IV congestive heart failure, CV event within three months, and those who received statin therapy with doses greater than those defined as 'low-dose' (average daily dose of 5 mg rosuvastatin, 10 mg atorvastatin, 10 mg simvastatin, 20 mg lovastatin, 40 mg pravastatin, 40 mg fluvastatin, or 2 mg pitavastatin) within four weeks of the trial were excluded. The study participants had a median age of 64 years, 61% were female, 89% were white, and 26% had established ASCVD. The baseline LDL-C was 128 mg/dl. Baseline characteristics were well-balanced between treatment arms. The study comprised of a 4-week run-in period during which patients received open-label 10 mg ezetimibe once daily and a single-blind placebo to assess tolerance to ezetimibe and compliance with the protocol. Patients with poor adherence during the run-in phase were excluded. At the end of the run-in phase, patients were randomized 2:1 to receive oral bempedoic acid 180 mg or identical placebo once daily for 12 weeks. All patients continued study-provided open-label 10 mg ezetimibe once daily and other stable background lipid-lowering therapies (e.g., low-dose statins) throughout the study. The primary endpoint was the percentage change in LDL-C from baseline to week 12. The key secondary endpoints included percentage change from baseline to week 12 in total cholesterol, apolipoprotein B non-HDL-C (total cholesterol minus HDL), and hsCRP.

Table 4.1. Trials of Bempedoic Acid

Trial (No. of Patients)	Population	Treatment Arms	Key Baseline Characteristics
Pivotal Trials			
CLEAR Wisdom (N=779)	ASCVD, HeFH, or both on maximally tolerated lipid-lowering therapy	1. Bempedoic acid 180 mg 2. Placebo	Age: 64 years Baseline LDL-C: 120.4 mg/dL Statin intolerance: 5.6%* ASCVD: 94.5% HeFH: 5.5%
CLEAR Harmony (N=2,230)	ASCVD, HeFH, or both on maximally tolerated lipid-lowering therapy	1. Bempedoic acid 180 mg 2. Placebo	Age: 66 years Baseline LDL-C: 103.2 mg/dL Statin intolerance: NR ASCVD: 97.6% HeFH: 3.5%
Ballantyne 2020 (N=301)	ASCVD, HeFH, or multiple CV risk factors on maximally tolerated lipid-lowering therapy	1. Fixed-dose combination bempedoic acid 180 mg + ezetimibe 10 mg 2. Bempedoic acid 180 mg 3. Ezetimibe 10 mg 4. Placebo	Age: 64 years Baseline LDL-C: 149.8 mg/dL Statin intolerance: 35.2% ASCVD/HeFH: 62.5%
Other Trials			
CLEAR Serenity (N=345)	ASCVD, HeFH, or hypercholesterolemia with statin intolerance	1. Bempedoic acid 180 mg 2. Placebo	Age: 65 years Baseline LDL-C: 157.6 mg/dL Statin intolerance: 100% ASCVD: 38.8% HeFH: 2%
CLEAR Tranquility (N=269)	Hypercholesterolemia with statin intolerance	1. Bempedoic acid 180 mg 2. Placebo	Age: 64 years Baseline LDL-C: 127.6 mg/dL Statin intolerance: 100% ASCVD: 25% HeFH: NR

ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, mg: milligram, mg/dL: milligram per deciliter, N: total number, No.: number, NR: not reported

*15.1% on no statin or low dose statin

Clinical Benefits of Bempedoic Acid

The section that follows evaluates the efficacy of bempedoic acid with or without ezetimibe, including the percentage LDL-C lowering effects of bempedoic acid versus control. As described above, one of the identified trials, Ballantyne 2020, evaluated the combination pill of bempedoic acid and ezetimibe. Since we found no data to suggest that ezetimibe modifies the effect of bempedoic acid, we considered bempedoic acid versus placebo to be equivalent to bempedoic acid/ezetimibe versus ezetimibe in our discussion of the clinical benefit of bempedoic acid below. We also describe the efficacy of the combination pill in a separate subsection below. Available data on clinical outcomes, including total mortality, CVD mortality, non-fatal MI, and stroke, are then discussed. Of note, none of the bempedoic acid trials were designed with clinical events as the primary outcome; as such, the number of events is low. Based on data availability, we conducted pairwise meta-analyses for the following outcomes: LDL-C, all-cause mortality, CV mortality, MI, and stroke.

LDL-C and Other Lipid Parameters

Table 4.2 presents the percentage reduction in LDL-C for bempedoic acid versus control observed in the Phase III trials. In four of the Phase III trials (CLEAR Wisdom, CLEAR Harmony, CLEAR Serenity, and CLEAR Tranquility), bempedoic acid was compared to placebo. The fifth trial, Ballantyne 2020, was a four-arm trial where participants were randomized to the bempedoic acid/ezetimibe combination pill, ezetimibe, bempedoic acid, or placebo. As mentioned above, we considered bempedoic acid/ezetimibe versus ezetimibe to be equivalent to bempedoic acid versus placebo. As such, for our meta-analysis, Ballantyne 2020 provided two separate comparisons - bempedoic acid/ezetimibe combination pill versus ezetimibe *and* bempedoic acid versus placebo (Table 4.2).

Table 4.2. Bempedoic Acid: Percentage Change in LDL-C from Baseline to Week 12

Trials	Population	Baseline LDL-C	Percent Reduction		
			Control	Bempedoic Acid	Between-Arm Difference
Bempedoic Acid vs. Placebo					
CLEAR Wisdom	ASCVD, HeFH, or both on maximally tolerated statin therapy	120.4 mg/dL	2.4 (NR)	-15.1 (NR)	-17.4 (-21.0, -13.9)
CLEAR Harmony	ASCVD, HeFH, or both on maximally tolerated statin therapy	103.2 mg/dL	1.6 (0.9)	-16.5 (0.5)	-18.1 (-20.0, -16.1)
Ballantyne 2020*	ASCVD, HeFH, or both on maximally tolerated statin therapy	149.2 mg/dL	1.8 (3.4)	-17.2 (2.6)	-19.0 (-27.8, -10.2)
CLEAR Serenity	Patients with statin intolerance	157.6 mg/dL	-1.3 (1.4)	-23.6 (1.4)	-21.4 (-25.1, -17.7)
CLEAR Tranquility	Patients with statin intolerance	127.6 mg/dL	5 (2.2)	-23.5 (2.0)	-28.5 (-34.4, -22.5)
Bempedoic Acid/Ezetimibe Combination Pill vs. Ezetimibe					
Ballantyne 2020*	ASCVD, HeFH, or both on maximally tolerated statin therapy	151.4 mg/dL	-23.2 (2.2)	-36.2 (2.6)	-13.0 (-19.7, -6.5)
Summary Estimate: Random Effect Meta-Analysis Bempedoic Acid vs. Placebo					-19.5 (-22.7, -16.4); p<0.0001; I^2 =69%

ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, I^2: I-squared, LDL-C: low-density lipoprotein cholesterol, SE: standard error

*Ballantyne 2020 is a four-arm trial (bempedoic acid/ezetimibe combination pill, ezetimibe, bempedoic acid, and placebo) that provided separate data for the combination pill versus ezetimibe & bempedoic acid versus placebo in the meta-analysis

The summary estimate for the percentage reduction in LDL-C after 12 weeks of treatment with bempedoic acid compared with control treatment is -19.5% (95% CI: -22.7 to -16.4, p<0.001) (Table 4.2). However, heterogeneity among these studies was high and statistically significant (I^2=69%, p<0.01). Sources of heterogeneity may include differences in the patient populations studied (e.g., background statin therapy and its intensity, baseline LDL-C levels) and differences in the intervention and comparison group (bempedoic acid/combination pill vs. placebo/ezetimibe). The percentage reduction in LDL-C appears to be greater in the statin-intolerant trials compared with trials where patients were on background statin therapy (21-28% vs. 17-19%). Additionally, the percentage reduction in LDL-C also appears qualitatively to be greater in the bempedoic acid alone

trials than that observed for bempedoic acid/ezetimibe versus ezetimibe (17-19% vs. 13%). These differences are further explored below.

Bempedoic acid also improved other lipid parameters. There were significant reductions in total cholesterol (9% to 18%), non-HDL-C (11% to 23%), apolipoprotein B (7% to 25%), and hsCRP (9% to 31%) with bempedoic acid compared with control.[72,73,75-77] There was also an observed reduction in HDL cholesterol (4% to 6%). There was no statistically significant change in triglycerides in any of the studies.

LDL-C Lowering by Patient Population

HeFH (primary and secondary prevention): We did not identify any bempedoic acid trial conducted exclusively in the HeFH population. The included studies enrolled very few patients with HeFH (1% - 5%). A subgroup analysis by HeFH status was conducted using two of the pivotal trials (CLEAR Wisdom and CLEAR Harmony). The results showed a marginally higher LDL-C reduction (MD: –22.3, 95% CI: –33.3 to –11.4) in the HeFH patients compared to the other patients (MD: –18.3, 95% CI: –20.1 to –16.6); however, the difference was not statistically significant (p-value for interaction =0.65).[74]

Established ASCVD (secondary prevention): The three pivotal trials (CLEAR Wisdom, CLEAR Harmony, and Ballantyne 2020) primarily enrolled patients with established ASCVD. Our meta-analysis including only these three studies showed there was a 17.7% LDL-C reduction (95% CI: -19.3, -16.1, p<0.0001, I2=0%) with bempedoic acid compared to control (Table 4.3).

Statin intolerant: As described above, the CLEAR Serenity trial and the CLEAR Tranquility trial enrolled only patients with statin intolerance on low dose statin or no statin therapy. Overall, the percentage reduction in LDL-C appears to be greater in the statin-intolerant trials (21% to 28%) than the other studies where patients were on background statin therapy (13% to 19%) (Table 4.2). We conducted a subgroup analysis across all trials to evaluate these potential differences further. The results of the subgroup analysis are presented in Table 4.3. The results showed there was a 24.6% LDL-C reduction (95% CI: -31.5 to -17.6, p<0.0001, I^2=75%) with bempedoic acid treatment compared to placebo for statin-intolerant patients, and a 17.7% LDL-C reduction (95% CI: -19.3 to -16.1, p<0.0001, I^2=0%) with bempedoic acid treatment compared to placebo among patients on maximally tolerated statins. The test for subgroup difference just reached statistical significance (Q=3.87, p=0.05).

Of note, the CLEAR Serenity and the CLEAR Tranquility trials enrolled few patients with established ASCVD (40% in CLEAR Serenity and 25% in CLEAR Tranquility). A review of the data submitted by the manufacturer under our academic-in-confidence policy showed no significant difference in the percentage LDL-C reduction between patients with and those without established ASCVD.

Table 4.3. Bempedoic Acid: Percentage Change in LDL-C from Baseline to Week 12: Subgroup Analyses by Statin Tolerance

Population	Trials included	Mean Difference (95% CI)	p-Value	I^2
Overall	All included trials	-19.5 (-22.7, -16.4)	<0.0001	69%
Patients with ASCVD, HeFH, or both on maximally tolerated statin therapy	CLEAR Wisdom, CLEAR Harmony, Ballantyne 2020	-17.7 (-19.3, -16.1)	<0.0001	0%
Patients with statin intolerance	CLEAR Serenity, CLEAR Tranquility	-24.6 (-31.5, -17.6)	<0.0001	75%

95% CI: 95% confidence interval, ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, I^2: I-squared

Bempedoic Acid/Ezetimibe Combination

As described above, we identified one trial that evaluated the efficacy and safety of the bempedoic acid/ezetimibe fixed-dose combination pill versus ezetimibe, bempedoic acid, and placebo. At week 12, LDL-C lowering was significantly greater in the bempedoic acid/ezetimibe combination arm compared to the other three arms of the trial. Specifically, the placebo adjusted LDL-C reduction in the bempedoic acid/ezetimibe arm was 38%. This value was noted to be slightly less than the additive effect of the placebo-adjusted bempedoic acid (25%) and ezetimibe monotherapy (19%) arms compared with placebo in the trial. Compared to the bempedoic acid monotherapy arm, the combination pill reduced LDL-C by 19%; compared with the ezetimibe monotherapy arm, the bempedoic acid/ezetimibe combination pill reduced LDL-C by only 13%.

Table 4.4. Bempedoic Acid/Ezetimibe: Percentage Change in LDL-C and Other Lipid Parameters at 12 Weeks

Treatment Arms	LDL-C Percentage Reduction (SE)	LDL-C Between-Group Difference (95% CI)	
		vs. Placebo	vs. Bempedoic Acid + Ezetimibe
Bempedoic Acid + Ezetimibe (n=86)	-36.2 (2.6)	-38 (-46.5, -29.6)	Reference
Ezetimibe (n=88)	-17.2 (2.6)	-19 (NR)	-13 (-19.7, -6.5)
Bempedoic acid (n=86)	-23.2 (2.2)	-25 (NR)	-19 (-26.1, -11.9)
Placebo (n=41)	+1.8 (3.4)	Reference	-38 (-46.5, -29.6)

95% CI: 95% confidence interval, LDL-C: low-density lipoprotein cholesterol, n: number, NR: not reported, SE: standard error

Clinical Outcomes

There is a five-year ongoing clinical outcome study (CLEAR Outcomes [NCT02993406], n= 14,032) evaluating the effect of 180 mg bempedoic acid tablet on major adverse cardiovascular events (CV

death, nonfatal MI, nonfatal stroke, or coronary revascularization) in patients with a history of statin intolerance. The trial is expected to be completed in 2022.[90]

As described above, all but one of the included trials were designed with LDL-C lowering as the primary outcome. However, all-cause mortality and CV outcome events were recorded and reported as part of the safety evaluation in these trials. Specifically, the CLEAR Wisdom and the CLEAR Harmony trials present data on all-cause mortality, CV mortality, non-fatal stroke, non-fatal MI, and MACE at 52 weeks. The results of the meta-analyses on these outcomes are described below.

Table 4.5. Clinical Outcomes at 52 Weeks: Meta-Analyses of the CLEAR Wisdom and Harmony Trials

Outcome	RR (95% CI)	I^2	N	No. of Events (%)	
				Bempedoic Acid (N=2009)	Placebo (N=999)
All-Cause Mortality	2.25 (0.76 - 6.67)	0%	3,008	19 (1.0)	4 (0.4)
CV Mortality	1.52 (0.41 -5.70)	0%	3,008	10 (0.5)	3 (0.3)
Non-Fatal Stroke	1.11 (0.34 -3.61)	0%	3,008	9 (0.5)	4 (0.4)
Non-Fatal MI	0.54 (0.25 -1.15)	0%	3,008	25 (1.2)	22 (2.2)
MACE*	0.79 (0.58 -1.07)	0%	3,008	100 (5.0)	63 (6.3)

CV: cardiovascular, RR: risk ratio, I^2: I-squared, MACE: major adverse cardiac event, MI: myocardial infarction, N: total number, No.: number

*pre-specified exploratory outcome in the CLEAR Wisdom and the CLEAR Harmony trials comprising of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina

Numbers of events were small, and all 95% confidence intervals were non-significant. There was a higher incidence of all-cause mortality and CV mortality in the bempedoic acid group compared to the placebo group. Of the 19 deaths in the bempedoic acid group, 10 were due to CV events, five were cancer-related, three were due to sepsis, and one was acute poisoning with carbon dioxide. The CLEAR Wisdom and the CLEAR Harmony trials also assessed five-point adjudicated MACE, defined as a composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina. The meta-analysis results showed a lower event rate on MACE with bempedoic acid compared to placebo; however, this difference was not statistically significant.

Health-Related Quality of Life

We did not identify any studies that assessed the impact of bempedoic acid on health-related quality of life.

Harms

The majority of the adverse events (AEs) observed in the bempedoic acid trials were mild or moderate. AEs with an incidence equal to or greater than 5% in the trials are presented in Appendix Table D8-D10. Table 4.6 presents the pooled analysis of the CLEAR trials on any AEs, serious AEs, discontinuation due to AEs, and some selected AEs. The AEs of particular interest occurring with more frequency in the bempedoic acid group than the placebo group were muscle-related events (e.g., pain in extremity, muscle spasms, tendon rupture), hyperuricemia, gout, elevated liver enzymes (ALT, AST), and changes in renal laboratory parameters (e.g., GFR, blood creatinine level) (Table 4.6). Bempedoic acid received a label warning for hyperuricemia and tendon rupture.[91]

There was a slightly higher incidence of serious AEs and discontinuation due to AEs in the patients treated with bempedoic acid compared to placebo-treated patients in all trials. Overall, serious adverse events occurred in 14% of patients on bempedoic acid versus 13% of patients on placebo. Discontinuation due to AEs occurred in 11% of patients on bempedoic acid compared to 8% of patients on placebo. Serious AEs reported included all-cause mortality and CV events, details of which have been presented in the section above. The most common AEs leading to discontinuation were diarrhea, muscle-related events (e.g., pain in extremity, muscle spasms), elevated liver enzymes, and headache.

Table 4.6. Safety Events: Pooled Analysis of CLEAR Wisdom, CLEAR Harmony, CLEAR Serenity, and CLEAR Tranquility

Outcome	No. of Events (%)		p-Value
	Bempedoic Acid (N=2,424)	Placebo (N=1,197)	
Any AE	1,771 (73.1)	868 (72.5)	0.75
Serious AE	341 (14.1)	159 (13.3)	0.54
AE Associated with Study Drug	583 (24.1)	243 (20.3)	0.01
AE Leading to Discontinuation	273 (11.3)	93 (7.8)	0.001
Death	19 (0.8)	4 (0.3)	0.12
Myalgia	118 (4.9)	63 (5.3)	0.63
Muscle Spasms	89 (3.7)	31 (2.6)	0.09
Tendon Rupture*	11 (0.5)	0	NR
Pain in Extremity	75 (3.1)	21 (1.8)	0.02
Increased Uric Acid	51 (2.1)	6 (0.5)	<0.001
Gout	33 (1.4)	5 (0.4)	0.008
Elevated Liver Enzymes (ALT or AST)	67 (2.8)	15 (1.3)	0.004
Glomerular Filtration Rate Decrease	16 (0.7)	1 (<0.1)	0.02
Blood Creatinine Level Increase	19 (0.8)	4 (0.3)	0.12

AE: adverse event, N: total number

*FDA Integrated Review for Nexletol (bempedoic acid) 2020[79]

Like the other bempedoic acid trials, most AEs observed in the bempedoic acid/ezetimibe combination pill trial (Ballantyne 2020) were mild or moderate. In general, there were more treatment-emergent AEs in the bempedoic acid-treated patients (bempedoic acid/ezetimibe combination pill and bempedoic acid alone) than in the ezetimibe and placebo arms. The most common treatment-related AEs in the bempedoic acid/ezetimibe arm were hyperuricemia and muscle-related events (Table 4.7). Rates of serious AEs and discontinuation due to AEs were similar in the active treatment groups (bempedoic acid/ezetimibe combination pill, bempedoic acid, and ezetimibe groups). There were no reports of gout in the Ballantyne 2020 trial, and the occurrence of tendon rupture was not reported in this trial.

Table 4.7. Safety Events Observed in the Bempedoic Acid plus Ezetimibe Combination Pill Trial

Outcome	No. of Events (%)			
	Bempedoic Acid + Ezetimibe (n=85)	Bempedoic Acid (n=88)	Ezetimibe (n=81)	Placebo (n=80)
Any Treatment-Emergent AE	55 (62.4)	58 (65.9)	47 (54.7)	18 (43.9)
Serious AE	8 (9.4)	7 (8.0)	9 (10.5)	1 (2.4)
AE Associated with Study Drug	13 (15.3)	12 (13.6)	9 (10.5)	4 (9.8)
AE Leading to Discontinuation	7 (8.2)	9 (10.2)	10 (11.6)	2 (4.9)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia	2 (2.4)	5 (5.7)	2 (2.3)	1 (2.4)
Muscle Spasms	2 (2.4)	1 (1.1)	4 (4.7)	0 (0)
Tendon Rupture	NR	NR	NR	NR
Pain in Extremity	2 (2.4)	2 (2.3)	1 (1.2)	1 (2.4)
Increased Uric Acid	3 (3.5)	1 (1.1)	0 (0)	0 (0)
Gout	0 (0)	0 (0)	0 (0)	0 (0)
Elevated Liver Enzymes	1 (1.2)	0 (0)	0 (0)	0 (0)
Glomerular Filtration Rate Decrease	NR	NR	NR	NR
Blood Creatinine Level Increase	3 (3.5)	1 (1.1)	0 (0)	0 (0)

AE: adverse event, n: number, No.: number, NR: not reported

Trials of Inclisiran

We identified four trials (three Phase III and one Phase II) of inclisiran that met our inclusion criteria. Two of the Phase III trials enrolled patients with ASCVD primarily, while the third was conducted in HeFH patients with and without ASCVD. The trials are described in detail below (Table 4.8 provides an overview of each trial; additional trial details can be found in Appendix Table D).

Pivotal Trials of Inclisiran

ORION 10 and 11

The ORION 10 and 11 trials were Phase III randomized controlled trials of inclisiran that included patients with established ASCVD or ASCVD risk equivalent (type 2 diabetes, HeFH, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent).[88] The ORION 10 trial was conducted in the United States and included 1,561 adults with ASCVD with LDL-C levels of 70 mg/dl or higher on maximally tolerated statin therapy with or without additional lipid-lowering therapy such as ezetimibe. The ORION-11 trial was conducted in Europe and South Africa and included 1,617 adults with ASCVD and LDL-C ≥ 70 mg/dl or ASCVD risk equivalent and LDL-C ≥ 100 mg/dl on maximally tolerated statin therapy without or without additional lipid-lowering therapy such as ezetimibe. Patients with known New York Heart Association (NYHA) Class IV congestive heart failure, MACE within 3 months, uncontrolled cardiac arrhythmia, active liver disease, and those who received PCSK9-inhibitors within 90 days of were excluded in both trials.

The characteristics of the population enrolled in each trial were similar with respect to gender and race, but the ORION 11 trial included some patients without established ASCVD. In the ORION 10 trial, the study participants had a mean age of 66 years, 31% were female, 86% were white, 89% were on a statin, 1% had HeFH, and 100% had established ASCVD. The baseline LDL-C was 105 mg/dl. In the ORION 11 trial, study participants had a mean age of 65, 28% were female, 98% were white, 95% were on a statin, 1% had HeFH, and 87% had established ASCVD. Thirteen percent of patients in the ORION 11 trial had ASCVD risk equivalent, of whom 65% had diabetes, 15% had HeFH, and 20% had 10-year predicted risk of CV disease of ≥20%. The baseline LDL-C was 106 mg/dl. Baseline demographics and disease characteristics were well-balanced between treatment arms in each trial.

Trial procedures were similar in both trials. The study participants were randomized 1:1 to 300 mg of subcutaneous inclisiran (day 1, day 90, day 270, and day 450) or identical placebo and were followed for 18 months. The co-primary outcomes in each trial were placebo adjusted percentage change in LDL-C from baseline to day 510 and time adjusted percentage change in LDL-C from day 90 to day 540. The key secondary endpoints were absolute change in LDL-C and percentage change from baseline to day 510 in total cholesterol, HDL, non-HDL-C (total cholesterol minus HDL), and levels of PCSK9.

ORION 9

The ORION 9 trial was a Phase III multinational, randomized trial of inclisiran conducted in 482 patients with HeFH in whom LDL-C levels were elevated (LDL-C ≥ 100 mg/dl) despite receiving maximally tolerated statin therapy with or without ezetimibe.[84] Patients with known NYHA Class IV

congestive heart failure, MACE within 3 months, uncontrolled cardiac arrhythmia, active liver disease, and those who received PCSK9-inhibitors within 90 days of the trial were excluded. The study participants had a median age of 56 years, 53% were female, 94% were white, 100% had HeFH, and 27% had established ASCVD. The baseline LDL-C was 153 mg/dl. Baseline characteristics were well-balanced between treatment arms. The participants were randomized 1:1 to 300 mg of subcutaneous inclisiran (day 1, day 90, day 270, and day 450) or identical placebo and followed up for 18 months. The co-primary outcomes were placebo adjusted percentage change in LDL-C from baseline to day 510 and time adjusted percentage change in LDL-C from day 90 to day 540. The key secondary endpoints were absolute change in LDL-C and percentage change from baseline to day 510 in total cholesterol, HDL, non-HDL-C (total cholesterol minus HDL), and levels of PCSK9.

Other Trials of Inclisiran

ORION 1

The ORION 1 trial was a Phase II multicenter trial conducted in 501 patients with ASCVD (with LDL-C ≥ 70 mg/dl) or an ASCVD risk equivalent (with LDL-C ≥ 100 mg/dl).[85] Patients were required to have been receiving stable doses of statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy. Patients with known NYHA Class II, III, or IV congestive heart failure, MACE within 3 months, uncontrolled cardiac arrhythmia, active liver disease, and those who received PCSK9-inhibitors within 90 days of the trial were excluded. The study participants had a median age of 63 years, 36% were female, 95% were white, 6% had HeFH, and 69% had established ASCVD. The baseline LDL-C was 129 mg/dl. There were two study arms, a single dose of inclisiran or placebo or two doses of inclisiran or placebo (day 1 and day 90). Enrolled patients were randomly assigned to one of four study groups within each arm: a single dose of placebo or 200, 300, or 500 mg of inclisiran or two doses of placebo or 100, 200, or 300 mg of inclisiran. Of note, these doses are different from the dose that was evaluated in ORION 9, 10 & 11. We evaluated only two of the groups (two doses of inclisiran 200 mg vs. two doses of placebo) in our review. The primary efficacy outcome was the percentage in LDL-C from baseline to day 180. Data on adverse events were obtained through day 210. This trial was primarily included in our safety evaluation of inclisiran. We did not include it in the meta-analysis of LDL-C reduction because of the different dosing procedures and the shorter follow-up duration (180 days vs. 540 days in the Phase III trials).

Table 4.8. Trials of Inclisiran

Trial (No. of Patients)	Population	Treatment Arms	Key Baseline Characteristics
Pivotal Trials (Phase III trials)			
ORION-9 (N=482)	HeFH and/or untreated LDL-C >190 mg/dL & family history of FH, elevated cholesterol, or early heart disease on maximally tolerated statin therapy ± ezetimibe	1. Inclisiran 300 mg 2. Placebo	Age: 56 years Baseline LDL-C: 153.1 mg/dL Statin intolerance: 9.5% ASCVD: 27.4% HeFH: 100%
ORION-10 (N=1561)	ASCVD on maximally tolerated lipid-lowering therapy	1. Inclisiran 300 mg 2. Placebo	Age: 66 years Baseline LDL-C: 104.6 mg/dL Statin intolerance: 10.8% ASCVD: 100% HeFH: 1.3%
ORION-11 (N=1617)	ASCVD or ASCVD-Risk equivalent on maximally tolerated lipid-lowering therapy	1. Inclisiran 300 mg 2. Placebo	Age: 65 years Baseline LDL-C: 105.5 mg/dL Statin intolerance: 5.3% ASCVD: 87.4% HeFH: 1.7%
Phase II Trial			
ORION-1 (N=501)	ASCVD or ASCVD-Risk equivalent on maximally tolerated lipid-lowering therapy	Single-dose regimen 1. Inclisiran 200 mg 2. Inclisiran 300 mg 3. Inclisiran 500 mg 4. Placebo Two-dose regimen 1. Inclisiran 100 mg 2. Inclisiran 200 mg 3. Inclisiran 300 mg 4. Placebo	Age: 63 years Baseline LDL-C: 128 mg/dL Statin intolerance: 6.4% ASCVD: 69% HeFH: 6%

ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, mg: milligram, mg/dL: milligram per deciliter, N: total number, No.: number

Clinical Benefits of Inclisiran

The section that follows evaluates the efficacy of inclisiran, including the percentage LDL-C lowering effects of inclisiran versus placebo. Available data on clinical outcomes, including total mortality, CV mortality, fatal and non-fatal MI, and stroke are then discussed. Of note, none of the inclisiran trials were designed with clinical events as the primary outcome, and as such, the number of events reported in these trials is low. Based on data availability, we conducted pairwise meta-analyses for the following outcomes: LDL-C, all-cause mortality, CV mortality, MI, stroke, and safety events.

LDL-C and Other Lipid Parameters

Table 4.9 presents the results of the percentage reduction in LDL-C with inclisiran versus placebo. Overall, inclisiran therapy decreased LDL cholesterol levels by 51% from baseline (MD: -50.5, 95% CI: -45.5 to -55.5) compared to placebo (Table 4.9). There was no between-trial heterogeneity for this outcome (I^2=0%, p=0.37). Similarly, the summary estimate for the time adjusted change in LDL-C after day 90 and up to day 540 was 50.5% (95% CI: -46.9 to -54.1). The LDL-C reductions by patient population are presented below.

Inclisiran also improved other lipid parameters compared to placebo. HDL cholesterol increased by 2.6% to 6.1% in the ORION trials. A pooled analysis of phase III trials showed significant reductions in PCSK9 (83%), total cholesterol (32.4%), non-HDL-C (46.4%), apolipoprotein B (41.9%), and lipoprotein(a) (20%) with inclisiran compared with placebo (all p<0.0001).[89]

Table 4.9. Percentage Change in LDL-C from Baseline to Day 510

Trials (Population Enrolled)	Baseline LDL-C	Percent Reduction (95% CI)		
		Placebo Group	Inclisiran Group	Between-Arm Difference
ORION 9 (HeFH)	153 mg/dL	8.2 (4.3, 12.2)	-39.7 (-43.7, -35.7)	-47.9 (-53.5, -42.3)
ORION 10 (ASCVD)	105 mg/dL	1 (NR)	-51.3 (NR)	-52.3 (-55.7, -48.8)
ORION 11 (ASCVD + ASCVD risk equivalent)	106 mg/dL	4 (NR)	-45.8 (NR)	-49.9 (-53.1, -46.6)
Summary Estimate	Random Effect Meta-Analysis of Inclisiran vs. Placebo			-50.5 (-55.5, -45.5); p<0.001; I^2=0.00

95% CI: 95% confidence interval, ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, mg/dL: milligram per deciliter, NR: not reported

LDL-C Lowering by Patient Population

HeFH (primary and secondary prevention): As described above, the ORION 9 trial included 482 patients with HeFH, both with and without established ASCVD.[84] The percentage LDL-C reduction in the HeFH patient population on inclisiran was 47.9% (95% CI: -42.3% to -53.5%) compared to placebo.[84] Similarly, the time adjusted change in LDL-C after day 90 and up to day 540 was 44.3% (95% CI: -48.5 to -40.1). These results are similar to what was observed in the overall population.

Established ASCVD (secondary prevention): All participants enrolled in the ORION 10 trial had established ASCVD, while 88% of participants in the ORION 11 trial had established ASCVD. In the ORION 10 trial, inclisiran therapy decreased LDL-C levels by 52.3% from baseline (95% CI: -48.8 to -55.7) compared to placebo.[88] In the ORION 11 trial, inclisiran decreased LDL-C levels by 53.3% from baseline (95% CI: -50.1 to -56.6) compared to placebo among patients who had established ASVD.[88] This finding was consistent with the finding in the overall population.

Statin intolerant: In the ORION trials, 8.2% of patients were not on statins at baseline (9.5% in ORION 9, 10.8% in ORION 10, 5.3% in ORION 11). These patients were assumed to be statin intolerant because the inclusion criteria for ORION trials stated that patients not on statin must have a history of intolerance to all doses of at least two different statins.[84,88] We conducted a subgroup analysis of the ORION trials based on statin tolerance. The results showed a 47.2% LDL-C reduction with inclisiran treatment compared to placebo in the statin-intolerant group and a 53.9% LDL-C reduction in those on statin. This difference was not statistically significant (Q=1.9, p=0.2).

Clinical Outcomes

There is a 5-year ongoing clinical outcome study evaluating the effect of inclisiran on coronary heart disease, MI, fatal or non-fatal ischemic stroke, and urgent coronary revascularization procedure, with an expected completion date in 2024 (ORION 4 [NCT03705234], n=15,000).[92]

As described above, the included trials (ORION 9, 10 & 11) were designed with LDL-C lowering as the primary outcome. However, all-cause mortality and cardiovascular outcomes were reported as safety events in these trials. The results of the meta-analysis on these outcomes are described below.

Table 4.10. Clinical Outcomes: Meta-Analyses of the ORION Trials

Outcome	RR (95% CI)	I^2	N	No. of Events (%)	
				Inclisiran	Placebo
All-Cause Mortality	0.99 (0.59-1.69)	0%	3,779	27 (1.4)	27 (1.4)
CV Mortality	1.09 (0.54-2.19)	0%	3,655	17 (0.9)	15 (0.8)
Stroke	0.69 (0.12-4.17)	75%	3,655	13 (0.7)	15 (0.8)
Fatal and Non-Fatal MI	0.87 (0.12-6.18)	57%	3,655	33 (1.8)	41 (2.3)
CV Composite*	0.76 (0.60-0.96)	0%	3,655	131 (7.1)	172 (9.4)

95% CI: 95% confidence interval, CV: cardiovascular, I^2: I-squared MI: myocardial infarction, No.: number, RR: risk ratio

*pre-specified exploratory outcome in the ORION trials defined as a cardiovascular basket of non-adjudicated terms, including those classified in the medical dictionary for regulatory activities as CV mortality, and any signs or symptoms of cardiac arrest, non-fatal myocardial infarction, or stroke.

The meta-analysis findings on the safety events reported in ORION 1, 9, 10, and 11 suggest that inclisiran did not reduce the risk of all-cause mortality or the risk of CV mortality. There was also no statistically significant difference in the occurrence of stroke and MI in patients randomized to inclisiran compared with placebo. The ORION trials also assessed a composite CV outcome as a pre-specified exploratory endpoint. The outcome was defined as a basket of non-adjudicated cardiovascular terms, including those classified in the medical dictionary for regulatory activities as CV mortality and any signs or symptoms of cardiac arrest, non-fatal MI, or stroke. The meta-

analysis results showed a lower event rate on the exploratory CV endpoint with inclisiran compared to placebo.

Health-Related Quality of Life

We did not identify any studies that assessed the impact of inclisiran on health-related quality of life.

Harms

The majority of adverse events (AEs) observed in inclisiran trials were mild or moderate.[84,88] AEs with an incidence equal to or greater than 5% in any of the trials are presented in Appendix Table D8-D10. The majority of the AEs occurred with similar incidence in the inclisiran and placebo groups. Table 4.11 presents the meta-analyses results on any AEs, serious AEs, discontinuation due to AEs, and some selected AEs. The most common treatment-related AE occurring with more frequency in the inclisiran group was injection site reaction, which occurred in 5.4% of patients in the inclisiran group versus 0.8% in the placebo group. Serious adverse events occurred in 20% of patients on inclisiran versus 23% of patients on placebo. Serious adverse events reported included all-cause mortality and CV events, details of which have been presented in the section above. Other serious adverse events reported in the ORION 10 and 11 trials included cancer-related deaths and new, worsening, or recurrent cancers, incidences of which were low and were similar among patients in both arms of the trials.

Table 4.11. Safety Events: Meta-Analysis of ORION 1, 9, 10 & 11

Outcome	RR (95% CI)	I^2	N	No. of Events (%)	
				Inclisiran	Placebo
Any AE	1.01 (0.97-1.04)	0%	3,779	1,477 (78)	1,459 (77)
Serious AE	0.88 (0.72-1.06)	40%	3,779	381 (20)	425 (23)
AE Leading to Discontinuation	1.20 (0.77-1.86)	0%	3,779	45 (2.4)	36 (1.9)
Injection Site Reaction	6.38 (2.91-13.9)	41%	3,779	103 (5.4)	15 (0.8)
Myalgia	1.09 (0.67-1.76)	0%	2,220	34 (3.1)	31 (2.8)
Elevated Liver Enzymes: ALT>3x ULN	1.20 (0.48 -3.53)	0%	3,779	10 (0.5)	7 (0.3)
Elevated Liver Enzymes: AST>3x ULN	0.79 (0.31-2.05)	0%	3,779	8 (0.4)	10 (0.5)
Blood Creatinine Level Increase>5x ULN	1.19 (0.66 -2.15)	0%	3,779	24 (1.2)	20 (1.1)

95% CI: 95% confidence interval, AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase, I^2: I-squared, N: total number, No.: number, RR: risk ratio, ULN: upper limit of normal

Heterogeneity and Subgroups

We sought information on the following subgroups:

- Patients with HeFH with and without established ASCVD (primary and secondary prevention)
- Patients with established ASCVD at relatively higher risk (e.g., patients with a recent myocardial infarction)
- Patients with statin intolerance

We found one RCT of inclisiran that was conducted exclusively in patients with HeFH. The results of this trial have been described above (see Clinical Benefit Section). However, the trial did not present data on subgroups of patients with and without established ASCVD (primary vs. secondary prevention). As described above, for bempedoic acid, the trials enrolled very few patients with HeFH, and we found no data on the subgroups of patients with HeFH with and without established ASCVD.

We did not identify any RCTs that assessed the impact of inclisiran or bempedoic acid on subgroups of patients with established ASCVD at relatively higher risk (e.g., patients with a recent MI). As noted above, these patients were excluded from the trials.

Data on the subgroup of patients with statin intolerance has been described above (see Clinical Benefit Section).

Uncertainties and Controversies

For bempedoic acid, data are limited to short-term LDL-lowering. The impact of bempedoic acid on the reduction of cardiovascular events has yet to be demonstrated, as outcomes trials are ongoing, and it is unclear whether bempedoic acid's mechanism of action makes it more likely to have a similar long-term effect on MACE rates as statins. There is also uncertainty about whether the increased risk seen in early trials of hyperuricemia and gout, as well as a risk of tendon rupture, will be important real-world problems. Additionally, there was uncertainty about mortality benefit, as the confidence intervals in our meta-analysis included potential harm. Ongoing follow-up studies are expected to provide additional information on these issues.

Concerns about generalizability to broader patient populations is an additional area of uncertainty for bempedoic acid. There was substantial heterogeneity in the patient populations enrolled in the clinical trials, with two trials (CLEAR Serenity and CLEAR Tranquility) exclusively enrolling statin-intolerant patients, of which a minority had established ASCVD and HeFH. Furthermore, the bempedoic acid/ezetimibe combination was evaluated in only one small RCT that was of fair quality, with differential loss to follow-up in the trial and post-hoc analysis conducted due to irregularities at several trial sites. Finally, there is little evidence on bempedoic acid use among

patients with HeFH or in racially/ethnically diverse populations, as very few patients with these characteristics were enrolled in the studies. Thus, any differential impact of the drug on those populations is currently unknown.

Given the evidence in early trials, some clinical experts are likely to argue that bempedoic acid offers modestly greater relative effectiveness in patients who are not on statins. There is a potentially plausible argument, based on its mechanism of action, that statins "block" the full effectiveness of bempedoic acid. However, others may view this argument with skepticism. In either case it remains unknown whether the higher percent LDL-C reduction seen in clinical trials in the statin-intolerant population is enough to translate into a greater reduction in cardiovascular outcomes compared with other populations. Finally, although the combination bempedoic acid/ezetimibe represents a potential increase in convenience for those needing to take both drugs to reach their LDL-C goal and may increase ezetimibe use in the real-world, findings from one study (Ballantyne 2020) suggest that the effect of bempedoic acid on LDL-C lowering may be less in the presence of ezetimibe than when compared with placebo.

For inclisiran, the degree of LDL-C lowering compared with placebo appears to be substantial and in the same general range as found for PCSK9 inhibitors whose mechanism of action lies along the same biochemical pathway. However, data on inclisiran are limited to short-term biochemical outcomes; long-term data on MACE and safety are lacking. One important controversy is whether the degree of LDL-C lowering with inclisiran will translate into reduction in MACE rates that are more comparable to those seen with statins or with PCSK9 inhibitors, the latter of which have shown variable reduction in MACE rates in their clinical outcomes trials relative to their degree of LDL-C lowering. This may be in part due to short follow-up duration of the trials, and ongoing outcomes studies may shed more light on this issue. Additionally, although inclisiran works along the same pathway as PCSK9-inhibitors, it has a novel mechanism of action that interferes with PCSK9 production, rather than inhibiting PCSK9 action. Thus, whether long-term safety data from PCSK9 inhibitors also can be extrapolated to inclisiran remains to be seen.

Trials of inclisiran enrolled relatively few patients with statin intolerance. Meta-analysis of LDL-C lowering in this patient population showed that statin intolerant patients had a slightly lower percentage of LDL-C lowering than patients on statins, although this difference was not statistically significant and is based on a small number of patients. Further data is needed to explore whether there is a differential effect of inclisiran on patients with statin intolerance.

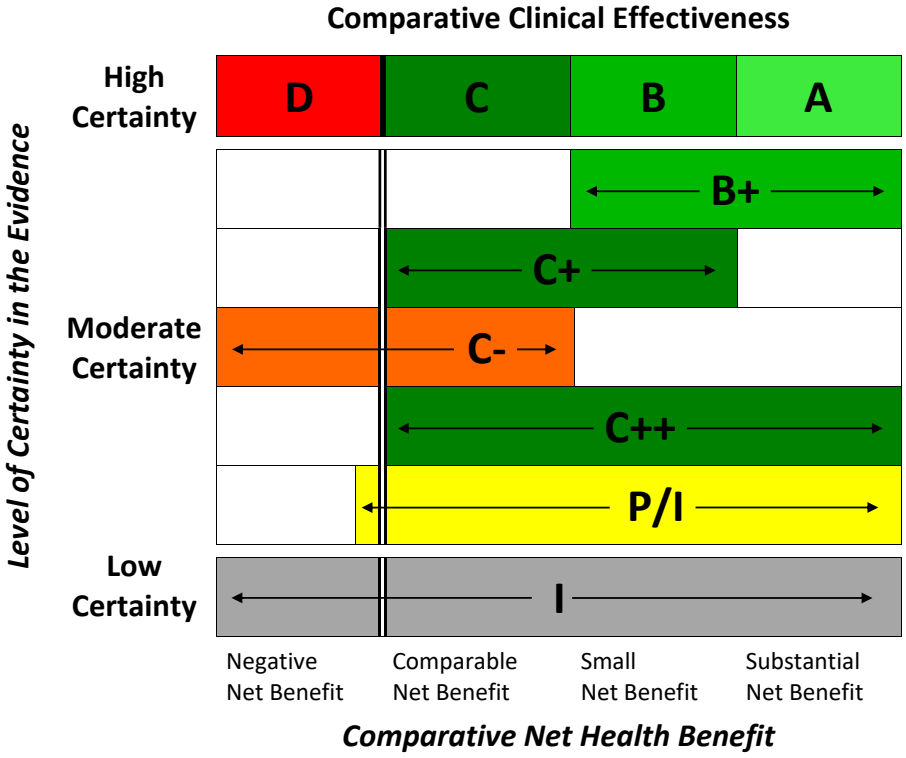
One important difference between inclisiran and PCSK9 inhibitors is the dosing regimen. Inclisiran has a twice-yearly dosing schedule compared with the twice-monthly or monthly dosing schedule of PCSK9-inhibitors. Data are not available, however, on the degree to which fewer injections of lipid-lowering drugs and/or injections delivered in the clinical setting would translate into better real-world adherence and outcomes, although data from other diseases such as osteoporosis suggest

that in some cases, patients may prefer injectable therapy delivered by health care providers, and that there may be adherence benefit from this type of delivery model.[93]

Finally, there is a common and important lack of racial/ethnic diversity in the patients enrolled in the inclisiran trials. As with so many novel agents, the early data on inclisiran does not reflect the diversity of the patient population for which it is intended. Any differences in relative safety or effectiveness across racial and ethnic populations remain unknown.

4.4 Summary and Comment

Figure 4.1. 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 likelihood of a negative net health benefit*
I = "Insufficient" *– Any situation in which the level of certainty in the evidence is low*

Using the ICER Evidence Matrix (Figure 4.1), we assigned evidence ratings independently for inclisiran compared to placebo and bempedoic acid compared with placebo (including bempedoic acid/ezetimibe vs ezetimibe) for patients with HeFH and secondary ASCVD.

Bempedoic Acid versus Placebo (Including Bempedoic Acid/Ezetimibe vs. Ezetimibe)

The available data for bempedoic acid demonstrates the drug's efficacy in lowering LDL-C over twelve weeks. There may be an even larger reduction in LDL-C from treatment with bempedoic acid in patients with statin intolerance. However, longer-term efficacy on LDL-C lowering and reduction in cardiovascular events remain to be determined, and there are limited data on efficacy in the HeFH population. Furthermore, bempedoic acid is associated with moderate to severe adverse events such as gout and tendon rupture, both of which, if demonstrated to occur at clinically significant rates in real-world use, may have significant impacts on patients taking the drug. We also considered the uncertainty around mortality benefit, which require longer-term data to confirm.

Given these safety concerns and the relatively modest degree of LDL-lowering, we judge the evidence provides moderate certainty of a comparable or small net health benefit, with a high certainty of at least a comparable net health benefit ("C+").

Inclisiran versus Placebo

For inclisiran, all available data suggest that it substantially lowers LDL-C compared with placebo, with very few safety concerns. Whether the dosing schedule is advantageous for improving adherence compared with PCSK9 inhibitors is currently unknown; real-world data are required to confirm this benefit. The longer-term trials underway to examine the impact of inclisiran on cardiovascular events and overall mortality are also needed because history has shown that reductions in LDL-C do not always translate into improved overall clinical outcomes (e.g., clofibrate). Nonetheless, inclisiran has a mechanism of action linked closely to the mechanism of PCSK9 inhibitors, which have demonstrated longer-term positive outcomes, and the magnitude of the LDL-C reduction seen with inclisiran, in combination with nearly two years of data showing no significant adverse events, lends confidence to the likelihood that the drug will also produce a long-term net health benefit for most patients. Uncertainty remains regarding the magnitude of that overall benefit, and how it compares to that of PCSK9 inhibitors, but we believe the current evidence offers high certainty of at least a small net health benefit for inclisiran when used for patients who have need of significant reduction in LDL-C despite maximally tolerated oral lipid-lowering therapy. This equates to an ICER evidence rating of "Incremental or Better" (B+).

5. Long-Term Cost Effectiveness

5.1 Overview

Although the comparative clinical effectiveness evaluation encompasses evidence from a broader set of patient populations, the economic model focuses on evaluating the cost effectiveness of inclisiran and of bempedoic acid in combination with ezetimibe in patients with established ASCVD, including subgroup analyses of individuals with HeFH.

The analysis is based upon a state-transition Markov decision analytic model. For bempedoic acid, we estimate the cost effectiveness of the combination pill only, as it is priced the same as bempedoic acid monotherapy. Our analyses of incremental cost effectiveness compare each of these treatments with ezetimibe and maximally tolerated statin therapy. The base-case analysis assumes a health care sector perspective (i.e., focusing on direct medical care costs only), and a lifetime time horizon.

For this evaluation, we developed a *de novo* decision analytic model, informed by key clinical trials, registries, health care claims, and prior relevant economic models. The key input for effectiveness of each drug was the percent reduction in LDL-C achieved among individuals receiving the therapy. The model translated LDL-C reduction into changes in major adverse CV events (MACE, defined in this economic section as a composite of acute coronary syndrome [ACS], stroke, and CV death) and mortality. Furthermore, in this definition, ACS includes MI and hospitalizations for unstable angina. The model assumed that the relationship between LDL-C lowering with each drug and the subsequent reduction in MACE rates would be identical to that observed with statins (based on the meta-analysis performed by the Cholesterol Treatment Trialists' Collaboration). In a sensitivity analysis, we assume that the relationship between LDL-C reduction with inclisiran and MACE rates would be identical to that observed in the completed trials (with 2-3 years of follow-up data) of the currently approved PCSK9 inhibitors evolocumab and alirocumab.[14]

Model outcomes include MACE, total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years gained (evLYGs, which assume that any incremental years of survival would result in perfect health-related quality-of-life), and total costs for each intervention over a lifetime time horizon. Costs and outcomes were discounted at 3% per year.

5.2 Methods

Model Structure

We developed a state-transition Markov model 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 5.1A). Model cycle length is one year.

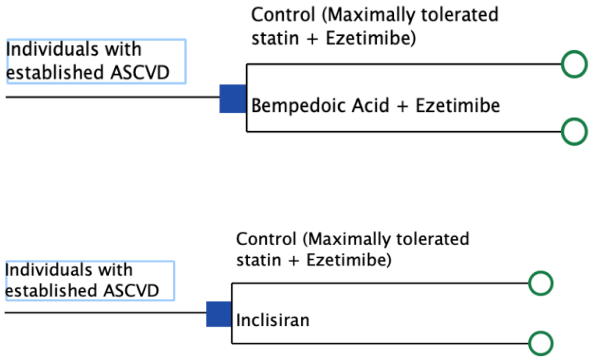
The Markov model contains the following states (Figure 5.1B):

- History of ACS (including MI and unstable angina)
- History of stroke
- History of ACS and stroke
- History of other ASCVD, such as stable angina, prior revascularization without prior ACS, or stroke
- Dead from CV causes
- Dead from non-CV causes

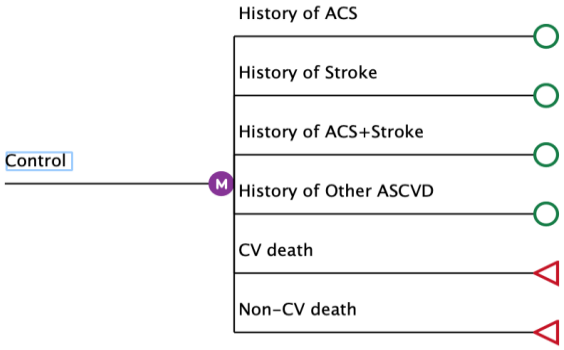
In each annual cycle, a subset of the cohort may experience an acute coronary syndrome (ACS, fatal or non-fatal), a stroke (fatal or non-fatal), or die from other CV or non-CV causes. They may also undergo elective percutaneous or surgical revascularization (Figure 5.1C). The cohort is followed until all members turn 95 years of age or die.

Figure 5.1. Model Framework

A:

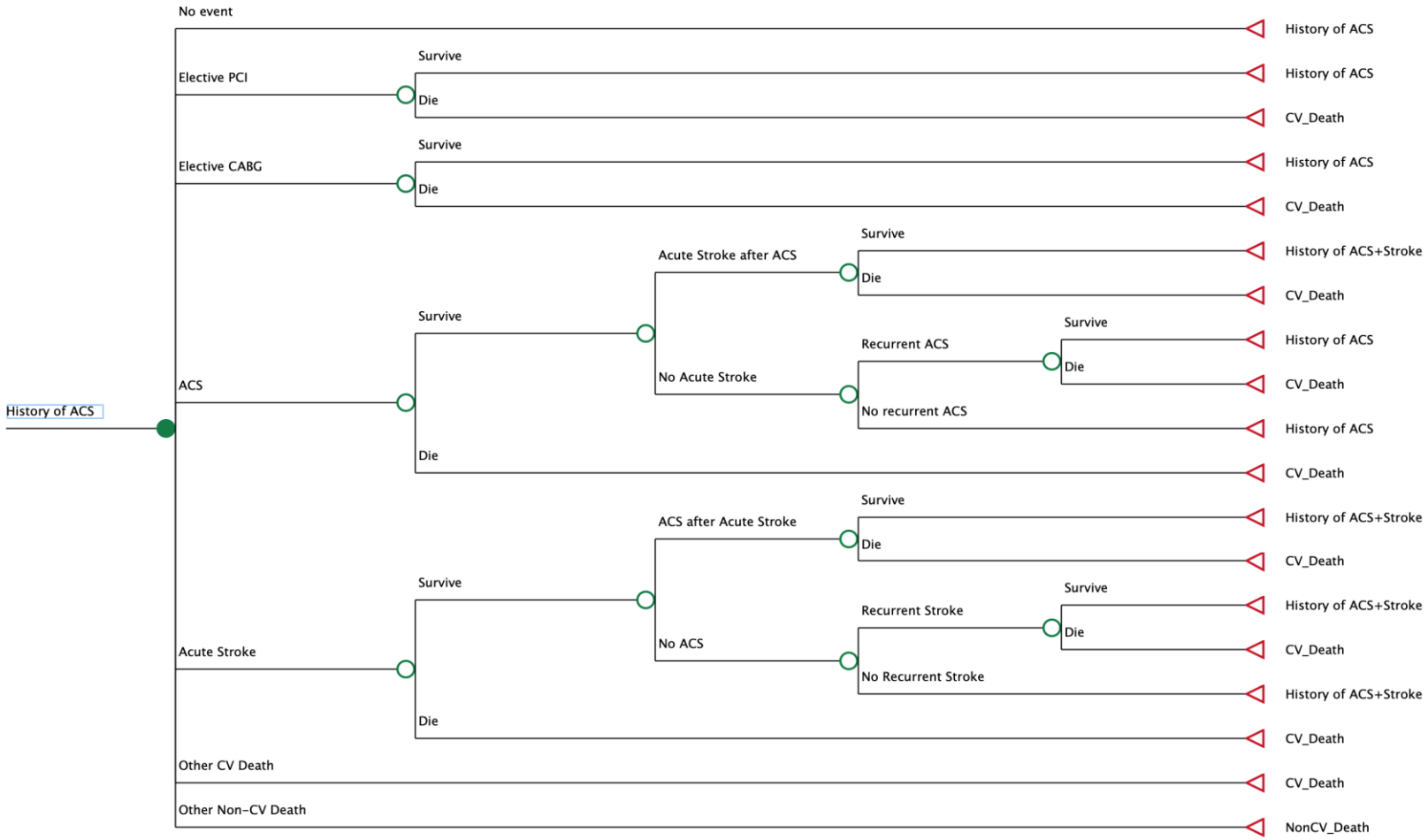


B (Replicated for each arm in A):



ACS: acute coronary syndrome, ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular

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



ACS: acute coronary syndrome, CV: cardiovascular

The model has been developed in TreeAge Pro (TreeAge Software LLC, Williamstown, Massachusetts).

Intervention and Comparator Populations

The population of focus for the economic evaluation is patients with established ASCVD who need additional lipid lowering despite maximally tolerated lipid-lowering therapy (ezetimibe and maximally tolerated statins). Our goal was to examine the cost-effectiveness of these novel lipid-lowering therapies in real world populations, assuming that the efficacy observed in clinical trials would be replicated and sustained in clinical practice. Our simulated cohort was therefore assumed to have demographic and clinical characteristics (such as age or baseline LDL-C level) that would be expected in a real-world population with established ASCVD that would be eligible for each treatment. This also replicates the approach we took for evaluation of evolocumab and alirocumab in our prior work.[6-8]

Key population characteristics were estimated from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey conducted every two years by the National Center for Health Statistics that is designed to produce nationally representative estimates of risk factors and disease prevalence.[13] The NHANES cycles from 2009 to 2016 were pooled to obtain stable estimates. NHANES was approved by the National Center for Health Statistics Research Ethics Board. For the purpose of the NHANES analysis, we evaluated US adults age 35 years or older, with prior ASCVD, and an LDL-C level ≥70mg/dL on statin therapy. The mean age was 66 years, and 39.1% were women. Of these individuals, 4.2% were receiving ezetimibe. We estimated the effect of treating all these individuals with ezetimibe (assuming that the addition of ezetimibe to statin therapy would reduce LDL-C levels by 23.5%, see Table 5.3). An individual whose LDL-C level remained ≥ 70mg/dL after addition of ezetimibe was considered eligible for incremental lipid-lowering therapy. In this manner, we estimated that the mean LDL-C level of the cohort of individuals with established ASCVD who were receiving both statin therapy as well as ezetimibe would be 88.8±1.2 mg/dL.

We used the sampling weights provided by NHANES to account for the complex survey design. Thus, the model cohort was broadly representative of the US population with established ASCVD.

Table 5.1. Baseline Population Characteristics

	Value	Source
Starting Age, years	66	NHANES (2009-2016)
Statin Intolerance, %*	10	Assumed
Baseline LDL-C Level among Patients on Maximally Tolerated Statin and Ezetimibe, mg/dL, mean±SE	88.8±1.2	NHANES (2009-2016)

LDL-C: low-density lipoprotein cholesterol, SE: standard error

*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%.[94]

Heterogeneity and Subgroups

In order to explore higher risk subpopulations who may derive a greater benefit from the therapies, and to facilitate qualitative comparison with subpopulations in prior ICER reviews of the PCSK9 inhibitors, the model explores important "high-risk" subgroups of ASCVD patients:

- **Patients with HeFH and established ASCVD**
  For the purpose of identifying individuals with HeFH in NHANES, we included US adults age 35 years or older, with prior ASCVD, who met one of four criteria, as in our prior work.[95]
  - LDL-C ≥ 150 mg/dL, on statin, + family history of coronary heart disease
  - LDL-C ≥ 190 mg/dL, off statin, + family history of coronary heart disease
  - LDL-C ≥ 200 mg/dL, on statin, no family history of coronary heart disease
  - LDL-C ≥ 250 mg/dL, off statin, no family history of coronary heart disease

  The mean age of this population was 62 years, and as described above, we adjusted the baseline to reflect that all individuals would receive maximally tolerated statin therapy (which would reduce LDL-C levels by 35% among individuals not on statin therapy) and ezetimibe (which would reduce LDL-C levels by an additional 23.6% among individuals on statin therapy, see Table 5.3). Individuals whose LDL-C level remained ≥70mg/dL after treatment with a statin and ezetimibe were considered eligible for incremental lipid-lowering therapy. Using NHANES sampling weights to account for survey design, we estimated that the baseline LDL-C level in patients with HeFH on maximally tolerated statin therapy and ezetimibe would be 139.2±6.0 mg/dL.

- **Patients intolerant to statins**
  We assumed that pre-treatment LDL-C levels are similar in individual's intolerant to statins and those on statin therapy. We therefore estimated the pre-treatment LDL-C levels among statin-intolerant individuals by simulating de-treatment of statin/ezetimibe in NHANES participants receiving these therapies. For this adjustment, we assumed that statin therapy reduces LDL-C levels by 35%, while ezetimibe reduces LDL-C levels by 23.6% in individuals on statins and 18.56% in individuals not on statins (see Table 3 for details). For instance, if a participant was estimated to have an LDL-C of 100 mg/dL on statin therapy, the pre-statin LDL-C was assumed to be 100/(1-0.35)=154 mg/dL. Because all statin-intolerant patients were assumed to receive ezetimibe, the LDL-C was then assumed to be lowered by 18.56% from ezetimibe therapy. In the prior example, the post-ezetimibe LDL-C level in said NHANES participant would be 154*(1-0.1856) ≈ 125 mg/dL. Individuals whose LDL-C remained ≥ 70 mg/dL after ezetimibe treatment were considered eligible for incremental lipid-lowering therapy. This process of de-treatment (to estimate LDL-C levels without any lipid-lowering therapy) followed by complete ezetimibe treatment was used to estimate the mean baseline LDL-C levels in the cohort of statin-intolerant individuals. For individuals not

on statins, we estimated the LDL-C after treatment with ezetimibe. We then estimated a weighted LDL-C level on ezetimibe, of 127.1±1.7 mg/dL.

Next, to estimate the MACE rate in the statin-tolerant population, the baseline MACE rate in the statin-tolerant population was multiplied by the inverse of the rate ratio for MACE with statin therapy. For instance, statins were assumed to reduce LDL-C by 35% and the rate of ACS by 24% per mmol/L reduction in LDL-C.[14] Thus, with statin therapy (had they been able to tolerate it), the mean LDL-C level would have declined from 127.1 mg/dL to 82.6 mg/dL, a decline of 44.5 mg/dL or 1.15 mmol/L. As a result, the ACS rate would have declined to (1-0.24)^1.15 of the prior rate, i.e., to 73% of the pre-statin-therapy rate. Because the statin-intolerant individual is unable to take statin, they experience an ACS rate that is higher than that in the statin-tolerant population (=1/0.73 or 37% higher than in the population receiving statin therapy).

- **Patients with an ACS in the past year**
  Patients who survive an episode of ACS were assumed to be at elevated risk of recurrent ACS during the subsequent year (hazard ratio 3.45 compared with individuals with a similar age and clinical history who were more than one year beyond their last ACS episode; estimated from epidemiological and claims data in the Cardiovascular Disease Policy Model).[96] Although this high-risk subgroup has not been specifically addressed in randomized trials of bempedoic acid or inclisiran, we included them in the model to facilitate comparison with prior studies examining the cost-effectiveness of PCSK9 inhibitors.[95,96]

Treatment Strategies

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, and assuming that ezetimibe is clinically beneficial, the combination pill would be expected to dominate the bempedoic acid pill in any economic evaluation. We therefore chose to evaluate the value-based price of the combination pill rather than bempedoic acid alone in the economic 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.

Thus, all patients in the control arm received ezetimibe and 90% received statin therapy (the remaining 10% were assumed to be statin-intolerant). Of note, our modeling of these new interventions versus treatment that includes ezetimibe does not imply that ezetimibe is now commonly prescribed or that step therapy through ezetimibe should be recommended for all patients. Neither is true. Our modeling choice is based instead on our judgment, informed in discussions with clinical experts and payers, that the added value for money of these new treatments, and thus the suggested value-based prices, should reflect the added clinical value of these treatments beyond that obtained with treatment with statins and ezetimibe, both of which have demonstrated patient benefits and are considered standard of care within clinical guidelines.

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.[97-99]

Key Model Characteristics and Assumptions

Table 5.2. Key Model Assumptions

Assumption	Rationale
The cohort with pre-existing ASCVD includes individuals with a history of ACS, stroke, ACS and stroke, or other forms of ASCVD (e.g., stable angina, prior revascularization without history of ACS, etc.).	Clinical history determines baseline health-related quality-of-life, risk of future events, and health care costs.
Prior clinical history determines future risk of events.	For instance, patients with a history of ACS are at increased risk of recurrent ACS in the first year after an ACS event.
Age-specific risk of death from non-cardiovascular causes is similar to that observed in the general population	Similar to prior models. We varied this in sensitivity analyses, as patients with ASCVD typically have an increased burden of risk factors such as diabetes or chronic kidney disease that may also increase their risk of non-cardiovascular death.
Patients with established ASCVD who statin-intolerant have a higher baseline LDL-C 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-C levels by 35% on average and the risk of MACE by 22% per 1 mmol/L reduction in LDL-C levels (the actual proportion differs by specific type of MACE). [14]
Patients with HeFH with established ASCVD have higher event rates than the general population with established ASCVD.	Lifetime exposure to high levels of LDL-C 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 1.5x 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 achieves the same relative reduction in LDL-C levels in the study cohort as in the trial population.	We assume that relative reductions in LDL-C observed in the clinical trials can be replicated in the real world, though absolute reductions will vary based on baseline LDL-C levels. Of note, we assume that the effect of bempedoic acid is modified by concurrent treatment with statins (i.e., the relative reduction in LDL-C is higher among individuals deemed statin-intolerant and not receiving statins, compared with those receiving statins).
We assumed no interaction between bempedoic acid and ezetimibe for effectiveness.	Bempedoic acid/ezetimibe combination pill is being evaluated against statin + ezetimibe in the economic evaluation, but, since each arm includes ezetimibe, we model effectiveness based on the bempedoic acid vs. placebo meta-analysis presented in the Clinical Effectiveness section.

Lowering LDL-C levels with bempedoic acid/ezetimibe or inclisiran in patients with established ASCVD lowers the rates of future MACE.	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 of future reduction in MACE underpins the regulatory approval of bempedoic acid, and ongoing trials of inclisiran. To estimate the effectiveness of the intervention drugs, we use the long-term effectiveness data available for statins. In a sensitivity analysis, we rely on the mechanistic similarity of inclisiran with evolocumab and alirocumab (monoclonal antibodies that inhibit the PCSK9 enzyme) and assume that the LDL-C reduction due to inclisiran produces the equivalent MACE reduction (per mmol/L reduction in LDL-C) as observed in the available phase III trials of the currently approved PCSK9 inhibitors.
A recurrent ACS or stroke (i.e., an ACS event in a patient with a prior history of one or more ACS events, and a stroke in a patient with one or more prior strokes) is assumed to produce a short-term decrement in quality of life. In the long-term, quality of life returns to that prior to the recurrent event. A different type of MACE – e.g., a stroke in a patient with prior ACS, or an ACS event in a patient with prior stroke, may produce a permanent change in quality-of-life if the subsequent event produces a larger quality-of-life decrement than the prior baseline.	The assumption that recurrent events do not permanently alter the patient's quality-of-life is consistent with prior models and is driven by the scarcity of empirical data on the effect of recurrent events on quality-of-life.

ACS: acute coronary syndrome, ASCVD: atherosclerotic cardiovascular disease, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, MACE: major adverse cardiovascular events, PCSK9: proprotein convertase subtilisin/kexin type 9.

Model Inputs

Clinical Inputs

Transition Probabilities

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

Table 5.3. Key Model Inputs

Parameter	Base-Case Value	Range for Sensitivity Analyses	Distribution if Included in Probabilistic Analysis	Source, Comment
Base-Case Inputs				
Clinical History at the Start of the Model Cohort: Prior ACS Prior stroke Prior ACS and stroke*	 52.7% 27.1% 10.4%	N/A	N/A	Analysis of NHANES (2009-2016)[13]
Rate of ACS, per 100 Person-Years	Varies by age and prior clinical history (patients with prior history of ACS are at increased risk of recurrent ACS, particularly during the first year after ACS)	0.75-1.5x the base case	N/A	Estimated from rates observed in the National Inpatient Sample, calibrated to contemporary clinical trials and prior economic models[95,96,100]
Rate of Elective Coronary Revascularization, per 100 person-years	1.0768	0.8614-1.2922	Log normal	Estimated from the FOURIER trial;[101] range assumes ±20% from the base-case value
Proportion of Elective Revascularization that is Percutaneous (Rather than Surgical)	0.75	0.65-0.85	Beta	Review of contemporary clinical trials, registries[102-104]
Rate of Non-CV Death	Age-specific estimate	0.8x – 1.5x base-case value	N/A	CDC WONDER and US vital statistics;[105] lower end of range assumed; upper end of range derived from analysis of pooled epidemiological cohorts
Baseline Mean LDL-C in the	88.7mg/dL	86.34-91.1	Normal	NHANES (2009-2016)[13]

Control Arm (mg/dL)				
Effectiveness of Interventions				
Relative Reduction in LDL-C Level with Bempedoic Acid, %**	In patients on maximally tolerated statin: 17.7% In patients who are statin intolerant: 24.6%	16.1%-19.3% 17.6%-31.5%	Beta	Randomized trials of bempedoic acid compared with placebo[31,32,72,75,106]
Relative Reduction in LDL-C Level with Inclisiran, %	50.5%	45.4% -55.5%	Beta	Randomized trials of inclisiran[84,86,88,107]
Rate Ratio for ACS, per mmol/L Reduction in LDL-C	0. 76	0.73-0.79	Log normal	Based on published meta-analyses of randomized trials of statin therapy (endpoint: any major coronary event, statin v. control)[14]
Rate Ratio for Stroke, per mmol/L Reduction in LDL-C	0.85	0.80-0.90	Log normal	Based on published meta-analyses of randomized trials of statin therapy (endpoint: any stroke, statin v. control)[14]
Rate Ratio for CV Death, per mmol/L Reduction in LDL-C	0.86	0.82-0.90	Log normal	Based on published meta-analyses of randomized trials of statin therapy (end point: death from vascular causes, statin v. control)[14]
Rate Ratio for Elective Revascularization, per mmol/L Reduction in LDL-C	0.76	0.73-0.80	Log normal	Based on published meta-analyses of randomized trials of statin therapy (endpoint: any coronary revascularization, statin v. control)[14]

Subgroup Analyses				
Rate of MACE in HeFH with established ASCVD, per 100 Person-Years	1.5x general population rate	1-2x general population rate	-	Assumed
Rate of MACE in Patients Enrolled in the First Year After an MI, per 100 Person-Years	3.45x age- and history-matched population	2-4x general population rate	Log normal	Review of contemporary clinical trials and prior models[99,108]

ACS: acute coronary syndrome including unstable angina and myocardial infarction, 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

*The remainder were assumed to have a prior history of other forms of coronary heart disease.

**Bempedoic acid/ezetimibe combination pill is being evaluated against statin + ezetimibe in the economic evaluation. We assume that there is no interaction between bempedoic acid and ezetimibe for effectiveness. Because each arm includes ezetimibe, for estimates of LDL-C lowering, we use data from the bempedoic acid vs. placebo meta-analysis presented in the Clinical Effectiveness section.

Age-specific CV mortality for patients with established ASCVD was estimated from an analysis of pooled epidemiologic cohorts, where age-specific incidence rate of CVD death was calculated as the total number of CVD deaths in each age category divided by the total person-years at risk (unpublished data).[109-116]

Non-CV mortality rate was estimated as follows: we first estimated the age-specific non-CV deaths as a proportion of all-deaths from CDC WONDER (by excluding deaths related to the circulatory system). Then we applied this proportion to the annual probability of all-cause mortality from U.S. lifetables. In effect, we assumed that the age-specific non-CV mortality in this cohort was similar to the general US population.[105]

Health-Related Quality of Life

Estimates of health-related quality of life for each state were based on publicly available literature and were used consistently across treatments evaluated in the model. The base case incorporated health-related quality-of-life estimates from the Global Burden of Disease study as in prior models examining lipid-lowering therapies.

Table 5.4. Health-Related Quality-of-Life Inputs

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	Beta	Moran et al. (2014)[117,118] Murray et al. (2012)[119]
History of ACS	0.9648	0.9513-0.9764	Beta	Moran et al. (2014)[117,118] Murray et al. (2012)[119]
History of Stroke	0.8835	0.8456-0.9133	Beta	Moran et al. (2014)[117,118] Murray et al. (2012)[119]
History of ACS and Stroke	0.8524	0.8083-0.8987	Beta	Moran et al. (2014)[117,118] Murray et al. (2012)[119]
Transient Utility Tolls (Disutilities) for Acute Events				
Percutaneous Coronary Revascularization	0.0096	0.0041-0.0192	Beta	Kazi et al. (2014)[104]
Surgical Revascularization	0.0192	0.0096-0.0396	Beta	Kazi et al. (2014)[104]
ACS	0.0961 for 1 month	0.0621-0.1363 for 1 month	Beta	Moran et al. (2014)[117,118] Murray et al. (2012)[119]
Acute Stroke	0.1375 for 1 month	0.1022-0.1874 for 1 month	Beta	Moran et al. (2014)[117,118] Murray et al. (2012)[119]

ACS: acute coronary syndrome

Adverse Events

The incidence of serious adverse events related to the intervention drugs was estimated from the clinical review and included gout (for bempedoic acid/ezetimibe) and injection site reactions (for inclisiran). These quality-of-life penalties are only applied to the proportion of the cohort that experience the adverse event.

Table 5.5. Adverse Events

Parameter	Incidence per 100 Person-Years	Disutility (Range for Sensitivity Analyses)	Cost	Source
Gout (Bempedoic Acid)	1.0	0.01 for 1 month (0.005-0.02)	$520 ($260-$1040)	Published literature;* range of 0.5x-2x assumed[120,121]
Injection-Site Reactions (Inclisiran)	4.3	0.0003 (0.0000-0.0020) **	0	Prior economic evaluations of injectable therapies[122]

*Based on expert consensus, we assumed that half the patients who developed a gout flare would have one emergency room visit and one outpatient visit, whereas the remainder would have 2 outpatient visits. All patients were assumed to undergo phlebotomy to examine serum uric acid levels and a complete blood count at the initial visit and one serum uric acid level during follow-up.
**Assumes toll of 0.05 (0.00-0.01 in sensitivity analyses) for 2 days (1-7 days in sensitivity analyses).

Drug Utilization

In the base case, the model assumed 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 5.6. 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

Economic Inputs

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

Drug Costs

The annual cost of statin therapy, including associated costs of monitoring, was assumed to be $166.[123] The annual cost of generic ezetimibe was estimated using the median WAC obtained from Micromedex Red Book and was assumed to be $164.[124]

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 is 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 5.7. 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 assume that patients initiating a lipid-lowering treatment will receive lipid panels at the same rate as in the usual care arm. As patients with established ASCVD are likely to have regular clinic visits, we will not assume any additional monitoring costs specific to the interventions.

Adverse Event Costs

Injection-site reactions with inclisiran appear to be mild and are well tolerated. We therefore assumed no costs associated with these localized reactions. Treatment with bempedoic acid appears to increase serum uric acid levels, and, in some patients, can precipitate a flare of gout. In these patients we assumed additional costs related to management of the gout, as above. Although the FDA label of bempedoic acid contains a warning about tendon rupture, we did not model an increased risk of tendon rupture, as there was no difference in tendon rupture compared with placebo in a pooled analysis and a causal relationship between bempedoic acid and tendon rupture has not been established.[74]

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 acute events or revascularization procedures (estimated from the published literature, based on the National Inpatient Sample) (see methods used to estimate these costs have been previously described).[95,99,125]

Table 5.8. Other Costs (2020 US Dollars)

Input Parameter	Base-Case Values	Range for Sensitivity Analyses*	Distribution for Monte Carlo Simulations	Source
Costs of Coronary Heart Disease Care, USD				
Hospitalization for ACS, fatal	$45,477	$36,382-$54,572	Log normal	National Inpatient Sample, Peterson et al. (2015)[100,126]
Hospitalization for ACS, non-fatal	$27,296	$21,837-$32,755	Log normal	National Inpatient Sample, Peterson et al. (2015)[100,126]
CV costs in the first year after an ACS event	$16,800	$13,440-$20,160	Log normal	Medical Expenditure Panel Survey[127]
Chronic CV care costs	Vary by age and clinical condition	±20% of base-case value	Log normal	Medical Expenditure Panel Survey[127]
Cost of elective percutaneous coronary revascularization	$29,900	±20% of base-case value	Log normal	National Inpatient Sample, Peterson et al. (2015)[100,126]
Cost of elective coronary artery bypass graft surgery	$59,300	±20% of base-case value	Log normal	National Inpatient Sample, Peterson et al. (2015)[100,126]
Costs of Stroke Care, USD				
Stroke hospitalization, fatal	$21,284	$17,027-$25,541	Log normal	National Inpatient Sample, Peterson et al. (2015)[100,126]
Stroke hospitalization, non-fatal	$18,824	$15,059-$22,589	Log normal	National Inpatient Sample, Peterson et al. (2015)[100,126]
Post-Stroke Cost, First year after stroke	$18,855	$15,084-$22,626	Log normal	Medical Expenditure Panel Survey[127]
Background health care costs for management of non-CV health conditions	Varies by age and clinical history (i.e., prior ACS, prior stroke, both, or neither)	±20% of base-case value	Log normal	Medical Expenditure Panel Survey[127]

ACS: acute coronary syndrome, CV: cardiovascular, USD: US dollars

*Range of ±20% of the point-estimate used for sensitivity analyses.

For the modified societal perspective, we estimated productivity losses related to MACE, per ICER's reference case. Evidence suggests that workers have workplace absenteeism and short-term disability equal to 13.6 hours per month within the first year after a CV event, but no differences

beyond the first year.[128] We assumed these first-year annualized hours, 163.2 hours, would apply to all individuals in the model who experienced a CV event. The average hourly wage of $29.47 was assumed to apply to all hours no matter the working status of the individual.[129]

Model Outcomes

Model outcomes include MACE (defined as non-fatal ACS, 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. The methodology used to estimate evLYG may be found in Appendix E.

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 assumes a health care sector perspective (i.e., focus on direct medical care costs only). Productivity impacts are considered in a separate analysis as described above. Additionally, we performed a cost-consequence analysis to examine the incremental cost per MACE averted (for each intervention relative to its control).

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were performed by jointly varying all model parameters over 1000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Distributions are described in the input tables above. We performed 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) by systematically altering the price of the intervention drugs to estimate the maximum prices that would correspond to given cost-effectiveness thresholds.

We also performed two scenario analyses. In one scenario analysis, we assumed that the relationship between LDL-C lowering with inclisiran and subsequent reduction of MACE would be

similar to that observed in the outcome's trials of evolocumab and alirocumab (FOURIER and ODYSSEY OUTCOMES). For this analysis, we performed a meta-analysis of the two trials (Table 5.9).

Table 5.9. Inputs for Scenario Analysis: Relationship between LDL-C Lowering with Inclisiran and Risk of Major Adverse Cardiovascular Events based on Meta-Analysis of ODYSSEY Outcomes and FOURIER Clinical Trials

Outcome	Risk Ratio per mmol/L Reduction in LDL-C
MI/ACS	0.8313 (0.7681-0.8996)
Stroke	0.8036 (0.6748-0.9570)
CV death	0.9642 (0.8169-1.1381)
Revascularization (applied to elective revascularization in the model)	0.8749 (0.8150-0.9393)

ACS: acute coronary syndrome, CV: cardiovascular, LDL-C: low-density lipoprotein cholesterol, MI: myocardial infarction

Estimates of the quality of life of individuals living with ASCVD vary substantially based on the data source and method used to measure health-related quality of life. It is also highly dependent on whether co-morbidities that frequently accompany the diagnosis of ASCVD (e.g., diabetes, hypertension, etc.) are also accounted for, or only the quality-of-life penalty associated with ASCVD is included. We chose the latter approach in the base case, relying on inputs from the Global Burden of Disease Study. To explore the effect of uncertainty in the baseline quality of life on our findings, we performed a second scenario analysis in which we incorporated quality-of-life estimates based on an evaluation of the Medical Expenditure Panel Survey (MEPS).[130] Sullivan and Ghushchyan evaluated data from 38,678 adults by pooling the nationally representative MEPS from the years 2000-2002. We used their median unadjusted utilities (estimated from EQ-5D index scores) as the quality of life associated with chronic health states. Although the investigators were unable to estimate the change in quality of life associated with an acute event from the available survey data, our sensitivity analysis assumed that the beta coefficient from the censored least absolute deviations regression (controlling for age, comorbidity, gender, race, ethnicity, income, and education) represents the quality-of-life toll associated with the acute event (applied in the year of the acute event).

Table 5.10. Inputs for Scenario Analysis: Quality-of-Life Inputs Based on the Medical Expenditure Panel Survey

Condition	Base-Case Quality of Life	Source/Comment
Quality of Life Associated with a Chronic Health State*		
Post-ACS	0.7780	Sullivan 2006
Post-Stroke	0.7680	Sullivan 2006
Post-ACS and Stroke	0.7271	Estimated from Sullivan 2006 by applying the disutility of an MI (0.0409) to the post-stroke state
Other ASCVD	0.7940	Sullivan 2006 ("chronic ischemic heart disease")
Decrement in quality of life associated with acute events†		
ACS	0.0409	Sullivan 2006
Stroke	0.0524	Sullivan 2006
PCI	Same as base case	-
CABG	Same as base case	-

*Median unadjusted utility (estimated from EQ-5D index scores).

†Beta coefficient from the censored least absolute deviations regression (controlling for age, comorbidity, gender, race, ethnicity, income, and education).

Model Validation

We used several approaches to validate the model. First, we provided our Model Analysis Plan with preliminary model structure, methods, and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined key data inputs used in the model. For instance, we decided to apply the relationship between LDL-C lowering and health outcomes observed with statin therapy to both the intervention arms in the base case, applying the relationship between LDL-C lowering and PCSK9 inhibitors to the inclisiran arm in a scenario analysis. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will share the model with the relevant manufacturers for external verification around the time of publishing the draft report for this review. Finally, we compared results with other cost-effectiveness models in this therapy area, including models used for prior ICER reports. To the extent possible, outputs from the model were validated against the trial data of the interventions and any relevant observational datasets.

Threshold Analyses

We determined 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).

5.3 Results

Base-Case Results

Over the first five years of the model simulation, the MACE rate in the control arm was 5.06 per 100 person-years, reflecting the high rate of CV events in this population. This included 2.65 fatal and non-fatal ACS, 0.87 fatal and non-fatal strokes, and 2.51 deaths from CV causes per 100 person-years (Tables 5.11 and 5.12). Additional lipid-lowering with bempedoic acid/ezetimibe or inclisiran lowered MACE rates and prolonged survival. This resulted in savings in downstream CV costs, but these savings were offset by an overall increase in total health care spending, including the increased costs of lipid-lowering therapy. Assuming that any improvements in survival were at perfect quality-of-life (per the evLYG approach) improved the cost-effectiveness of the intervention in every subgroup studied.

Table 5.11. Results for the Base Case for Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin*

	Statin + Ezetimibe**	Bempedoic acid + Ezetimibe + Statin**
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07	15.35
Mean survival (discounted)	11.48	11.66
Incremental survival (discounted)	Comparator	0.18
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.57	10.74
Incremental QALYs (discounted)	Comparator	0.17
Lifetime MACE, mean number	1.01	0.95
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.65	2.37
Stroke	0.87	0.79
Death from cardiovascular causes	2.51	2.32
Composite MACE	5.06	4.75
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$185,000	$216,000
Spending on Lipid-Lowering Therapies	$4,000	$35,000
Spending on Cardiovascular Care	$106,000	$105,000
Background Health Care Costs	$75,000	$76,000
Incremental health care costs, 2020 USD (discounted)	Comparator	$31,000
ICER, $ per MACE averted	Comparator	$535,000
ICER, $ per life-year gained	Comparator	$175,000
ICER, $ per QALY gained	Comparator	$186,000
ICER, $ per evLYG	Comparator	$168,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin

†Rates of adverse events are estimated from the first five years of the model run.

**Credible intervals are reported in Appendix Table E2.

Table 5.12. Results for the Base Case for Inclisiran + Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin*

	Statin + Ezetimibe**	Inclisiran + Statin + Ezetimibe**
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07	15.80
Mean survival (discounted)	11.48	11.94
Incremental survival (discounted)	Comparator	0.46
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.57	11.01
Incremental QALYs (discounted)	Comparator	0.44
Lifetime MACE, mean number	1.01	0.86
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.65	1.81
Stroke	0.87	0.70
Death from cardiovascular causes	2.51	2.00
Composite MACE	5.06	4.34
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$185,000	$253,000
Spending on lipid-lowering therapies	$4,000	$73,000
Spending on cardiovascular care	$106,000	$103,000
Background Health Care Costs	$75,000	$78,000
Incremental Health Care Costs, 2020 USD (discounted)	Comparator	$68,000
ICER, $ per MACE averted	Comparator	$451,000
ICER, $ per life-year gained	Comparator	$147,000
ICER, $ per QALY gained	Comparator	$157,000
ICER, $ per evLYG	Comparator	$142,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*Using assumed placeholder price. The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin.

†Rates of adverse events are estimated from the first five years of the model run.

**Credible intervals are reported in Appendix Table E3.

Subgroup Analyses

Heterozygous Familial Hypercholesterolemia and Established ASCVD

Among patients with established ASCVD, MACE rates were higher among patients with HeFH (7.09 per 100 person-years) than in the general population (5.17 per 100 person-years). This meant that patients with HeFH and established ASCVD, who also had higher LDL-C levels at baseline than the general population with ASCVD, derived greater clinical benefits and achieved larger savings from averted events. The two therapies tested were therefore more economically attractive, i.e., had lower ICERs, in the HeFH plus ASCVD population than in the general population with ASCVD.

Table 5.13. Heterozygous Familial Hypercholesterolemia with Established ASCVD: Comparing Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin with Ezetimibe + Maximally Tolerated Statin*

	Statin + Ezetimibe	Bempedoic acid + Ezetimibe + Statin
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.29	15.84
Mean survival (discounted)	11.52	11.85
Incremental survival (discounted)	Comparator	0.33
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.59	10.90
Incremental QALYs (discounted)	Comparator	0.31
Lifetime MACE, mean number	1.33	1.23
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	4.03	3.39
Stroke	1.03	0.94
Death from cardiovascular causes	3.04	2.77
Composite MACE	7.09	6.85
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$207,000	$239,000
Spending on lipid-lowering therapies	$4,000	$36,000
Spending on cardiovascular care	$122,000	$119,000
Background Health Care Costs	$82,000	$84,000
Incremental Health Care costs, 2020 USD (discounted)	Comparator	$32,000
ICER, $ per MACE averted	Comparator	$347,000
ICER, $ per life-year gained	Comparator	$95,000
ICER, $ per QALY gained	Comparator	$101,000
ICER, $ per evLYG	Comparator	$92,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020). Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.
*The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin
†Rates of adverse events are estimated from the first five years of the model run.

Table 5.14. Heterozygous Familial Hypercholesterolemia with Established ASCVD: Comparing Inclisiran + Ezetimibe + Maximally Tolerated Statin with Ezetimibe + Maximally Tolerated Statin*

	Statin + Ezetimibe	Inclisiran + Statin + Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.29	16.79
Mean survival (discounted)	11.52	12.43
Incremental survival (discounted)	Comparator	0.91
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.59	11.45
Incremental QALYs (discounted)	Comparator	0.85
Lifetime MACE, mean number	1.33	1.07
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	4.03	2.31
Stroke	1.03	0.73
Death from cardiovascular causes	3.04	2.25
Composite MACE	7.09	6.11
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$207,000	$279,000
Spending on lipid-lowering therapies	$4,000	$76,000
Spending on cardiovascular care	$122,000	$116,000
Background Health Care Costs	$82,000	$87,000
Incremental Health Care Costs, 2020 USD (discounted)	Comparator	$71,000
ICER, $ per MACE averted	Comparator	$282,000
ICER, $ per life-year gained	Comparator	$78,000
ICER, $ per QALY gained	Comparator	$84,000
ICER, $ per evLYG	Comparator	$76,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*Using assumed placeholder price. The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin.

†Rates of adverse events are estimated from the first five years of the model run.

Statin-Intolerant Individuals with Established ASCVD

Among patients with established ASCVD, statin-intolerant patients had higher LDL-C levels and higher MACE rates at baseline than the general population. As a result, statin-intolerant patients

derived a larger clinical benefit from each of the novel lipid-lowering therapies, which in turn improved their cost effectiveness relative to the control arm. This was particularly true for bempedoic acid/ezetimibe, because bempedoic acid produces a larger relative reduction in LDL-C levels among individuals not on a statin.

Table 5.15. Statin-Intolerant Individuals with Established ASCVD: Comparing Bempedoic Acid/Ezetimibe with Ezetimibe*

	Statin + Ezetimibe	Bempedoic acid + Ezetimibe + Statin
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	14.39	14.92
Mean survival (discounted)	11.05	11.38
Incremental survival (discounted)	Comparator	0.34
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.16	10.49
Incremental QALYs (discounted)	Comparator	0.32
Lifetime MACE, mean number	1.16	1.04
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	3.64	2.91
Stroke	1.08	0.90
Death from cardiovascular causes	2.95	2.67
Composite MACE	6.11	5.79
Direct Health care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$184,000	$214,000
Spending on lipid-lowering therapies	$2,000	$33,000
Spending on cardiovascular care	$110,000	$107,000
Background Health Care Costs	$73,000	$75,000
Incremental health care costs, 2020 USD (discounted)	Comparator	$30,000
ICER, $ per MACE averted	Comparator	$238,000
ICER, $ per life-year gained	Comparator	$86,000
ICER, $ per QALY gained	Comparator	$92,000
ICER, $ per evLYG	Comparator	$83,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin

†Rates of adverse events are estimated from the first five years of the model run.

Table 5.16. Statin-Intolerant Individuals with Established ASCVD: Comparing Inclisiran + Ezetimibe with Ezetimibe*

	Ezetimibe	Inclisiran + Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	14.39	15.46
Mean survival (discounted)	11.05	11.73
Incremental survival (discounted)	Comparator	0.68
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.16	10.80
Incremental QALYs (discounted)	Comparator	0.64
Lifetime MACE, mean number	1.16	0.92
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	3.64	2.33
Stroke	1.08	0.77
Death from cardiovascular causes	2.95	2.28
Composite MACE	6.11	5.28
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$184,000	$250,000
Spending on lipid-lowering therapies	$2,000	$70,000
Spending on cardiovascular care	$110,000	$104,000
Background Health Care Costs	$73,000	$77,000
Incremental health care costs, 2020 USD (discounted)	Comparator	$66,000
ICER, $ per MACE averted	Comparator	$275,000
ICER, $ per life-year gained	Comparator	$97,000
ICER, $ per QALY gained	Comparator	$103,000
ICER, $ per evLYG	Comparator	$93,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*Using assumed placeholder price. The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin.

†Rates of adverse events are estimated from the first five years of the model run.

Patients with a History of Recent ACS

Among patients with established ASCVD, patients who experienced an ACS are at increased risk of recurrent ACS in the following year. This results in a small improvement in the incremental cost

effectiveness of these novel therapies among individuals with a recent ACS history than in the general secondary prevention-eligible population.

Table 5.17. Individuals with Established ASCVD and Recent ACS: Comparing Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin with Ezetimibe + Maximally Tolerated Statin*†

	Statin + Ezetimibe	Bempedoic acid + Ezetimibe + Statin
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.05	15.33
Mean survival (discounted)	11.47	11.65
Incremental survival (discounted)	Comparator	0.18
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.77	10.94
Incremental QALYs (discounted)	Comparator	0.17
Lifetime MACE, mean number	1.13	1.06
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	5.07	4.41
Stroke	1.00	0.88
Death from cardiovascular causes	2.50	2.34
Composite MACE	7.52	7.32
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$187,000	$217,000
Spending on lipid-lowering therapies	$4,000	$35,000
Spending on cardiovascular care	$112,000	$110,000
Background Health Care Costs	$72,000	$73,000
Incremental health care costs, 2020 USD (discounted)	Comparator	$30,000
ICER, $ per MACE averted	Comparator	$416,000
ICER, $ per life-year gained	Comparator	$170,000
ICER, $ per QALY gained	Comparator	$176,000
ICER, $ per evLYG	Comparator	$161,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin

†Rates of adverse events are estimated from the first five years of the model run.

Table 5.18. Individuals with Established ASCVD and Recent ACS: Comparing Inclisiran + Ezetimibe + Maximally Tolerated Statin with Ezetimibe + Maximally Tolerated Statin*†

	Statin + Ezetimibe	Inclisiran + Statin + Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.05	15.79
Mean survival (discounted)	11.47	11.93
Incremental survival (discounted)	Comparator	0.47
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.77	11.22
Incremental QALYs (discounted)	Comparator	0.45
Lifetime MACE, mean number	1.13	0.95
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	5.07	3.37
Stroke	1.00	0.81
Death from cardiovascular causes	2.50	2.02
Composite MACE	7.52	6.92
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$187,000	$254,000
Spending on lipid-lowering therapies	$4,000	$73,000
Spending on cardiovascular care	$112,000	$107,000
Background Health Care Costs	$72,000	$74,000
Incremental Health Care Costs, 2020 USD (discounted)	Comparator	$67,000
ICER, $ per MACE averted	Comparator	$352,000
ICER, $ per life-year gained	Comparator	$143,000
ICER, $ per QALY gained	Comparator	$147,000
ICER, $ per evLYG	Comparator	$135,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*Using assumed placeholder price. The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin.

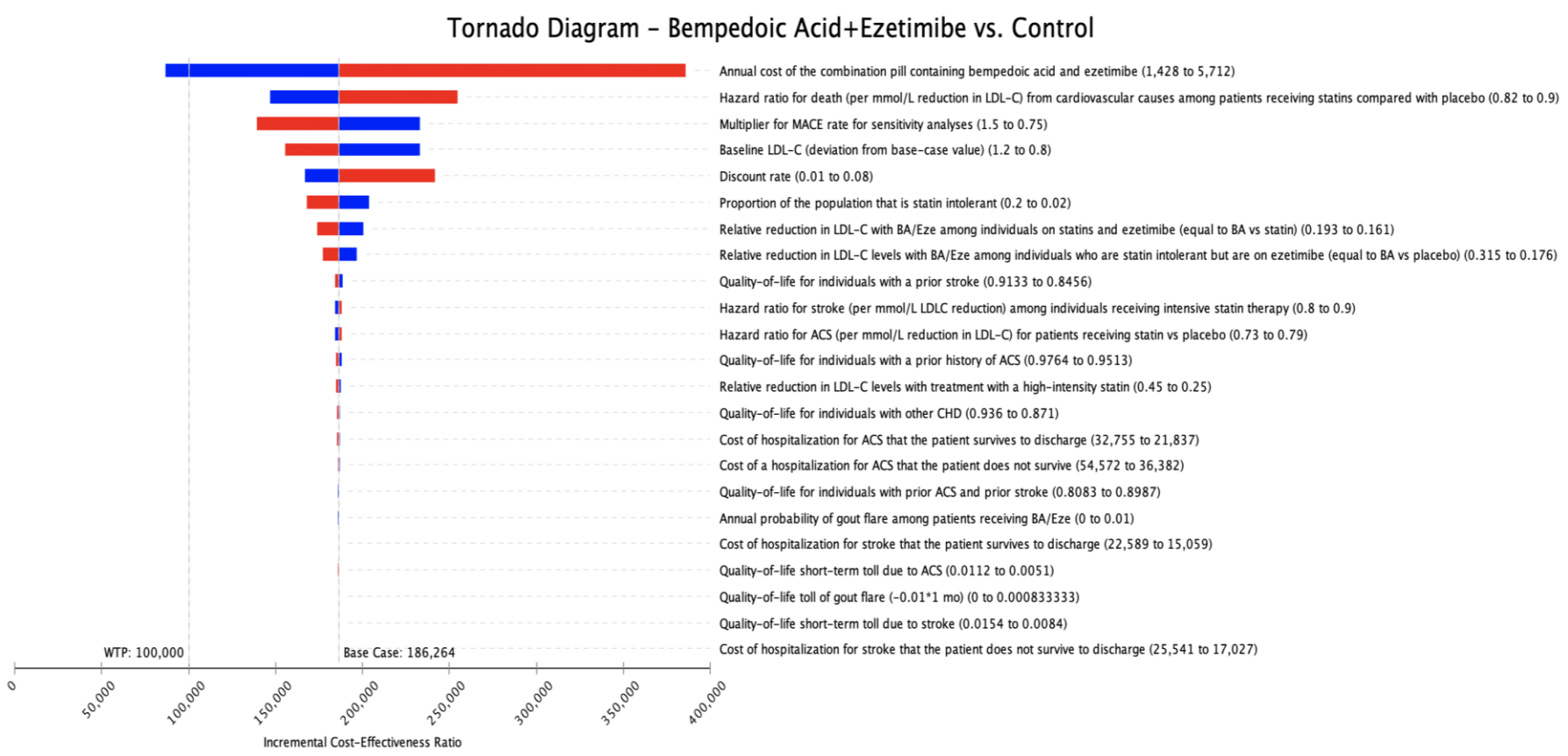
†Rates of adverse events are estimated from the first five years of the model run.

Sensitivity Analysis Results

To examine the effect of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in the incremental cost-effectiveness ratio (in dollars per QALY).

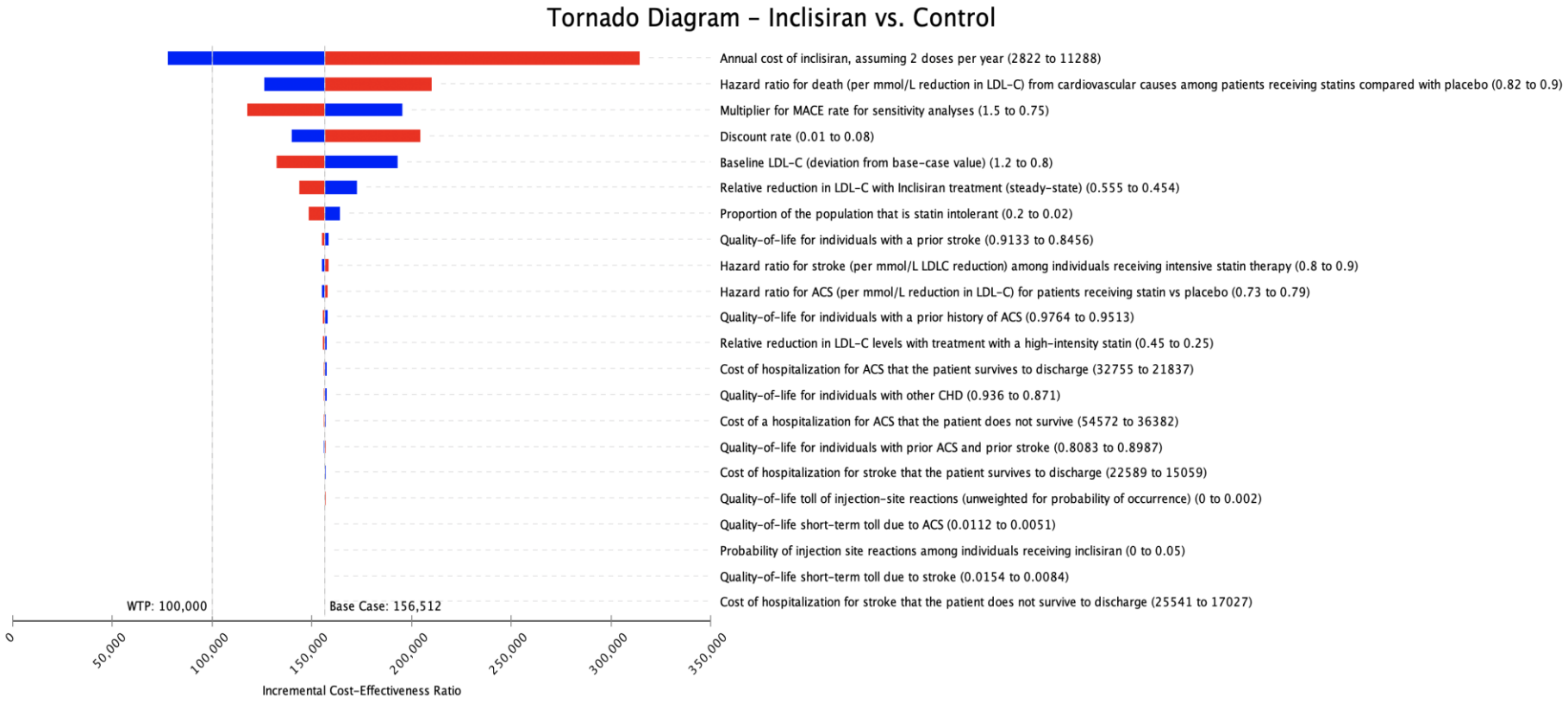
The incremental cost-effectiveness ratio was most sensitive to the cost of the drug, the relationship between LDL-C lowering and reduction in CV death, the rate of MACE, and baseline LDL-C level (which was varied ±20% from base-case value in the figure below). In contrast, it was not very sensitive to assumptions about the magnitude of quality-of-life decrements from prior ASCVD events.

Figure 5.2. Tornado Diagram for One-Way Sensitivity Analyses of Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin vs. Ezetimibe + Maximally Tolerated Statin



As with bempedoic acid/ezetimibe, the incremental cost-effectiveness ratio of inclisiran relative to the control was most sensitive to the cost of the drug, the relationship between LDL-C lowering and reduction in CV death, and the baseline rate of MACE. In contrast, it was not very sensitive to assumptions about the magnitude of quality-of-life decrements from prior ASCVD events.

Figure 5.3. Tornado Diagram for One-Way Sensitivity Analyses of Inclisiran + Ezetimibe + Maximally Tolerated Statin vs. Ezetimibe + Maximally Tolerated Statin



The model assumed that the rate of death from non-cardiovascular causes in the study population would be similar to that observed in the age-matched general population. Because patients with ASCVD have a higher prevalence of diabetes and hypertension than the general population, it is plausible that the rate of non-cardiovascular death (from conditions like diabetes complications or renal failure) may also be higher among the modeled cohort than in the general population. Non-cardiovascular death is a competing risk in the model as it is not altered by lipid-lowering therapy. Assuming a higher rate of non-cardiovascular death therefore makes the use of lipid-lowering therapies less economically attractive. For instance, assuming that the model cohort has a 50% higher rate of non-cardiovascular death than the general population increases the incremental cost-effectiveness ratio of bempedoic acid/ezetimibe compared with usual care from $186,000 per QALY gained to $202,000 per QALY gained, and the incremental cost-effectiveness ratio of inclisiran compared with usual care from $157,000 per QALY gained to $170,000 per QALY gained.

In probabilistic sensitivity analyses, we drew 1,000 samples of key input parameters from pre-specified statistical distributions (with replacement). Each combination was then used in the model to produce 95% credible intervals of key outcomes. We also used the results of these 1,000 simulations to estimate the proportion of simulations in which a particular therapy is the optimal choice at various cost-effectiveness thresholds.

The use of bempedoic acid/ezetimibe was cost-effective relative to the control arm in none of the simulations at a threshold of $100,000 per QALY gained and only 6.3% of the simulations at a threshold of $150,000 per QALY gained.

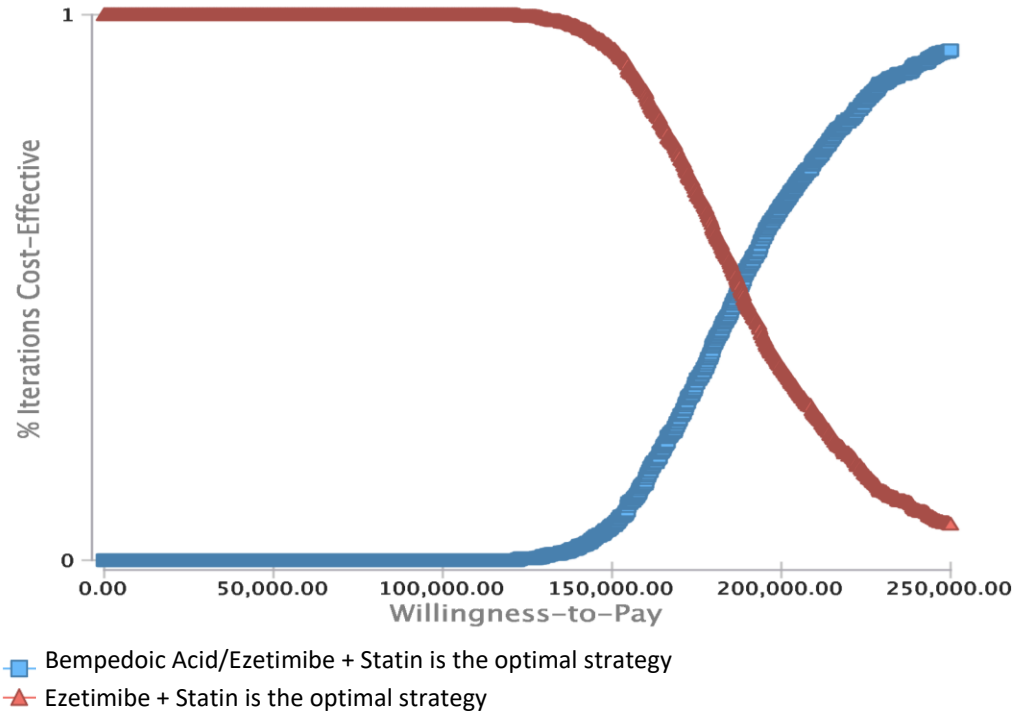
Table 5.19. Probabilistic Sensitivity Analysis Results: Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Bempedoic Acid/Ezetimibe	0%	0%	6.3%	64.8%	93.4%

QALY: quality-adjusted life years

Probabilistic sensitivity analyses can also be presented as acceptability curves, which indicate the proportion of simulations that are cost-effective at varying willingness-to-pay thresholds (Figure 5.4).

Figure 5.4. Acceptability Curve: Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin



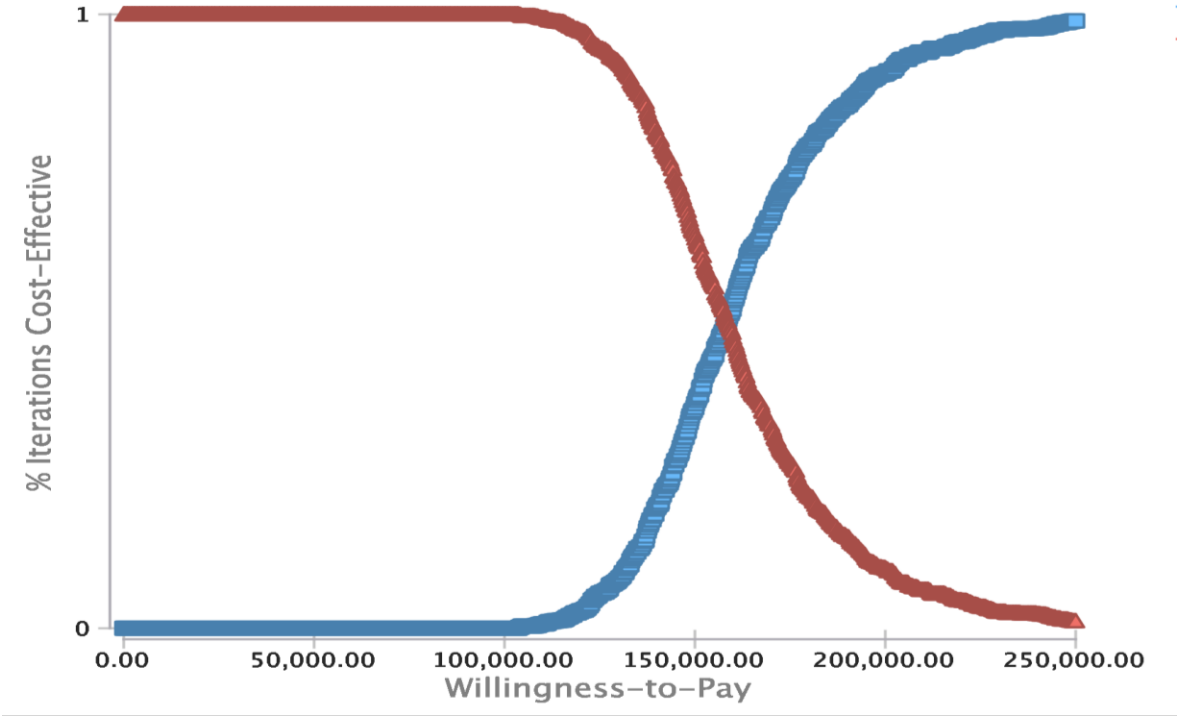
The use of inclisiran was cost-effective relative to the control arm in 0% of the simulations at a threshold of $100,000 per QALY gained and 35.9% of the simulations at a threshold of $150,000 per QALY gained.

Table 5.20. Probabilistic Sensitivity Analysis Results: Inclisiran + Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Inclisiran	0%	0%	35.9%	90.3%	98.9%

QALY: quality-adjusted life years

Figure 5.5. Acceptability Curve: Inclisiran + Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin



Scenario Analyses Results

The long-term effect of the LDL-C reduction with inclisiran on MACE is currently being evaluated in large, randomized trials, but is currently unknown. The base case assumed that the effect of LDL-C lowering with inclisiran would be similar to an equivalent reduction in LDL-C with a statin. However, in a scenario analysis, we assumed that the effect of inclisiran (per mmol/L reduction in LDL-C) would be identical to that observed with currently approved PCSK9 inhibitors evolocumab and alirocumab (as observed in the FOURIER and ODYSSEY Outcomes trials).

Table 5.21. Inclisiran Results using the Relationship Between LDL-C Reduction and MACE Rates from a Meta-analysis of PCSK9 Inhibitors*†

	Statin + Ezetimibe	Inclisiran + Statin + Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07	15.26
Mean survival (discounted)	11.48	11.60
Incremental survival (discounted)	Comparator	0.12
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.57	10.69
Incremental QALYs (discounted)	Comparator	0.12
Lifetime MACE, mean number	1.01	0.90
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.65	2.14
Stroke	0.87	0.67
Death from cardiovascular causes	2.51	2.34
Composite MACE	5.06	4.67
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$185,000	$248,000
Spending on lipid-lowering therapies	$4,000	$71,000
Spending on cardiovascular care	$106,000	$102,000
Background Health Care Costs	$75,000	$76,000
Incremental health Care costs, 2020 USD (discounted)	Comparator	$64,000
ICER, $ per MACE averted	Comparator	$599,000
ICER, $ per life-year gained	Comparator	$529,000
ICER, $ per QALY gained	Comparator	$522,000
ICER, $ per evLYG	Comparator	$464,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*Using assumed placeholder price. The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin.

†Rates of adverse events are estimated from the first five years of the model run.

In a separate scenario analysis, we incorporated the quality-of-life estimates from the Medical Expenditure Panel Survey.[130] Doing so increased the lifetime incremental cost-effectiveness ratio for bempedoic acid/ezetimibe from $186,000 per QALY gained to $221,000 per QALY gained and for

inclisiran from $157,000 per QALY gained to $186,000 per QALY gained. Additional results can be found in Tables 5.22 and 5.23.

Table 5.22. Bempedoic Acid/Ezetimibe Compared with Usual Care in Patients with Established ASCVD: Scenario Analysis Incorporating Quality-of-Life Estimates from the Medical Expenditure Panel Survey

	Statin + Ezetimibe	Bempedoic Acid/Ezetimibe + Statin
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07	15.35
Mean survival (discounted)	11.48	11.66
Incremental survival (discounted)	Comparator	0.18
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	8.81	8.95
Incremental QALYs (discounted)	Comparator	0.14
Lifetime MACE, mean number	1.01	0.95
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.65	2.37
Stroke	0.87	0.79
Death from cardiovascular causes	2.51	2.32
Composite MACE	5.06	4.75
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$185,000	$216,000
Spending on lipid-lowering therapies	$4,000	$35,000
Spending on cardiovascular care	$106,000	$105,000
Background Health Care Costs	$75,000	$76,000
Incremental health care costs, 2020 USD (discounted)	Comparator	$31,000
ICER, $ per MACE averted	Comparator	$530,000
ICER, $ per life-year gained	Comparator	$175,000
ICER, $ per QALY gained	Comparator	$221,000
ICER, $ per evLYG	Comparator	$168,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin

†Rates of adverse events are estimated from the first five years of the model run.

Table 5.23. Inclisiran Compared with Usual Care in Patients with Established ASCVD: Scenario Analysis Incorporating Quality-of-Life Estimates from the Medical Expenditure Panel Survey

	Statin + Ezetimibe	Inclisiran + Statin + Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07	15.80
Mean survival (discounted)	11.48	11.94
Incremental survival (discounted)	Comparator	0.46
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	8.81	9.17
Incremental QALYs (discounted)	Comparator	0.37
Lifetime MACE, mean number	1.01	0.86
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.65	1.81
Stroke	0.87	0.70
Death from cardiovascular causes	2.51	2.00
Composite MACE	5.06	4.34
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$185,000	$253,000
Spending on lipid-lowering therapies	$4,000	$73,000
Spending on cardiovascular care	$106,000	$103,000
Background Health Care Costs	$75,000	$78,000
Incremental health care costs, 2020 USD (discounted)	Comparator	$68,000
ICER, $ per MACE averted	Comparator	$451,000
ICER, $ per life-year gained	Comparator	$147,000
ICER, $ per QALY gained	Comparator	$186,000
ICER, $ per evLYG	Comparator	$142,000

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)

Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*Using assumed placeholder price. The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin.

†Rates of adverse events are estimated from the first five years of the model run.

Modified Societal Perspective

We conducted a scenario analysis by assigning an annualized productivity-related cost of $4,810 to each acute CV event in the model. This scenario did not discriminate against those who were not

working as it assigned the same cost to all individuals who experienced an event. This had a small effect on the incremental cost-effectiveness ratio: it declined from $186,000 to $185,000 per QALY gained for bempedoic acid/ezetimibe and from $157,000 to $155,000 for inclisiran (each compared with its own control, i.e., maximally tolerated statin and ezetimibe).

Threshold Analysis Results

Annual prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and evLYG are listed in Table 5.24 below. See appendix for additional methodological details regarding the evLYG approach. As expected, using an evLYG approach increases the threshold prices for the two lipid-lowering therapies, each compared with its own control.

Table 5.24. Threshold Annual Prices in Individuals with Established ASCVD

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	4,018	2,856	910	1,600	2,300	3,100
evLYG	4,018	2,856	980	1,800	2,600	3,400
Inclisiran						
QALYs Gained	N/A*	5,644**	1,800	3,600	5,400	7,200
evLYG	N/A*	5,644**	2,000	4,000	6,000	7,900

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Heterogeneity and Subgroups

Concordant with the higher baseline risk and lower incremental cost-effectiveness ratios in subgroups of interest (patients with ASCVD who also carry a diagnosis of HeFH or statin-intolerance, or have had a recent ACS), the threshold drug price in each of these populations is higher than in the general population with ASCVD.

Table 5.25. Threshold Annual Prices in Individuals with Established ASCVD and Heterozygous FH

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	4,018	2,856	1,500	2,800	4,100	5,400
evLYG	4,018	2,856	1,600	3,100	4,500	6,000
Inclisiran						
QALYs Gained	N/A*	5,644**	3,400	6,700	10,100	13,500
evLYG	N/A*	5,644**	3,700	7,400	11,100	14,900

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Table 5.26. Threshold Annual Prices in Statin-Intolerant Individuals with Established ASCVD

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	4,018	2,856	1,700	3,100	4,500	5,900
evLYG	4,018	2,856	1,800	3,400	5,000	6,500
Inclisiran						
QALYs Gained	N/A*	5,644**	2,800	5,500	8,200	10,800
evLYG	N/A*	5,644**	3,100	6,100	9,000	12,000

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Table 5.27. Threshold Annual Prices in Individuals with Established ASCD and Recent ACS

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	4,018	2,856	990	1,700	2,500	3,200
evLYG	4,018	2,856	1,100	1,900	2,700	3,500
Inclisiran						
QALYs Gained	N/A*	5,644**	2,000	3,900	5,700	7,600
evLYG	N/A*	5,644**	2,200	4,200	6,200	8,300

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

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. We conducted numerous sensitivity analyses to ensure the model was producing findings consistent with expectations.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

We found no prior economic evaluation of inclisiran or bempedoic acid/ezetimibe from a US health care sector perspective. We compared the MACE rates observed in our model with corresponding rates in contemporary clinical trials.[101,108] We also compared survival in our model with that reported in prior simulation models of secondary prevention. Our model had similar rates of MACE but higher rates of CV death than that observed in cardiology trials (Table 5.28). This is likely because real world populations have higher CV and competing (non-cardiovascular) risk. The MACE rate as estimated from the first five years of the model was 5.06 per 100 patient-years of follow-up, which was concordant with prior work with the Cardiovascular Disease Policy Model (which estimated a MACE rate of 4.2 per 100 person-years in a real-world cohort with established ASCVD and 6.2 per 100 person-years in a higher-risk cohort of patients with a recent history of ACS).[99]

Table 5.28. Comparison of Model Outputs with Event Rates Observed in Contemporary Randomized Trials

	FOURIER (patients with ASCVD)[101]	ODYSSEY OUTCOMES (patients with recent ACS)[108]	Model Output*
ACS (MI + Hospitalization for angina)	0.0292	N/A	0.0261
Nonfatal MI/ACS	0.0204	0.0282	0.0175
Stroke	0.0087	N/A	0.0087
CV death	0.0078	0.0105	0.0248
Non-CV death	0.0064	0.0043	0.0119
Any death	0.0143	0.0150	0.0367
MACE:** Nonfatal ACS + Nonfatal stroke + CV Death	0.0349	N/A	N/A
Nonfatal MI + Nonfatal stroke + CV Death + Revascularization + angina	0.0545	N/A	0.0694
Nonfatal MI + Nonfatal stroke + CV Death + Angina	N/A	0.0420	0.0506
Elective Revascularization	0.0171	N/A	0.0188

ACS: acute coronary syndrome, CV: cardiovascular, MACE: major adverse cardiovascular events, MI: myocardial infarction, N/A: not applicable

*The model grouped MI and unstable angina into ACS, but the majority of ACS events were myocardial infarctions, making the model MACE rates comparable to the corresponding rates reported in the randomized trials.

**MACE definitions vary by study so not all endpoints are available for each study.

Life expectancy in the model population was similar to that observed in a prior model which used survival data from the Centers for Medicare and Medicaid Services to estimate long-term survival after ACS (15.1 undiscounted life years in the current model and 15.2 undiscounted life years in the prior model).[104]

Uncertainty and Controversies

- Long-term trials examining the relationship between LDL-C lowering with bempedoic acid/ezetimibe and inclisiran and MACE are currently ongoing. In the absence of outcomes data, we modeled this relationship based on prior evidence for statin therapy. Our findings are sensitive to assumptions about this relationship, as demonstrated by the substantial discrepancy in the cost-effectiveness of inclisiran depending on whether we use data from statin trials or PCSK9 inhibitor trials to model its effectiveness. Our findings should be updated when outcomes data become available.

- We assumed that patients intolerant of statins achieve a larger LDL-C reduction with the addition of bempedoic acid/ezetimibe than patients receiving statin therapy. This was based on

observed LDL-C reductions in clinical trials. Whether this translates to larger clinical benefits in statin-intolerant patients as assumed in our model merits further investigation.

- Many statin-intolerant patients are able to tolerate a small dose of a statin, particularly if alternative drugs and dosing regimens are patiently explored before patients with statin-associated side-effects are designated intolerant.[131,132] Our economic evaluation assumes that statin-intolerant patients are on no statin therapy, and its findings would therefore overestimate the clinical and economic benefit of lipid-lowering if extrapolated to all patients with statin-associated side effects.

- Patients with HeFH are at increased risk of MACE due to lifelong exposure to high LDL-C levels, however, the extent to which this elevated risk persists in the secondary prevention population is uncertain. In a recent Norwegian study of genetically verified FH, among 232 survivors of an acute MI, risk of recurrent MI was 2.5 times that in matched controls without FH (although it is unclear how many of these individuals had homozygous FH, which places individuals at considerably higher risk of MACE than HeFH).[133] Because the incremental cost-effectiveness of lipid-lowering therapy is sensitive to the absolute rate of MACE in the target population, this should be the subject of future epidemiological research.

- Our model, like prior models examining secondary prevention of ASCVD, does not assume any permanent quality-of-life reduction from recurrent MACE of the same type as prior events. For instance, when a patient with a prior MI has a second MI, there is a short-term decrement in the quality-of-life but then, in the long-term, the quality-of-life returns to that prior to the MI. A stroke in this setting would cause the quality-of-life to decline further. This assumption is driven by the scarcity of empirical data on the effect of recurrent events on quality-of-life. This assumption, however, undervalues the prevention of recurrent events in the secondary prevention population.

- Our model did not incorporate pill- and injection-related disutilities, as prior modeling of lipid-lowering agents has shown that, at a population level, even a modest therapy-related disutility can offset any health gains from lipid-lowering.

5.4 Summary and Comment

The arrival of two new lipid-lowering therapies expands the therapeutic options available to patients with established ASCVD. This is a welcome development, given that this high-risk group of patients continues to experience recurrent CV events despite optimal therapy with statins and ezetimibe. Our findings suggest that bempedoic acid/ezetimibe would produce a modest improvement in outcomes among individuals with established ASCVD who need additional lipid-lowering despite treatment with maximally tolerated statin and ezetimibe but, at current prices, is unlikely to achieve the commonly cited cost-effectiveness threshold of $150,000 per QALY gained

or the $150,000 per evLYG thresholds. On the other hand, the large reduction in LDL-C with twice yearly injections of inclisiran are projected to translate to substantial reductions in MACE. At a placeholder price of $5,644 per year – the current average FSS price of PCSK9 inhibitors – inclisiran approaches a cost-effectiveness threshold of $150,000 per QALY (and falls below $150,000 per evLYG) when compared with background therapy of maximally tolerated statin and ezetimibe. In sensitivity analyses, our findings are most sensitive to the cost of the lipid-lowering therapy, its effect on LDL-C, and the relationship between LDL-C lowering with that drug and reduction in MACE (particularly CV death). In particular, the cost effectiveness of inclisiran would far exceed conventional thresholds (at $522,000 per QALY or $464,000 per evLYG) if its effect on CV outcomes is similar to that observed in the phase III trials of PCSK9 inhibitors (as in the scenario analysis) rather than the effect of statins (as in our base case). Future epidemiological and real-world analyses are needed to ascertain contemporary rates of MACE in individuals with established ASCVD, and ongoing trials will clarify whether LDL-C lowering with either agent results in a concordant reduction in MACE.

Improving the cost-effectiveness of high-cost preventative therapies can be achieved in one of two ways: a) lowering the price of the drug, or b) identifying a high-risk subgroup that may derive a larger absolute benefit with therapy. At current estimated prices net of rebates and other concessions, bempedoic acid/ezetimibe is unlikely to achieve the commonly cited cost-effectiveness thresholds of $100,000-$150,000 per QALY or per evLYG, and a -reduction in net price of 44% and 19% would be necessary for bempedoic acid/ezetimibe to meet conventional cost-effectiveness thresholds of $100,000 per QALY gained and $150,000 per QALY gained, respectively. For inclisiran, the large reduction in LDL-C is projected to translate to substantial reductions in MACE. At a placeholder price of $5,644 per year – the current average FSS price of PCSK9 inhibitors – inclisiran approaches a cost-effectiveness threshold of $150,000 per QALY (and falls slightly below $150,000 per evLYG) when compared with background therapy of maximally tolerated statin and ezetimibe.

We also found that the cost effectiveness of either agent is improved when used exclusively higher risk subgroups such as patients with established ASCVD who are also statin-intolerant or who have HeFH. The incremental cost-effectiveness ratio for bempedoic acid/ezetimibe improves to $101,000 per QALY gained when used among patients with established ASCVD and HeFH, and drops further to $92,000 per QALY gained for patients with established ASCVD who are statin-intolerant. The big improvement in cost effectiveness among statin-intolerant individuals relates to the higher baseline LDL-C level as well as a larger relative reduction in LDL-C compared not on a statin compared with those already receiving a statin. The incremental cost-effectiveness of inclisiran is also improved when the drug is used in subgroups of individuals with established ASCVD who are at higher risk of recurrent events and therefore derive a larger clinical benefit than our base-case cohort. By extension, we would expect the incremental cost-effectiveness ratios to be substantially higher, and the use of these novel therapies less economically attractive than in our base case,

when used in populations at lower risk of CV events compared with our base-case cohort, such as individuals receiving lipid-lowering therapies for the primary prevention of ASCVD. Our findings should therefore not be extrapolated to the primary prevention population without adjustment for baseline risk of CV events. A possible exception may be individuals with HeFH, where lifelong exposure to high LDL-C levels can result in a high risk of MACE even among individuals without established ASCVD.

These findings are consistent with prior cost-effectiveness evaluations of PCSK9 inhibitors, which noted that the cost-effectiveness of these agents was highly dependent on drug price. At their launch price of approximately $14,350, their incremental cost-effectiveness exceeded $400,000 per QALY gained, and their use would not have been cost-effective even in higher-risk subgroups unless accompanied by a substantial price reduction. However, over time, there has been a 60% reduction in the WAC of evolocumab and alirocumab (with even deeper discounts in net price), that may be due in part to systematic cost-effectiveness analyses, market pressure from unapproved or abandoned prescriptions, and other manufacturer decisions to assist patients with high patient out-of-pocket costs. Although inclisiran's administration schedule (twice a year by a health care provider) may be advantageous compared with evolocumab and alirocumab (self-administration twice a month), it remains to be seen how the initial pricing of the drug, potential out-of-pocket costs, physician incentives, patient preference, and long-term health outcomes will affect uptake of inclisiran if approved.

The use of a standardized set of cost-effectiveness thresholds enables us to estimate the optimal price of a novel therapy that based on its value to the health system. Given the disproportionate burden of CV disease among vulnerable populations in the US (defined by race/ethnicity, socioeconomic status, or rurality), it is critical that these higher-risk subgroups have equitable access to effective lipid-lowering novel therapies. This will require that the prices of these therapies reflect the value they bring to patients and the health system, and that payors reduce financial and non-financial barriers to access for appropriately priced therapies. Our hope that this cost-effectiveness analysis, along with the numerous sensitivity analyses presented here, can help enhance access to lipid-lowering therapies for individuals with established ASCVD. At the same time, we have previously shown that initiating statin therapy in all individuals with HeFH or established ASCVD who are not currently taking a statin would result in savings of 12 billion dollars over five years.[97] So, encouraging the uptake of statins in these high-risk populations is a public health priority.

6. Potential Other Benefits and Contextual Considerations

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 would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of inclisiran and bempedoic acid with or without ezetimibe to maximally tolerated lipid-lowering therapy, including statins +/- ezetimibe. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. Categories of Potential Other Benefit and Contextual Considerations

Contextual Considerations	Relevant Information
Acuity of need for treatment of individual patients based on the severity of the condition being treated	These are preventive therapies and although MACE can be fatal or severe there is relatively modest acuity of need for treatment. This is reflected in the relatively small proportional QALY shortfall compared to other conditions (see Table 6.2 in the report).
Magnitude of the lifetime impact on individual patients of the condition being treated	Although early MACE can lead to significant lifetime reductions in quality of life, on average the lifetime impact of ASCVD is relatively low, as reflected in the small absolute QALY shortfalls compared to other conditions (see Table 6.2 in the report). HeFH increases the risk for early MACE and therefore has a higher magnitude of lifetime impact.
Other (as relevant)	N/A

Potential Other Benefits or Disadvantages	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	As recurrent MACE typically occur in older adults, a reduction in MACE estimated from these treatments does not produce striking increases in work productivity – on average -- over the entire population of patients with ASCVD. However, patients with HeFH are at higher risk of events earlier in their life and are more likely to have benefits that would improve their ability to achieve major life goals.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Additional lipid-lowering offered by bempedoic acid and inclisiran for patients with established ASCVD and HeFH may translate into fewer CV events, thereby reducing caregiving needs among family members.
Patients' ability to manage and sustain treatment given the complexity of regimen	Among patients already on ezetimibe, the use of the bempedoic acid/ezetimibe combination pill offers an opportunity to escalate lipid-lowering therapy without increasing the pill-burden. Inclisiran offers twice yearly dosing, potentially administered in a health care setting, compared with twice monthly dosing of PCSK9 inhibitors. This may offer greater convenience

	to patients but whether it will increase long-term adherence is uncertain.
Health inequities	Cardiovascular disease is the most common cause of death across all racial and ethnic groups in the U.S. but is more prevalent among patients from minority communities. For example, deaths from heart disease are higher in Black Americans than in White Americans and other ethnic groups, and heart disease develops at a younger age in African-Americans. Additionally, women and minorities are less likely to be treated with statins and PCSK9 inhibitors and achieve LDL-C goals.
Other (as relevant): New option that may provide particular benefits for patients with statin intolerance	Bempedoic acid represents a new oral option for patients with statin intolerance and may offer a potential benefit to those who do not need the LDL reduction provided by PCSK9 inhibitors or inclisiran or prefer not to have injections. Inclisiran also offers a new treatment option for patients unable to tolerate statins but its role in therapy is likely to be viewed as similar to existing PCSK9 inhibitor drugs.

QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions,[134] and that giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[135,136] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[137] The ethical consequences of using absolute QALY shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[138,139] The proportional QALY shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob

them of a large percentage of their expected remaining lifetime. As with absolute QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For this population of adults with established ASCVD, the absolute shortfall was estimated to be 0.54 QALY, with a proportional shortfall of 0.04, representing a loss of 4% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition. For the population of adults with HeFH and established ASCVD, the absolute shortfall was estimated to be 3.09 QALYs, with a proportional shortfall of 0.18, representing a loss of 18% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition. To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table 6.2), using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[136]

Table 6.2. League Table of Absolute and Proportional QALY Shortfalls for Selected Conditions

	From ICER Reports			From iDBC tool[140]	
Condition	Age	% Male	Total Undiscounted QALYs with Standard of Care	Absolute Shortfall	Proportional Shortfall
Heterozygous FH with ASCVD	62	50	14.1	3.09	0.18
Secondary Prevention for ASCVD	66	61	13.9	0.54	0.04
Cystic Fibrosis	2	52	25.8	42.3	0.62
Secondary Progressive Multiple Sclerosis	48	39	3.0	24.5	0.89
Hemophilia A	18	100	38.6	13.3	0.26
Treatment-Resistant Major Depression	46	33	20.5	8.7	0.30
Moderate-to-Severe Ulcerative Colitis	40	59	27.4	6.2	0.19
BCG-Unresponsive High-Risk NMIBC	72	80	4.94	5.7	0.54

QALY: quality-adjusted life year

7. Health-Benefit Price Benchmarks

The ICER health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLYG gained.

The HBPB range for the annual price for bempedoic acid/ezetimibe in the broad population of eligible patients is from approximately $1,600 to $2,600, representing discounts from WAC of 36% to 60%. The corresponding HBPB range for the annual price of inclisiran in the broad population of eligible patients is from $3,600 to $6,000.

8. Potential Budget Impact

8.1 Overview

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of bempedoic acid with ezetimibe and inclisiran for the adult population with established ASCVD in need of further lipid lowering. We 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 potential 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 reports begun in the years 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.

8.2 Methods

We used 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 were undiscounted and estimated over a five-year time horizon, 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.

For this potential budget impact analysis, we estimated the 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 used 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,[15] 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,[16] we arrived 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.[17] Applying this proportion to the 2020-2024 average population resulted 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 assume that, at

whatever level of uptake is assumed over 5 years, 20% of these patients would initiate treatment in each of the five years, or approximately 2,042,000 patients per year.

For this analysis, we assumed that these drugs will be added on to optimal lipid-lowering therapy (i.e., maximally tolerated statin + ezetimibe). Given that bempedoic acid/ezetimibe is likely to be considered for patients with relatively lower LDL-C as compared to inclisiran, we made a rough assumption that approximately half of the total number of patients with ASCVD needing further lipid lowering would be considered for one drug or the other. Using the estimate from above of approximately 2,042,000 eligible patients per year, this assumption would equate to approximately 1,021,000 patients per year for each drug, at 100% uptake. Please note that we do not assume 100% uptake.

8.3 Results

Figure 8.1 illustrates the cumulative per-patient budget impact calculations for bempedoic acid (in combination with ezetimibe) compared to ezetimibe + maximally tolerated statin, based on the net price of $2,856 per year for bempedoic acid. The average potential budgetary impact for bempedoic acid was an additional per-patient cost of approximately $2,500 in year one, with cumulative costs rising to approximately $11,900 by year five. Net costs per year are presented along with cumulative net costs in Appendix Table E6.

Figure 8.1. Cumulative Net Cost Per Patient Treated with Bempedoic Acid (in Combination with Ezetimibe) at Net Price Over a Five-Year Time Horizon

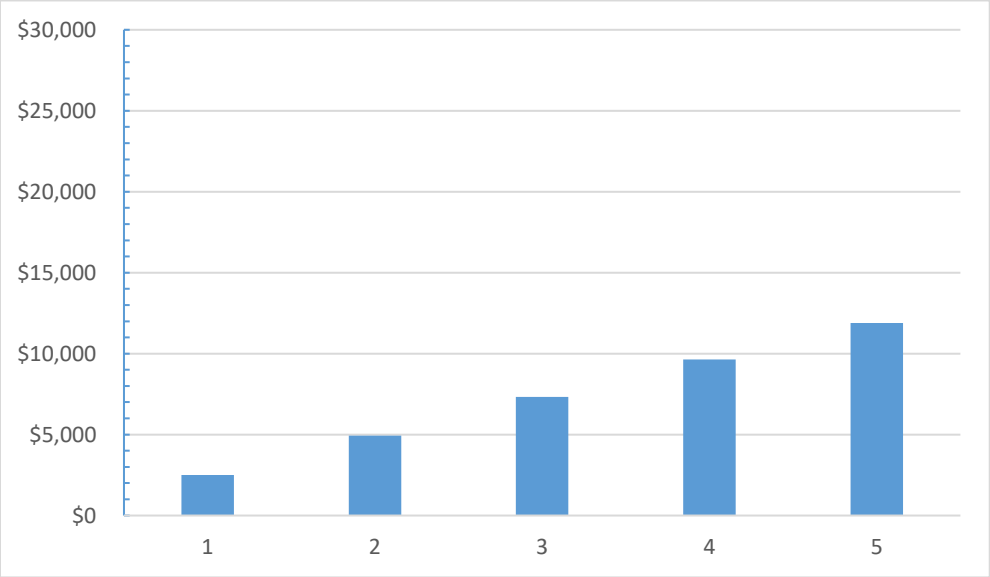


Figure 8.2 illustrates the cumulative per-patient budget impact calculations for inclisiran compared to ezetimibe + maximally tolerated statin, based on the assumed placeholder price of $5,644 per year for inclisiran. The average potential budgetary impact for inclisiran was an additional per-patient cost of approximately $8,000 in year one, with cumulative costs increasing to approximately $27,600 by year five. Detailed net costs per year are presented along with cumulative net costs in Appendix Table E6.

Figure 8.2. Cumulative Net Cost Per Patient Treated with Inclisiran at Assumed Placeholder Price Over a Five-Year Time Horizon

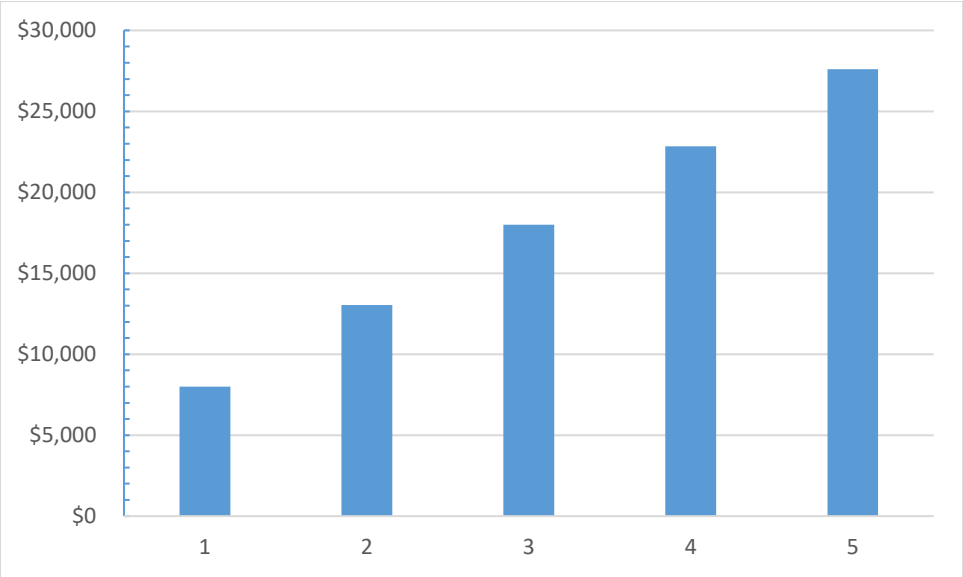


Figure 8.3 illustrates the potential budget impact of treatment of the eligible population with bempedoic acid/ezetimibe) at different prices on the vertical axis, based on the WAC ($4,018 per year), net price ($2,856 per year), and the threshold prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $2,300, $1,600, and $910 per year of treatment, respectively) along a horizontal axis that allows the reader to make assumptions on uptake as a percentage of eligible patients. As shown, only approximately 8% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the WAC, and approximately 11% at the current net price. At threshold prices linked to cost-effectiveness results, an increasing proportion of eligible patients could be treated as prices decrease, up to 49% of eligible patients at the price needed to reach the $50,000 per QALY threshold price.

Figure 8.3. Potential Budgetary Impact of Bempedoic Acid/Ezetimibe in Adults with Established ASCVD in Need of Further Lipid Lowering

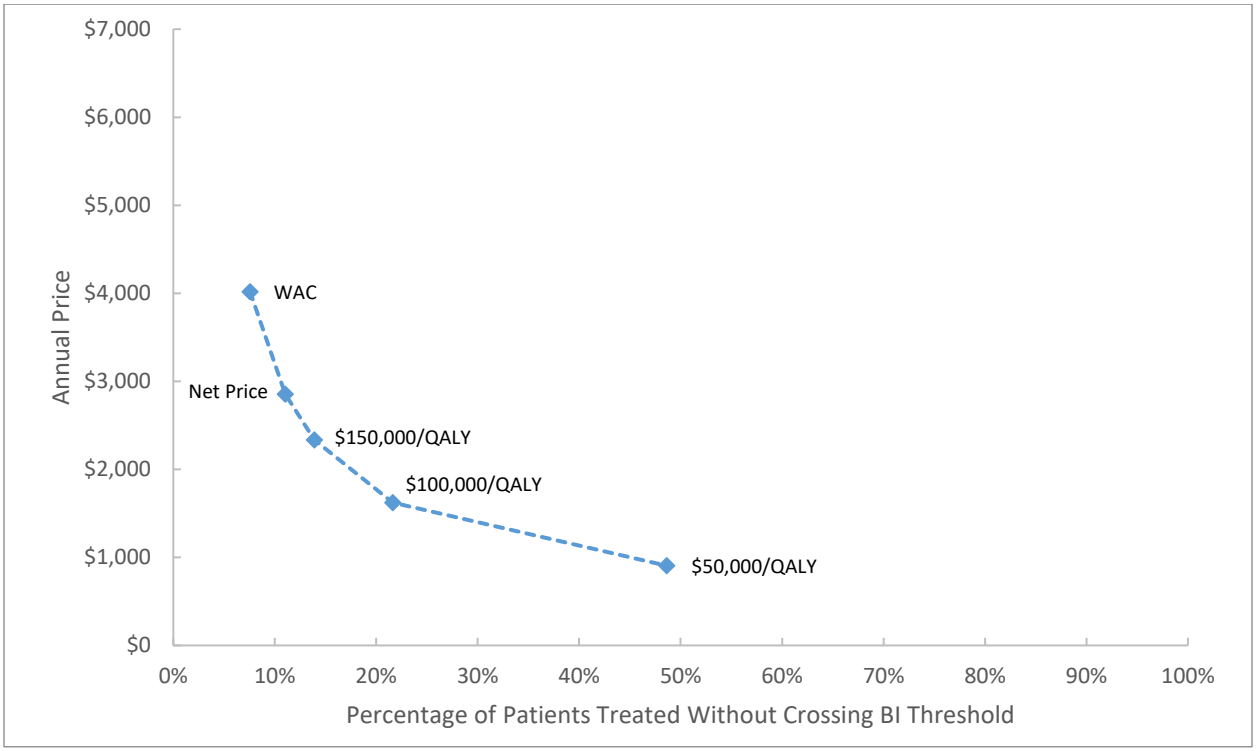
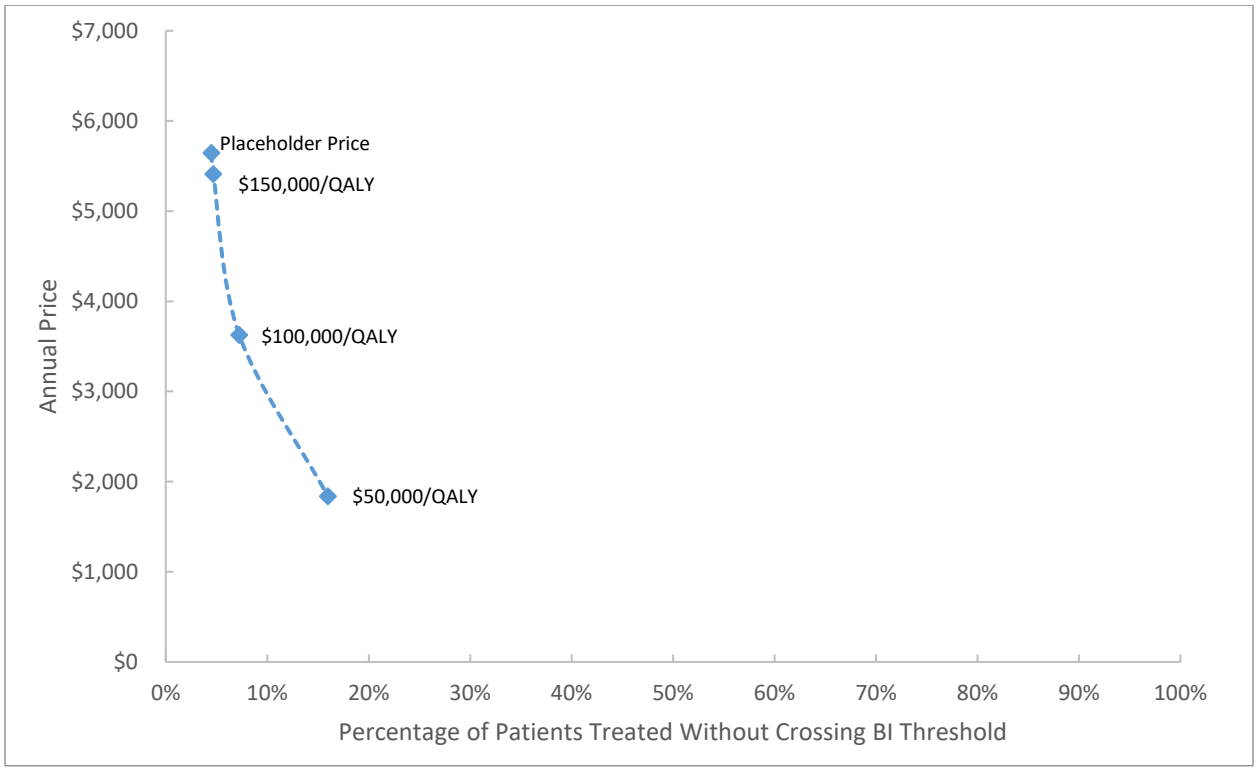


Figure 8.4 illustrates the potential budget impact of treatment with inclisiran, based on the assumed placeholder price ($5,644 per year), and the threshold prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $5,400, $3,600, and $1,800 per year, respectively) compared to ezetimibe + maximally tolerated statin. Given that the placeholder price we are using for inclisiran is higher than the net price of bempedoic acid, the potential short-term budget impact of inclisiran is more substantial. Approximately 4.5% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the assumed placeholder price. A similar proportion, approximately 4.7% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price. At the far lower $50,000 per QALY threshold price, approximately 16% of the eligible population (estimated at 1,021,000) could be treated without exceeding the ICER budget impact threshold.

Figure 8.4. Potential Budgetary Impact of Inclisiran in Adults with Established ASCVD in Need of Further Lipid Lowering



9. Summary of the Votes and Considerations for Policy

9.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the February 5th, meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of bempedoic acid with or without ezetimibe and inclisiran for patients with HeFH and for secondary prevention of ASCVD. Following the evidence presentation and public comments (public comments from the meeting can be accessed here), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to bempedoic acid with or without ezetimibe and inclisiran. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 9.1 below):

- Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

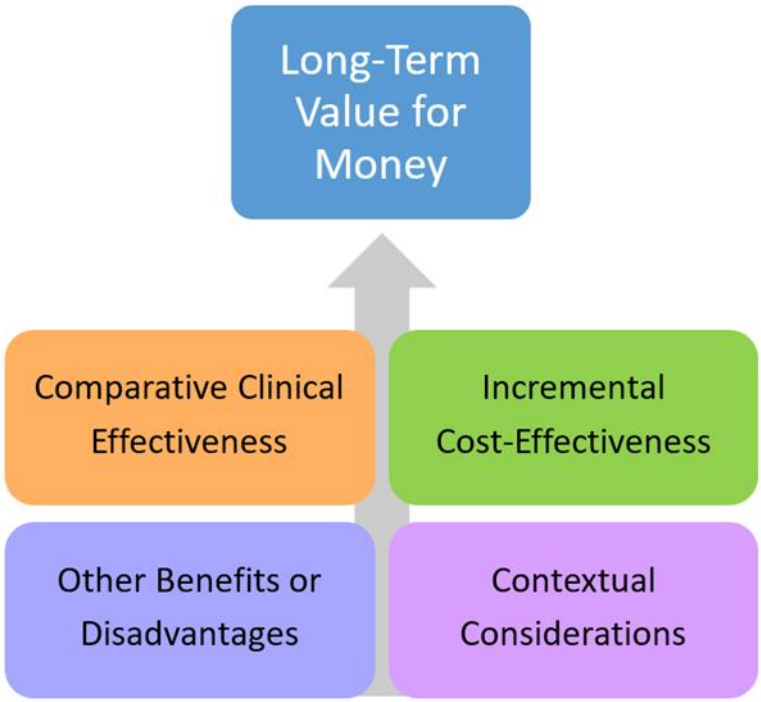
- Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

- Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

- Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 9.1. Conceptual Structure of Long-Term Value for Money



9.2 Voting Results

Clinical Evidence

Patient population for questions 1 and 2: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated oral lipid-lowering therapy.

1. Given today's evidence, is the evidence adequate to demonstrate that the net health benefit of adding **bempedoic acid alone** to usual care is superior to that provided by usual care alone?

Yes: 5 votes	***No: 9 votes***

One council member who voted "No" noted that the clinical trials for bempedoic acid had small sample sizes, with only one trial consisting of over 1,000 patients, and that there is a risk of adverse events. A council member who voted "Yes" said that even though the evidence may not demonstrate a large benefit over usual care alone, there is enough

evidence to demonstrate at least a small benefit in LDL lowering. Clinical experts also discussed that clinical outcomes trials for bempedoic acid are ongoing, and those results will be necessary to determine that magnitude of benefit.

a. Is the evidence adequate to demonstrate the net health benefit of adding **bempedoic acid alone** to usual care is superior to that provide by usual care alone in patients who have statin-associated side effects ("statin intolerant")?

Yes: 12 votes	No: 2 votes

Discussion noted that there was a higher relative reduction in LDL-C demonstrated in the statin intolerant population in the clinical trials, with no significant difference in harms.

b. Is the evidence adequate to demonstrate the net health benefit of adding **bempedoic acid alone** to usual care is superior to that provide by usual care alone in patients with HeFH?

Yes: 11 votes	No: 3 votes

Discussion noted that HeFH patients are more likely to start at a higher baseline LDL-C level, so they may achieve a larger absolute reduction in LDL-C with the addition of bempedoic acid.

2. With the evidence available today, is the evidence adequate to demonstrate that the net health benefit of adding **inclisiran** to usual care is superior to that provided by usual care alone?

Yes: 14 votes	No: 0 votes

Though outcomes trials are ongoing, Council members judged that because the mechanism of action of inclisiran is similar to that of PCSK9s, the LDL lowering seen with inclisiran will likely translate to positive clinical outcomes. In addition, it was noted that inclisiran has a favorable safety profile.

Contextual Considerations and Potential Other Benefits or Disadvantages

Question: When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* new effective treatment for the SECONDARY PREVENTION OF ASCVD, on the basis of the following contextual considerations:

1= Very low priority; 2 = Low priority; 3 = Average priority; 4 = High priority; 5= Very high priority

1. Acuity of need for treatment of individual patients based on the severity of the condition being treated

Very Low Priority	Low Priority	Average Priority	High Priority	Very High Priority
0 votes	5 votes	7 votes	2 votes	0 votes

Patient and clinical experts noted that there is wide variation in the degree of immediate risk among patients with established ASCVD, and that HeFH patients within the ASCVD population are at very high risk of cardiovascular events, even when asymptomatic. Though the acuity of need for preventative treatments may generally be considered low, the presence of high-risk subpopulations may have led most Council members to vote "Average" or "High" priority.

2. Magnitude of the lifetime impact on individual patients of the condition being treated

Very Low Priority	Low Priority	Average Priority	High Priority	Very High Priority
0 votes	2 votes	5 votes	5 votes	2 votes

Most CEPAC members voted that any new treatment for secondary prevention of ASCVD should be given average or high priority when judging overall long-term value for money. Though ASCVD generally occurs later in life, the subgroup of patients with HeFH are often diagnosed at a young age and may experience a higher lifetime impact of the disease.

Question: What are the relative effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcomes that inform judgment of the overall long-term value for money of BEMPEDOIC ACID?

1= Major negative effect; 2 = Minor negative effect; 3 = No difference; 4 = Minor positive effect; 5 = Major positive effect

3. Patients' ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 votes	5 votes	9 votes	0 votes

The majority of CEPAC members voted that the addition of bempedoic acid to maximally tolerated oral lipid-lowering therapy will have a minor positive effect on patients' ability to achieve major life goals. It was noted that because ASCVD is a chronic condition, any effective treatment will impact a patient's ability to achieve goals related to education, work, or family life. In addition, one patient expert emphasized that the addition of a non-statin treatment will greatly impact the lives of patients who cannot tolerate statins.

4. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 votes	3 votes	11 votes	0 votes

The majority of the Council voted that treatment with bempedoic acid would have a minor positive effect on caregivers' quality of life, by a slightly greater margin than for the previous question. One patient expert stated that she expected the quality-of-life impact to be similar for patients and caregivers, because their lives are closely linked. One CEPAC member added that because patients in the clinical trials were primarily older adults, she was concerned about the impact on their adult children who may need to sacrifice work, education, or childcare to care for their parents.

5. The problem of health inequity

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
1 vote	4 votes	9 votes	0 votes	0 votes

The majority of CEPAC members voted that addition of bempedoic acid to usual care will have no impact on the problem on health inequity. One clinical expert argued that any new drug will have lower uptake among people who are uninsured or on Medicaid and has the potential to exacerbate health inequities.

6. Other (as relevant): New treatment option for patients with statin intolerance

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 votes	1 vote	9 votes	4 votes

The majority of the CEPAC judged that because bempedoic acid presents a new treatment option for patients with statin intolerance, this should have a minor positive effect on its long-term value for money. One clinical expert previously discussed how any new non-statin treatment option would have the potential for a large impact on quality of life for patients with statin intolerance.

Question: What are the relative effects of INCLISIRAN versus PCSK9 INHIBITORS on the following outcomes that inform judgment of the overall long-term value for money of INCLISIRAN?

1= Major negative effect; 2 = Minor negative effect; 3 = No difference; 4 = Minor positive effect; 5 = Major positive effect

7. Patients' ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	1 vote	10 votes	2 votes	0 votes

The majority of CEPAC members judged that inclisiran will have no difference on patients' ability to achieve major life goals, in comparison to PCSK9 inhibitors. One patient argued noted that it is too early to compare inclisiran with PCSK9 inhibitors because inclisiran is not yet available, and there are no available data on clinical outcomes or adherence.

8. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	1 vote	12 votes	1 vote	0 votes

The majority of the CEPAC voted that inclisiran will have no difference on caregivers' quality of life, compared to PCSK9 inhibitors, for similar reasons as discussed above.

9. Health inequities

Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
0 votes	0 vote	13 votes	1 vote	0 votes

One clinical expert noted that if a treatment is woven into usual practice, it has the potential to reduce health disparities. Because inclisiran is intended to be administered during a patient's regular twice-yearly visit to their clinician, it could have the potential to narrow disparities. However, it could also widen disparities because patients of color may have more trouble getting to their clinician's office for treatment. For these conflicting reasons, the majority of CEPAC members voted "No Difference."

Long-Term Value for Money

Patient population for question 1: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

1. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **bempedoic acid with ezetimibe** to usual care versus usual care with **ezetimibe**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
13 votes	1 vote	0 votes

The incremental cost-effectiveness ratio for bempedoic acid with ezetimibe was above the commonly cited threshold of $150,000 per QALY gained and per evLYG in the overall population of patients with established ASCVD. Considering the cost-effectiveness results and the previous votes questioning whether the evidence is adequate to demonstrate a net health benefit of bempedoic acid in the overall population, a large majority of the CEPAC voted that adding bempedoic acid with ezetimibe to usual care represents low long-term value for money compared to usual care with ezetimibe.

Patient population for question 2: All adult patients with established ASCVD – with or without HeFH – who have elevated LDL-C levels and have statin-associated side effects ("statin intolerant").

2. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **bempedoic acid with ezetimibe** to usual care versus usual care with **ezetimibe.**

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
0 votes	12 votes	2 votes

Because statin-intolerant patients generally have a higher baseline LDL and achieve a greater relative risk reduction with bempedoic acid with ezetimibe, the incremental cost-effectiveness ratio in this group reduces to $92,000 per QALY gained, or $83,000 per evLYG. For this reason, the majority of the Council judged that at current pricing, adding bempedoic acid with ezetimibe to usual care represents intermediate long-term value for money when compared to usual care with ezetimibe.

Patient population for question 3: All adult patients with HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

3. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **bempedoic acid with ezetimibe** to usual care versus usual care with **ezetimibe.**

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
1 vote	13 votes	0 votes

The economic analyses produced an incremental cost-effectiveness ratio for bempedoic acid with ezetimibe of $101,000 per QALY and $92,000 per evLYG. Patients with HeFH generally have a higher baseline LDL and higher lifetime exposure to elevated LDL levels, so the majority of Council members voted that adding bempedoic acid to usual care represents intermediate long-term value for money when compared to treatment with usual care alone in this population.

Patient population for question 4: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

4. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **inclisiran** to usual care versus **usual care alone**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
10 votes	4 votes	0 votes

The incremental cost-effectiveness ratio for inclisiran added to usual care compared to usual care alone is $157,000 per QALY and $142,000 per evLYG. The average effectiveness of inclisiran was about 5.5 months of life. Based on these results, the clinical evidence, and potential other benefits and contextual considerations, the majority of the Council voted that at the assumed placeholder price for inclisiran, inclisiran added to usual care represents low long-term value for money when compared to usual care alone in the general ASCVD population.

Patient population for question 5: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels and have statin-associated side effects ("statin intolerant").

5. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **inclisiran** to usual care versus **usual care alone**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
1 vote	13 votes	0 votes

In the statin intolerant population, the incremental cost-effectiveness ratio for inclisiran improves to $103,000 per QALY and $93,000 per evLYG. For this reason, the majority of the Council voted that adding inclisiran to usual care represents intermediate long-term value for money compared with usual care alone in this population.

Patient population for question 6: All adult patients with HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.

6. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money at current pricing of adding **inclisiran** to usual care versus **usual care alone**?

Low Long-Term Value for Money	Intermediate Long-Term Value for Money	High Long-Term Value for Money
0 votes	10 votes	3 votes

The incremental cost-effectiveness ratio for inclisiran improved to $84,000 per QALY or $76,000 per evLYG in the HeFH population. For this reason, the majority of Council members voted that at the assumed placeholder price, adding inclisiran to usual care represents intermediate long-term value for money compared with usual care alone, with three Council members voting high long-term value for money.

9.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on bempedoic acid with or without ezetimibe and inclisiran to policy and practice. The policy roundtable members included two patient advocacy representatives, two clinical experts, two payer representatives, and two representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 9.1 Policy Roundtable Members

Policy Roundtable Member	Title and Affiliation
Cat Davis Ahmed, MBA	Vice President, Policy and Outreach, FH Foundation
Andrea Baer, MS, BCPA	Executive Director, The Mended Hearts, Inc.
Dave Busch, MS	Vice President Pharmacy, HealthPartners
Keith C. Ferdinand, MD	Gerald S. Berenson Endowed Chair in Preventive Cardiology and Professor of Medicine, John W. Deming Department of Medicine, Tulane School of Medicine
Michael Louie, MD, MPH, MSc	Head of Clinical Development, Medical Affairs, and Pharmacovigilance, Esperion Therapeutics
David Platt, MD	Vice President and Head, Cardiovascular, Renal & Metabolism Medical Unit, US Clinical Development and Medical Affairs, Novartis Pharmaceuticals
Erik Schindler, PharmD, BCPS	Director, Emerging Therapeutics and Outcome-Based Contracting, UnitedHealthcare Pharmacy
Salim S. Virani, MD, PhD	Professor in Cardiology and Cardiovascular Research Sections, Baylor College of Medicine

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

All stakeholders should ensure that the introduction of new therapies for high cholesterol do not exacerbate existing health inequities and should strive to decrease inequity in the health care system by decreasing cost and access barriers for patients to access effective therapies.

In particular:

- Manufacturers should price new therapies according to value to lower initial barriers to accessing therapy. Race and ethnicity have been shown to be a significant predictor of medication underuse, and disparities exist even with health insurance, in part due to drug costs. Pricing in alignment with and in reasonable proportion to the benefits for patients provides ample rewards for innovation while assuring greater affordability to the health care system. Responsible pricing fosters improved affordability and thus better access for patients.

- Payers can help reduce health inequities by recognizing the distinctive access barriers that disadvantaged communities can face and taking steps to assure that coverage criteria take into consideration challenges patients may have with transportation, family support, and greater comorbidity. Allowing greater choice among options of similar effectiveness with different modes of administration and side effect profiles can be one way to help remove barriers that may disproportionately affect communities of color.

- Clinicians and professional societies should take steps to improve outreach to patients in racial/ethnic minority populations, as these populations both bear a higher burden of ASCVD and, along with women, are more likely to be undertreated. This should include outreach strategies tailored to diverse populations (e.g., partnering with established community-based organizations for outreach, developing linguistically and culturally appropriate messaging, encouraging lipid-lowering treatment as part of preventive care messaging, and seeking non-clinical venues including, but not limited to, barbershops and salons, places of worship, community centers, and health fairs, to encourage screening and education regarding ASCVD).

- Researchers should work to increase recruitment and retention of minority populations for clinical trials to ensure that there is adequate data for analysis regarding efficacy and safety in racial/ethnic subpopulations. Researchers should also seek to use large, population-based data sources to elucidate populations in which underuse of effective therapies occurs.

All stakeholders should act to help increase awareness about the diagnosis and treatment of high cholesterol and, in particular, address the underdiagnosis and undertreatment of familial hypercholesterolemia (FH).

In particular:

- Clinicians should align their lipid screening protocols with clinical guidelines to ensure that all patients are being screened appropriately for lipid disorders.

- Payers should ensure that appropriate coverage is provided for diagnostic tests for FH but should also work with clinical experts to guide approaches to accepting clinical diagnosis based on obvious signs of early ASCVD in the setting of extremely high LDL-C cholesterol

- Manufacturers may consider direct-to-consumer advertising about FH and ASCVD to encourage consumers to seek testing for these conditions.

Along with encouraging steps to improve diet and exercise, all stakeholders should seek to increase utilization of effective therapies such as statins and ezetimibe for patients with established ASCVD and HeFH. These therapies are backed by extensive evidence, are safe for the vast majority of patients, and are far less expensive than other treatment options.

In particular:

- Payers should minimize barriers to obtaining effective therapies such as statins and ezetimibe. For ezetimibe, its current low level of utilization is in part due to barriers to prescribing that clinicians experienced in the past due to the drug's high price at launch and substantial prior authorization barriers. Today, backed by long-term evidence of clinical

benefit, support in clinical guidelines, and a lower price for the generic version, use of ezetimibe is inappropriately low and should be encouraged by all stakeholders for appropriate patients.

- Health systems should provide clinicians the time and support to implement shared decision-making to help patients make appropriate choices about lipid-lowering therapy. Some underuse of statins may be due to misconceptions about statin therapy and the importance of lifelong medical therapy for the treatment of ASCVD and HeFH. Shared decision-making can be effective in improving patient knowledge of the relative benefits and harms of treatment, in improving patient activation in the decision-making process, and potentially in improving patient adherence to therapy.

- Clinicians, health systems, and payers should seek ways to increase appropriate screening for lipid disorders and identify and reach out to eligible patients who are not currently on appropriate lipid-lowering therapy or at their LDL-C goal. This may include using electronic health record data or registries to identify and track patients, using clinical staff or other ancillary health providers (e.g., pharmacists) to assist in counseling patients about the importance of lipid-lowering therapy, and identifying and implementing effective methods for increasing uptake of statins.

- Professional societies should seek ways to increase uptake of effective therapies for lowering cholesterol at the population level, including working with clinicians and patient advocacy groups to develop evidence-based messaging around the benefits and harms of statin therapy, developing evidence-based patient education materials, and supporting research to identify underuse.

- Patient advocacy organizations should seek to increase awareness around effective therapies and frame the benefits and harms of statin therapy objectively so that patients can engage in shared decision-making with their clinicians and make decisions based on evidence rather than anecdotal experiences often amplified through social media.

Payers

Payers should develop consistent prior authorization criteria for lipid-lowering drugs and assure that the documentary burden and other administrative elements of prior authorization do not create an unreasonable burden on clinicians and patients.

One of the barriers to access to effective lipid-lowering therapies are the varied prior authorization criteria among payers. Although health plans are not legally able to collaborate to create common prior authorization criteria, they should seek forums with professional societies, guideline authors and patient groups, and use publicly available materials to establish norms and standards around

the approach to prior authorization, including whether step therapy on clinical grounds is appropriate. Doing so could streamline work for clinicians and increase access for patients.

Payers should also ensure that they take steps to implement prior authorization through administrative procedures that are transparent and efficient. Even the most clinically reasonable set of prior authorization criteria can be implemented in a way that creates an unreasonable burden through excessive requirements for prior medical records, labyrinthine algorithms, paper-based applications, and spotty responsiveness of payer representatives through phone or email. For example, prior authorization should be available through electronic formats not requiring fax or printed material; and re-authorization of coverage should be streamlined to reduce burden on clinicians and patients, given that ASCVD and HeFH are lifelong conditions and the need for therapy is not likely to change over the patient's lifetime. In considering how to design prior authorization content and procedural policies, payers should be aware of and seek to implement standards developed by ICER and other independent groups that help assure the appropriate implementation of prior authorization and step therapy policies.[141]

Payers should work with clinical experts and patient groups to develop consistent criteria and procedures for demonstrating drug intolerance due to statin associated side effects (SASE).

Statin associated side effects (SASE) are among the most common reasons to seek use of newer non-statin therapies such as PCSK9 inhibitors. Criteria for establishing SASE vary amongst health plans. For example, some health plans will look for claims for two trials of statin drugs with an initial denial if not found, requiring clinician appeal; others accept initial clinician attestation of SASE. Furthermore, periodic re-authorization is often required, adding to provider and patient burden and presenting an additional barrier to access of effective non-statin therapies.

Payers should work with clinical specialty societies and patient groups to establish a more consistent operational definition for the threshold of SASE that will qualify patients for coverage for additional therapies. This definition should then be implemented in an efficient manner. For initial prior authorization, payers may accept clinician attestation, or they may design an efficient algorithm based on claims data and/or medical records, but the latter option should be tested to ensure that it does not ensnarl clinicians and patients trying to gain appropriate treatment. Furthermore, if claims data or medical record data are required, payers should ensure that patients who are switching plans and may not have ready access to previous records are not required to re-try statins. One way to operationalize this safeguard for new-to-plan patients would be to institute a "transition of care" period during which clinician attestation is accepted for all patients during a time frame long enough to allow discussion and review of the patient's situation.

Payers should ensure that coverage criteria reflect the status of higher-risk subpopulations for whom therapies may be both more clinically effective and cost effective.

For certain populations in need of additional lipid lowering, some therapies may be more clinically and cost effective than in the general population. For example, bempedoic acid gives a greater degree of LDL-C lowering in patients with SASE, and so those patients may derive particular benefit from this treatment. In such cases, consideration should be given to broader coverage criteria (e.g., skipping step therapy with ezetimibe).

Drug-Specific Considerations for Bempedoic Acid with or without Ezetimibe

Bempedoic acid with or without ezetimibe represents an additional option for oral lipid-lowering therapy for patients with established ASCVD and/or FH. Bempedoic acid may be of greatest utility clinically in patients who have SASE or who are unwilling or unable to take injectable therapies, and consideration should be given to decrease barriers to treatment in these populations. Additionally, in particularly high-risk populations such as patients with FH or a recent cardiovascular event, steps to decrease barriers to treatment – such as more permissible criteria for skipping step therapy – should be considered to ensure timely access to treatment and avoid delays in care.

Patient Eligibility Criteria

a. **Diagnosis/patient population:** The FDA labeled use for bempedoic acid with or without ezetimibe is "as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia [HeFH] or established atherosclerotic cardiovascular disease [ASCVD] who require additional lowering of LDL-C." Diagnosis of HeFH can be established either by genetic testing for an LDL-C-raising gene defect or by clinical criteria (LDL-C ≥ 190 mg/dL with premature CAD or 1 first-degree relative similarly affected). Payers may choose to accept clinician attestation of these criteria or may institute a requirement for documentation. Diagnostic criteria for "established ASCVD" includes any evidence of coronary artery disease, peripheral artery disease, or cerebrovascular disease. Patients may qualify through cardiovascular events, symptoms, or abnormal testing (e.g., cardiac catheterization). For patients requesting coverage without established ASCVD or FH, some payers may wish to consider providing coverage for patients with LDL-C > 100 mg/dl who are at "high risk" for future ASCVD by means of a documented 10-year ASCVD risk of ≥ 20% and/or the presence of diabetes.

b. **Clinical eligibility criteria**: Current clinical guidelines establish 70 mg/dl as the threshold for LDL-C among patients with established ASCVD, so coverage criteria are likely to deny coverage initially for patients who are already below that level. The primary consideration for clinical eligibility will often be whether patients have had a reasonable trial of "maximally tolerated statin therapy." As noted earlier, criteria for establishing SASE vary amongst health plans. Following clinical guidelines, many health plans require two trials of statin drugs that have been halted because of side effects, but others require trials

with more than two statins. Patient advocates and clinical experts suggest that requiring more than two trials is counterproductive.

Some payers will accept clinician attestation to document adequate trials of statins with SASE, whereas other payers will require documentation of both. Payers should be aware, however, that patients may have had unsuccessful trials on statins many years previously, making it challenging or impossible to obtain past records in all cases.

c. **Exclusion:** Approximately 10% of patients with a history of gout had a gout event during the trial of bempedoic acid, but neither hyperuricemia nor history of gout were included as contraindications in the FDA label.

Step Therapy

Prior to the initiation of bempedoic acid with or without ezetimibe, patients should be on maximally tolerated statins or have documented SASE and not have reached their LDL-C goal according to clinical guidelines. Payers may wish to consider step therapy with ezetimibe prior to bempedoic acid, as some patients may reach their LDL-C goal with the combination of statin and ezetimibe, both of which are generic drugs and have been shown to improve cardiovascular outcomes. This would be consistent with the 2018 AHA/ACC clinical guidelines.[66] However, if patients are not on ezetimibe and are unlikely to reach their LDL-C goal with the addition of ezetimibe alone (e.g., ≥ 25% above their LDL-C goal with adherence to their maximally tolerated statin dose), payers should allow coverage for the combination pill of bempedoic acid with ezetimibe without requiring a first step through ezetimibe. Direct access for these patients to the combination pill would be consistent with appropriateness criteria for step therapy that step therapy should only be used when patients have an excellent chance to achieve treatment goals with the first-step therapy.[141]

Renewal Criteria

As ASCVD and FH are lifelong conditions, once approval has been given for therapy, barring new safety concerns, renewal of prior authorization should either not be necessary or be automatic to minimize burden on clinicians, pharmacists, and patients and prevent disruptions or delays in care.

Provider Qualification Criteria

Any provider should be able to prescribe bempedoic acid with or without ezetimibe; specialist consultation should not be necessary.

Drug-Specific Considerations for Inclisiran

Inclisiran will be considered as an option for patients also eligible for PCSK9 inhibitors. Until inclisiran has completed trials demonstrating its clinical effects, payers may choose to prefer PCSK9

inhibitors. However, if clinical outcomes data for inclisiran confirm assumptions of comparable effectiveness to PCSK9 inhibitors, either payers or manufacturers may suggest a lower price for one option if it is made the only option in the formulary. This approach to negotiating lower prices in return for exclusive formulary placement can be appropriate under certain circumstances, but payers and manufacturers should be aware that the very different delivery schedule and administration of inclisiran and the PCSK9 inhibitors may offer distinct advantages for some patients based on their living situation and other factors beyond mere preference. These factors should be carefully weighed with input from patient groups and clinical experts if excluding inclisiran or PCSK9 inhibitors from a formulary is ever under consideration.

Patient Eligibility Criteria

a. **Diagnosis/patient population:** Inclisiran has not been approved yet and therefore has no FDA labeled indication, but all of its trials enrolled adults with ASCVD, with some trials including patients with ASCVD equivalents. All trials required patients to be on maximally tolerated lipid lowering therapy. The ORION 9 trial enrolled patients with HeFH and/or untreated LDL-C >190 mg/dL and a family history of FH, elevated cholesterol, or early heart disease on maximally tolerated statin therapy ± ezetimibe. It seems likely that the FDA will consider a label broadly inclusive of these patient groups and one that may even be worded more broadly than the label for PCSK9 inhibitors (adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C).

   As with bempedoic acid, payers may wish to design coverage criteria that bring more specificity to the diagnostic criteria for these conditions. Diagnosis of HeFH can be established either by genetic testing for an LDL-C-raising gene defect or by clinical criteria (LDL-C ≥ 190 mg/dL with premature CAD or 1 first-degree relative similarly affected). Payers may choose to accept clinician attestation of these criteria or may institute a requirement for documentation. Diagnostic criteria for "established ASCVD" includes any evidence of coronary artery disease, peripheral artery disease, or cerebrovascular disease. Patients may qualify through cardiovascular events, symptoms, or abnormal testing (e.g., cardiac catheterization). For patients requesting coverage without established ASCVD or FH, some payers may wish to consider providing coverage for patients with LDL-C > 100 mg/dl who are at "high risk" for future ASCVD by means of a documented 10-year ASCVD risk of ≥ 20% and/or the presence of diabetes.

b. **Clinical eligibility criteria:** Current clinical guidelines establish 70 mg/dl as the threshold for LDL-C among patients with established ASCVD, so coverage criteria are likely to deny coverage initially for patients who are already below that level. The primary consideration for clinical eligibility will often be whether patients have had a reasonable trial of

"maximally tolerated statin therapy." As noted earlier, criteria for establishing SASE vary amongst health plans. Following clinical guidelines, many health plans require two trials of statin drugs that have been halted because of side effects, but others require trials with more than two statins. Patient advocates and clinical experts suggest that requiring more than two trials is counterproductive.

Some payers will accept clinician attestation to document adequate trials of statins with SASE, whereas other payers will require documentation of both. Payers should be aware, however, that patients may have had unsuccessful trials on statins many years previously, making it challenging or impossible to obtain past records in all cases.

c. **Exclusion:** There are no specific contraindications or risks uncovered in the pivotal trials to suggest specific clinical exclusion criteria.

Step Therapy

Prior to the initiation of inclisiran, patients should be on maximally tolerated statins or have documented SASE and not reached their LDL-C goal according to clinical guidelines. Payers may wish to consider step therapy with ezetimibe prior to inclisiran or PCSK9 inhibitors, as some patients may reach their LDL-C goal with the combination of statin and ezetimibe, both of which are generic drugs and have been shown to impact cardiovascular outcomes. This would be consistent with clinical guidelines. However, if patients are not on ezetimibe and are unlikely to reach their LDL-C goal with the addition of ezetimibe alone (e.g., ≥ 25% above their LDL-C goal with adherence to their maximally tolerated statin dose), payers should allow coverage for inclisiran without requiring a step through ezetimibe. A required step through bempedoic acid plus ezetimibe may be considered for patients close to their LDL-C threshold, but patient experts and clinical experts have suggested that for some patients the risk of poor adherence to additional oral treatment will create an important clinical opportunity for inclisiran to help patients reach LDL targets. Under such circumstances, direct access for these patients to inclisiran would be consistent with appropriateness criteria for step therapy that require that patients have an excellent chance at treatment success with the first-step therapy.[141]

Renewal Criteria

As ASCVD and FH are lifelong conditions, once approval has been given for therapy, barring new safety concerns, renewal of prior authorization should either not be necessary or be automatic to minimize burden on clinicians, pharmacists, and patients and prevent disruptions or delays in care.

Provider Qualification Criteria

If inclisiran is to be given in a healthcare setting, consideration should be given to allow prescribing by primary care clinicians who have access to consultation with lipid lowering specialists (e.g.,

cardiology, endocrinology, or other lipidologists). Although inclisiran does not present significant known risks, many patients with ASCVD or HeFH are likely to benefit if inclisiran administration is integrated into a broader care approach that is designed with input from a specialist. Allowing primary care prescribing with access to consultation would help address access concerns for patients in rural areas or those who have other challenges getting to specialty care centers.

Manufacturers

Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with independent assessments of the therapeutic value of their treatments. In particular, until cardiovascular outcomes data are available from ongoing trials, Novartis should fulfill its stated intent to set the price of inclisiran at or below the cost-effective range of pricing for PCSK9 inhibitors.

Drug prices that are set well beyond the cost-effective range for a drug or drug class can impact uptake and adherence. This was the case for the PCSK9 inhibitors evolocumab and alirocumab, where the initial pricing contributed to cumbersome prior authorization criteria by payers, which in turn led to slower than expected uptake and patient discontinuation of the drug due to high out-of-pocket costs. Furthermore, although inclisiran decreases LDL-C in the same range as PCSK9 inhibitors, cardiovascular outcomes data are not yet available and thus it is not clear whether the degree of LDL-C lowering will translate to MACE reduction that is similar to that of statins or PCSK9 inhibitors, which could affect inclisiran's ultimate value. Finally, inclisiran is expected to be delivered in a healthcare setting and thus could be classified under a drug plan's medical benefit rather than pharmacy benefit, which may affect administration costs for healthcare systems and out-of-pocket costs for patients. The manufacturer should take this into consideration when evaluating what a fair price is for inclisiran.

Manufacturers should include measurement of a broad set patient-important outcomes in clinical trials.

Current clinical trials are focused on measuring the degree of LDL-C lowering and the prevention of cardiovascular events. While these are appropriate primary outcomes to establish the clinical effectiveness of the drug, other patient-important outcomes such as quality of life play a role in patient and clinician choice of therapy and adherence to therapy. Therefore, inclusion of these outcomes in clinical trials will give patients and clinicians more information to consider during the treatment decision-making process and improve the quality of inputs into cost-effectiveness models.

Researchers

Researchers should seek to standardize definitions of ASCVD, major adverse cardiovascular events (MACE), and SASE (statin intolerance) in clinical trials to facilitate comparison of drugs and assist payers, clinicians, and patients in understanding which groups may benefit from a particular drug therapy.

A major challenge in interpreting clinical trial results is a lack of standardization of populations and outcomes. For example, ASCVD is variably defined as including coronary artery disease, peripheral vascular disease, cerebrovascular disease, but also certain conditions such as diabetes mellitus (so-called "ASCVD risk-equivalent" condition). This leads to heterogeneity in clinical trial populations and makes it difficult to compare the effectiveness of similar drugs and to identify subpopulations where a drug may be more effective. As more lipid-lowering therapies are developed, it is important to standardize definitions to assist payers with operationalizing coverage decisions, and clinicians and patients with choosing the right treatment for the right patient.

Researchers should use real world data to standardize definitions of "adherence to therapy" as part of trials that evaluate adherence and its impact on clinical outcomes.

In the future, the increase in availability of real-world data (e.g., electronic medical records, all-payer claims databases, clinical registries) will assist researchers in studying adherence to medication. However, there is currently no standard method of measuring adherence, and thus the external validity and applicability of such study findings are not clear. Additionally, standardized definitions may assist those entities collecting data in ensuring that data are collected in ways to maximize both internal and external validity of the data and increase the likelihood that the information is useful to payers, clinicians, and other stakeholders.

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This is the first ICER review of inclisiran and bempedoic acid.

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Appendix A. Search Strategic Results

Table A1. 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

Table A2. Search Strategy of MEDLINE via Ovid* for Inclisiran and Bempedoic Acid

1	Hypercholesterolemia/ or Hyperlipoproteinemia Type II/ or Cardiovascular Diseases/
2	(((high or elevated) adj (cholesterol or LDL* or low-density lipoprotein)) or hypercholesterolemia or hypercholesterolemia or HeFH or heterozygous familial hypercholesterolemia or familial hypercholesterolemia or FH).ti,ab
3	(((cardiovascular or heart or coronary or atherosclero*) adj2 (disease* or disorder* or syndrome*)) or ASCVD or CVD).ti,ab.
4	1 or 2 or 3
5	(inclisiran or ALN-PCSsc or ALNPCSsc or ALN PCSsc or ALN-60212 or ALN60212 or ALN 60212).ti,ab
6	(bempedoic acid or Nexletol or Nexlizet or ezetimibe or ETC1002 or ETC 1002 or ETC-1002).ti,ab.
7	5 or 6
8	4 and 7
9	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
10	8 not 9
11	(exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non-human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.)
12	10 not 11
13	limit 12 to English language

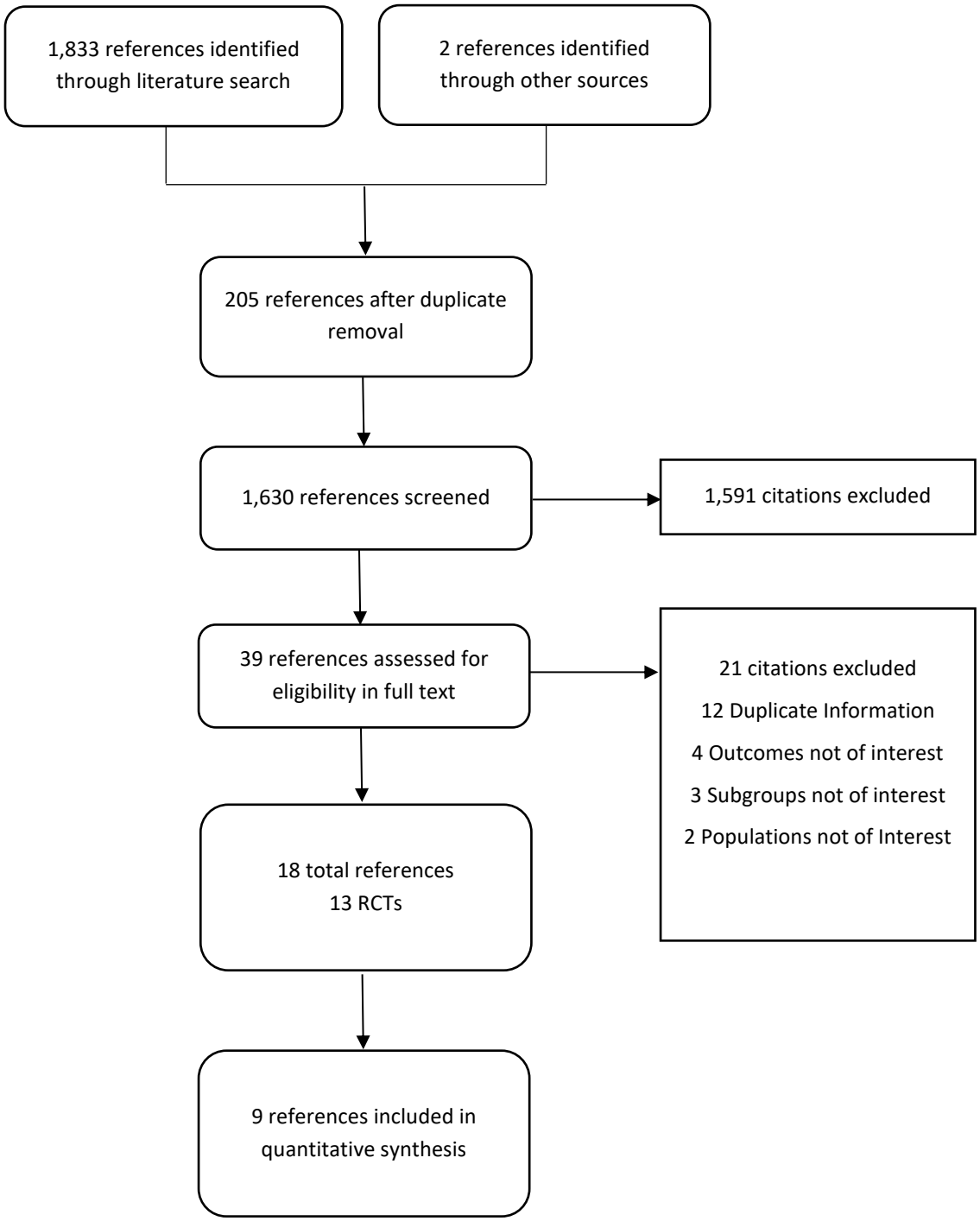
*Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

Table A3. Search Strategy of EMBASE for Inclisiran and Bempedoic Acid

#1	'Hypercholesterolemia'/exp OR 'Cardiovascular Disease'/mj
#2	(((high OR elevated) NEAR/1 (cholesterol OR ldl* OR 'low-density lipoprotein')):ti,ab) OR hypercholesterolemia:ti,ab OR hypercholesterolaemia:ti,ab OR hefh:ti,ab OR 'heterozygous familial hypercholesterolemia':ti,ab OR 'familial hypercholesterolemia':ti,ab OR fh:ti,ab
#3	(((cardiovascular OR heart OR coronary OR atherosclero*) NEAR/2 (disease* OR disorder* OR syndrome*)):ti,ab) OR ascvd:ti,ab OR cvd:ti,ab
#4	#1 OR #2 or #3
#5	inclisiran:ti,ab OR 'aln-pcssc':ti,ab OR alnpcssc:ti,ab OR 'aln pcssc':ti,ab OR 'aln-60212':ti,ab OR aln60212:ti,ab OR 'aln 60212':ti,ab
#6	'bempedoic acid':ti,ab OR nexletol:ti,ab OR nexlizet:ti,ab OR ezetimibe:ti,ab OR 'etc1002':ti,ab OR 'etc 1002':ti,ab OR 'etc-1002':ti,ab
#7	#5 OR #6
#8	#4 AND #7

#9	'case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
#10	#8 NOT #9
#11	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#12	#10 NOT #11
#13	#12 AND [English]/lim
#14	#13 AND [medline]/lim
#15	#13 NOT #14

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Inclisiran and Bempedoic Acid ± Ezetimibe



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified two previous systematic reviews of Inclisiran and three previous systematic reviews for bempedoic acid. The systematic reviews are summarized below:

Inclisiran

Khan, S. Meta-Analysis of Inclisiran for the Treatment of Hypercholesterolemia[142]

This systematic literature review and meta-analysis evaluated the efficacy and safety of inclisiran in patients with hypercholesterolemia. Three RCTs of inclisiran were included in their analysis (ORION 9, 10, and 11). One of the trials (ORION 9) enrolled participants with familial hypercholesterolemia, while the other two trials (ORION 10 & 11) enrolled participants with either established atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalent. Results of the meta-analysis showed that inclisiran reduced LDL-C levels by 51% (Difference: -50.53; 95%CI -52.73 to -48.34; p<0.001) and was associated with a 24% reduction in major adverse cardiovascular events (MACE) (RR 0.76; 95%CI 0.61 to 0.94; p=0.01) compared with placebo. Also, there was a 37% reduction in total cholesterol (p<0.001), a 41% reduction in ApoB (p<0.001), and a 45% reduction in non-HDL-C (p <0.001) with inclisiran compared to placebo. Inclisiran was not associated with increases in major adverse events (RR 1.01; 95% CI 0.91 to 1.05; p=0.58). However, there was a higher incidence of injection site reaction in the inclisiran group compared with placebo (RR 6.24; 9%CI 1.66 to 14.63; p<0.001).

Asbeutah, A et al. A Meta-Analysis of Cardiovascular Outcomes in Patients with Hypercholesterolemia Treated with Inclisiran[143]

This systematic literature review and meta-analysis evaluated the efficacy of inclisiran in cardiovascular events. Four trials were identified and included in the study (ORION 9, 10, 11, and 1). Three of the included trials reported data on myocardial infarction and stroke (ORION 9, 10, and 11). The meta-analysis showed no statistically significant difference in the risk of myocardial infarction in patients randomized to inclisiran (1.8%) compared to placebo (2.3%) (RR 0.85; 95%CI 0.37 – 1.95; p=0.70; I^2 = 57%). Additionally, there were no statistically significant differences in risk of stroke in patients randomized to inclisiran (0.7%) versus placebo (0.8%) (RR 0.69; 95% CI 0.11 – 4.21; p=0.69; I^2 =75%). Lastly, all four RCTs reported on cardiovascular mortality and there were no observed significant reductions in the inclisiran arm (0.9%) compared to the placebo arm (0.8%) (RR 1.11; 95%CI 0.56 – 2.21; p=0.77; I^2 = 0%). The authors noted that the significant decrease in LDL-C

with inclisiran was not consistent with any significant decrease in cardiovascular ischemic endpoints at this time.

Bempedoic Acid

Cicero, A. Efficacy and safety of bempedoic acid for the treatment of hypercholesterolemia: A systematic review and meta-analysis[144]

This systematic review and meta-analysis evaluated the efficacy and safety of bempedoic acid in patients with hypercholesterolemia. The systematic search identified 10 RCTs, including both phase II and III studies, enrolling a total of 3,788 patients across the active and placebo arms. Within the 10 RCTs, follow-up ranged from four to 52 weeks with a variety of treatment schedules. The population enrolled included those affected by hypercholesterolemia regardless of statin therapy, patients with type 2 diabetes, and statin-intolerant individuals. Data from the meta-analyses showed that bempedoic acid significantly reduced LDL-C (MD -22.94%; 95%CI -26.63 to -19.25; p<0.001; I^2=77.3%). Bempedoic acid also significantly reduced total cholesterol (MD -14.94; 95%CI -17.31 to -12.57; p<0.001; I^2=76.1%), non-HDL-C (MD -18.17%; 95%CI -21.14 to -15.19; p<0.001; I^2=87.2), ApoB (MD -15.18; 95%CI -17.41 to -12.95; p<0.001; I^2=81.4%), HDL-C (MD -5.83%; 95%CI -6.14 to -5.52; p<0.001; I^2 = 33.4%), and hsCRP (MD -27.03; 95%CI -31.42 to -22.64; p <0.001; I^2 = 0%). Also, bempedoic acid was shown to decrease the risk of new-onset or worsening diabetes (OR 0.59; 95%CI 0.39 to 0.90; p=0.01; I^2=0%). Finally, bempedoic acid was positively associated with an increased risk of discontinuation of treatment (OR 1.37; 95%CI 1.06 to 1.76; p=0.015; I^2= 0%). The authors identified the small number of patients enrolled in studies, heterogeneity of patient populations, and lack of data on cardiovascular events and mortality as key limitations of the review. The authors concluded that bempedoic acid significantly reduced LDL-C, total cholesterol, and non-HDL-C with no significant increases in serious adverse events.

Di Minno, A. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia: Systematic Review and Meta-Analysis of Randomized Controlled Trials[145]

This systematic review and meta-analysis evaluated the efficacy and safety of bempedoic acid in patients with hypercholesterolemia. The systematic search identified seven RCTs that included 2,767 bempedoic acid-treated patients and 1,469 placebo-treated patients with a mean follow-up duration of 25 weeks. Three of the seven studies enrolled patients with ASCVD or ASCVD risk factors, HeFH, or both receiving maximally tolerated statin therapy alone or in combination with other lipid-lowering therapy. Two studies enrolled patients with ASCVD or ASCVD risk factors that are statin intolerance, while the remaining two studies enrolled patients with hypercholesterolemia on maximally tolerated statin therapy with elevated LDL-C. A significant reduction in LDL-C at 12 weeks was seen in patients receiving bempedoic acid compared to placebo (MD -17.5%; 95%CI -

22.9 to -12.0; p<0.001; I^2 =80.3%). Significant reduction in the bempedoic acid arm compared to placebo was also seen for total cholesterol (MD -10.9%; 95%CI -13.3 to -8.5), non-HDL-C (MD -12.3%; 95%CI -15.3 to -9.2), and ApoB (MD -10.6%; 95%CI -13.2 to -8.02). Both arms displayed a similar rate of any adverse event (OR 1.086; 95%CI 0.943 to 1.25); however, the treatment continuation rate was higher in the bempedoic acid arm than the placebo arm (OR 1.39; 95%CI 1.107 to 1.753; P=0.005). Lastly, patients in the bempedoic acid arm showed both a significant increase in uric acid (MD 0.7 mg/dL; 95%CI 0.5 to 0.9; p<0.01) and gout flare (OR 3.2; 95%CI 0.12 to 8.2; p=0.002) as compared to the placebo arm. The authors concluded that bempedoic acid significantly reduced LDL-C, total cholesterol, non-HDL-C, and has an acceptable safety profile.

Dai, L. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: A systematic review and meta-analysis of randomized controlled trials[146]

This systematic review and meta-analysis evaluated the efficacy and safety of bempedoic acid in hypercholesterolemic patients. The literature search identified 10 studies that met the inclusion criteria and were eligible for the meta-analysis. Across the 10 studies, 2,736 patients received bempedoic acid, and 1,368 received placebo. The meta-analysis results showed that bempedoic acid lowered LDL-C by 23% (MD -23.16%; 95%CI -26.92 to -19.04). Significant reductions were also seen in non-HDL-C (MD -18.3%; 95%CI -21.65 to -14.95), total cholesterol (MD -14.62%; 95%CI -17.08 to -12.16), apoB (MD -14.77%; 95%CI -16.85 to -12.7), and HDL-C (MD -3.8%; 95%CI -5.54 to -2.06. Compared to placebo, there was no statistically significant change in triglycerides. The improvements in lipid parameters and biomarkers were maintained at weeks 24 and 52. Bempedoic acid did not increase the risk of overall adverse events compared to placebo (OR 1.02; 95%CI 0.88 to 1.18), although the incidence of AEs leading to discontinuation was higher in the bempedoic acid arm (OR 1.44; 95%CI 1.14 to 1.82). The authors concluded that bempedoic acid is both well tolerated and effective as a lipid-lowering agent in patients with hypercholesterolemia with or without other impacting factors (e.g., T2DM, statin intolerance, etc.)

Appendix C. Ongoing Studies

Figure C1. Ongoing Studies

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Inclisiran					
Trial to Assess the Effect of Long-Term Dosing of Inclisiran in Subjects with High CV Risk and Elevated LDL-C (ORION-8) NCT03814187 Sponsor: Novartis Pharmaceuticals	Open-Label Extension Study of the Phase III Lipid-Lowering Trials Actual Enrollment: 2991	1) Inclisiran 300mg SC on Day 1, 90, and then every 180 days to day 990 *subjects who received blinded placebo in the feeder study will receive blinded inclisiran and subjects who received blinded inclisiran in the feeder study will received blinded placebo on day 1 in ORION-8. Subjects from the OL ORION-5 study will not receive any injection of study drug/placebo on day 1.	Inclusions Completion of a previously qualifying Phase III lipid-lowering ORION feeder study ORION-9, 10, 11, or 5), meaning the subject received the last dose of study drug and completed the final study visit per applicable protocol. On current lipid-lowering therapies (such as a statin and/or ezetimibe) from previous study with no planned medication or dose change during study participation Exclusions Any uncontrolled or serious disease, or any medical or surgical condition or underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with interpretation of the clinical study results. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 3 years, Active liver disease	Proportion of subjects reaching on treatment LDL-C targets of <70 mg/dL or <100 mg/dL for their respective level of ASCVD risk at entry of study	December 2023
An Extension Trial of Inclisiran Compared to Evolocumab in Participants with	Open-Label, Active Comparator Extension Trial	1) Inclisiran 300 mg SC on day 1 and every 180 days thereafter up to 4 years	Inclusions Completion of Study MDCO-PCS-15-01 and no contraindication to receiving inclisiran or evolocumab	Percent Change in LDL-C at Day 210	February 2022

Cardiovascular Disease and High Cholesterol (ORION-3) NCT03060577 Sponsor: Novartis Pharmaceuticals	Estimated Enrollment: 490	2) Evolocumab 140 mg SC on day 1 and every 14 days thereafter until day 336. Then participants will switch to receive inclisiran 300 mg SC on day 360 and then every 180 days thereafter up to 4 years	Exclusions Any uncontrolled or serious disease, or any medical or surgical condition or underlying known disease or surgical, physical, or medical condition that, in the opinion of investigator, might interfere with interpretation of results Serious comorbid disease which reduces life expectancy to shorter than duration of trial Active liver disease		
A Study of Inclisiran in Participants with Homozygous Familial Hypercholesterolemia (HoFH) (ORION-5) NCT03851705 Sponsor: Novartis Pharmaceuticals	Two-Part Double - Blind, Placebo Controlled/Open-Label Multicenter Study Actual Enrollment: 56	1) Inclisiran 300 mg SC on days 1 and 90 2) Placebo SC on days 1 and 90 3) Inclisiran 300 mg SC on days 270, 450, and 630	Inclusions Diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration >500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents Subjects on statins should be receiving a maximally tolerated dose. Subjects not receiving statins must have documented evidence of intolerance to at least two different statins. Subjects on lipid-lower therapies (such as statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation. Fasting central laboratory LDL-C concentration ≥130 mg/dL (3.4 mmol/L). Triglyceride concentration <400 mg/dL (4.5 mmol/L) Exclusions Use of mipomersen or lomitapide therapy within 5 months of screening	Percent Change in LDL-C at Day 150	September 2021

			Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9 New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25% Major adverse cardiovascular event within 3 months prior to randomization Planned cardiac surgery or revascularization Active liver disease		
A Randomized Trial Assessed the Effects of Inclisiran on Clinical Outcomes Among People with Cardiovascular Disease (ORION-4) NCT03705234 Sponsor: University of Oxford and the Medicines Company	Double-Blind, Placebo Controlled, Randomized Controlled Trial Estimated Enrollment: 15,000	1) Inclisiran 300 mg SC at randomization, 3 months, and then every 6 months 2) Matched Placebo	Inclusions History or evidence of at least one of the following: prior myocardial infarction, prior ischemic stroke, or peripheral artery disease as evidence by prior lower extremity artery revascularization or aortic aneurysm repair Exclusions Acute coronary syndrome or stroke less than 4 weeks before the screening visit or during the run-in period Coronary revascularization procedure planned within the next 6 months Known chronic liver disease Current or planned renal dialysis or transplantation Previous exposure to inclisiran Previous, current, or planned treatment with a monoclonal antibody targeting PCSK9, or with drug known to be contra-indicated with inclisiran (none currently known)	Number of participants with a major adverse cardiovascular event, defined as time to first occurrence of coronary heart disease death, myocardial infarction, fatal or non-fatal ischemic stroke, or urgent coronary revascularization procedure up to 5 years	December 2024
Bempedoic Acid					
Evaluation of Major Cardiovascular Events in	Double-Blind, Placebo Controlled,	1) Bempedoic Acid 180 mg orally once daily	Inclusions	Time from randomization to first occurrence of one of the	August 2022

Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated with Bempedoic Acid (ETC-1002) or Placebo NCT02993406 Sponsor: Esperion Therapeutics	Randomized Controlled Trial Actual Enrollment: 14,014	2) Matched Placebo	Adults between 18 and 85 years old with history of, or at high risk for, cardiovascular disease including coronary artery disease, symptomatic peripheral arterial disease, cerebrovascular atherosclerotic disease, or at high risk for cardiovascular event Patient reported history of statin intolerance (inability to tolerate 2 or more statins, one at low dose) Fasting blood LDL-C ≥ 100 at screening Exclusions Fasting blood triglycerides greater than 500 mg/dL at screening Recent history of major cardiovascular events, transient ischemic attack, or unstable or symptomatic cardiac arrhythmia History of severe heart failure Uncontrolled hypertension or uncontrolled diabetes	following adjudicated composite endpoints: CV death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization up to 3.75 years	

ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, HoFH: homozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, mg/dL: milligram per deciliter, mmol/L: millimole per liter, PCSK9: proprotein convertase subtilisin/kexin type 9, SC: subcutaneous
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator 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. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to bempedoic acid. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

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 Appendix Table F2).[147] 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.

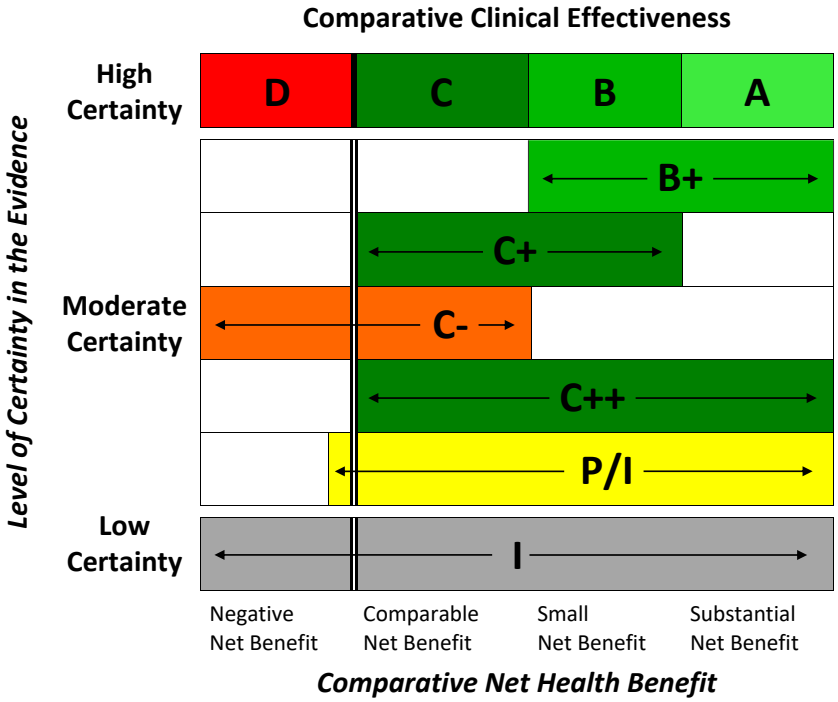
ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

1. The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects; and

2. The level of certainty in the best point estimate of net health benefit[71,148]

Figure D1. 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 likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Evidence Tables

Table D1. Study Design

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
Inclisiran Trials							
ORION 9[84] NCT03397121	482	US, Canada, Europe, & South Africa	Phase III DB, PC RCT 540 days	- Percent change in LDL-C from baseline to day 510 - Time-adjusted percent change in LDL-C from baseline between day 90 and day 540	1. Inclisiran 300 mg (n=242) 2. Placebo (n=240) at days 1, 90, 270, and 450	- ≥18 years - HeFH; and/or untreated LDL-C >190 mg/dL & family history of FH, elevated cholesterol, or early heart disease that may indicate HeFH - LDL-C ≥100 mg/dL - Maximally-tolerated dose of statin unless evidence of intolerance to ≥2 statins	- NYHA class IV heart failure -MACE within 3 months - Uncontrolled cardiac arrhythmia - Active liver disease - Tx within 90 days with monoclonal antibodies directed towards PCSK9
ORION 10[88] NCT03399370	1561	US	Phase III DB, PC RCT 540 days	- Percent change in LDL-C from baseline to day 510 - Time-adjusted percent change in LDL-C from baseline between day 90 and day 540	1. Inclisiran 300 mg (n=781) 2. Placebo (n=780) at days 1, 90, 270, and 450	- ≥18 years - History of ASCVD (CHD, CVD or PAD) - LDL-C ≥70 mg/dL - Maximally-tolerated dose of statin unless evidence of intolerance to ≥2 statins	- NYHA class IV heart failure -MACE within 3 months - Uncontrolled cardiac arrhythmia - Active liver disease - Tx within 90 days with monoclonal antibodies directed towards PCSK9

ORION 11[88] NCT03400800	1617	Europe & South Africa	Phase III DB, PC RCT 540 days	- Percent change in LDL-C from baseline to day 510 - Time-adjusted percent change in LDL-C from baseline between day 90 and day 540	1. Inclisiran 300 mg (n=810) 2. Placebo (n=817) at days 1, 90, 270, and 450	- ≥18 years - History of ASCVD (CHD, CVD or PAD) or ASCVD risk equivalent (T2DM, FH, 10-year ASCVD risk ≥20%, or equivalent) - LDL-C ≥70 mg/dL for ASCVD; LDL-C ≥100 mg/dL for risk-equivalent - Maximally-tolerated dose of statin unless evidence of intolerance to ≥2 statins	- NYHA class IV heart failure -MACE within 3 months - Uncontrolled cardiac arrhythmia - Active liver disease - Tx within 90 days with monoclonal antibodies directed towards PCSK9
ORION 1[85] NCT02597127	501	US, Canada, & Europe	Phase II DB, PC RCT 210 days	-Percent change from LDL-C from baseline to day 180	Single-dose regimen: 1. Inclisiran 200 mg (n=60) 2. Inclisiran 300 mg (n=61) 3. Inclisiran 500 mg (n=65) 4. Placebo (n=65) at day 1 Two-dose regimen 1. Inclisiran 100 mg (n=61) 2. Inclisiran 200 mg (n=62) 3. Inclisiran 300 mg (n=63) 4. Placebo (n=62) at days 1 and 90	- ≥18 years - History of ASCVD (CHD, CVD or PAD) or ASCVD risk equivalent (symptomatic atherosclerosis, T2DM, FH, 10-year ASCVD risk ≥20%, or equivalent and has a target LDL-C <100 mg/dL) - LDL-C ≥70 mg/dL for ASCVD; LDL-C ≥100 mg/dL for ASCVD risk equivalent - Maximally-tolerated dose of statin	- NYHA class II, III, or IV heart failure -MACE within 6 months - Uncontrolled cardiac arrhythmia - History of hemorrhagic stroke. - Active liver disease - Tx within 90 days with monoclonal antibodies directed towards PCSK9
Phase III Bempedoic Acid Trials							

CLEAR Wisdom[75] NCT02991118	779	North America & Europe	Phase III DB, PC RCT 52 weeks	- Percent change in LDL-C from baseline to week 12	1. Bempedoic acid 180 mg (n=522) 2. Placebo (n=257) once daily	- ≥18 years - ASCVD with CHD or CHD risk equivalents (cerebrovascular atherosclerotic disease and symptomatic PAD), HeFH, or both - LDL-C ≥ 100 mg/dL at the first screening visit and ≥ 70 mg/dL 1 week before randomization -Maximally tolerated lipid-lowering therapy	- CHD event within 3 months of screening - Severe renal impairment - BMI ≥ 50 kg/m2 - Total fasting triglyceride level ≥ 500 mg/dL - Use of Cholestin
CLEAR Harmony[77] NCT02666664	2230	US, Canada, and Europe	Phase III DB, PC RCT 52 weeks	- Patient incidence of AEs as assessed by MedDRA 18.1	1. Bempedoic acid 180 mg (n=1488) 2. Placebo (n=742) once daily	- ≥18 years - ASCVD with established CHD or CHD risk equivalents (PAD, ischemic stroke), HeFH, or both - LDL-C ≥70 mg/dL -Maximally tolerated statin therapy either alone or in combination with other LLT for at least 4 weeks	- Use of gemfibrozil or simvastatin at doses greater than 40 mg per day - Use of any PCSK9 inhibitor starting 4 weeks before trial entry was prohibited but permitted after trial week 24 if LDL-C level ≥ 170 mg/dL and had increased 25% from baseline - Renal dysfunction or nephritic syndrome - Recent MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac

							arrhythmia within 3 months prior to screening - Liver disease or dysfunction
CLEAR Serenity[76] NCT02988115	345	US and Canada	Phase III DB, PC RCT 24 weeks	- Percent change in LDL-C from baseline to week 12	1. Bempedoic acid 180 mg (n=234) 2. Placebo (n=111) once daily	- ≥18 years - Secondary prevention (CAD, symptomatic PAD, and/or cerebrovascular atherosclerotic disease), primary prevention (those requiring lipid-lowering therapy based on national guidelines), or HeFH - LDL-C ≥130 mg/dL for primary prevention and ≥100 mg/dL for patients with HeFH and secondary prevention -History of statin intolerance	- Significant CVD or CV event in the past 3 months - BMI ≥ 50 kg/m2 - Total fasting triglyceride level ≥ 500 mg/dL - Renal dysfunction or nephrotic syndrome or history of nephritis - Undergone endovascular or surgical intervention for peripheral vascular disease within 3 months before screening - Liver disease or dysfunction, uncontrolled hypertension, uncontrolled hypothyroidism
CLEAR Tranquility[72] NCT03001076	269	US, Canada, and Europe	Phase III, DB, PC RCT 12 weeks 4-week run-	- Percent change in LDL-C from baseline to week 12	1. Bempedoic acid 180 mg (n=181) 2. Placebo (n=88) once daily	- ≥18 years -LDL-C ≥100 mg/dL -History of statin intolerance, were on no more than low-dose statin	- Fasting blood triglycerides greater than or equal to 500 mg/dL - BMI ≥ 50 kg/m2

			in phase with ezetimibe			therapy (which could include no statin)	- Recent history of clinically significant cardiovascular disease - Use of statin therapy where doses greater than those defined as "low-dose" within 4 weeks prior to screening
Ballantyne 2020[73] NCT03337308	301	US	Phase III, DB, PC RCT 12 weeks	- Percent change in LDL-C from baseline to week 12	1. Fixed-dose combination bempedoic acid 180 mg and ezetimibe 10 mg (n=86) 2. Bempedoic acid 180 mg (n=88) 3. Ezetimibe 10 mg (n=86) 4. Placebo (n=41) once daily	- ≥18 years -ASCVD, HeFH, or multiple CV risk factors (diabetes plus one other risk factor or three CVD risk factors from the following list: age [men≥45 years, women≥55 years]; family history of CHD; smoking; hypertension; low HDL-C; or coronary calcium score above the 95th percentile for the patient's age, sex, and race/ethnicity. -LDL-C ≥130 mg/dL for patients with multiple risk factors -LDL-C ≥ 100 mg/dL for patients with HeFH and/or ASCVD - Treated with maximally tolerated statin therapy at stable dose for at least 4 weeks prior to screening	- Total fasting triglyceride ≥ 400 mg/dL - Renal dysfunction or nephrotic syndrome or history of nephritis - Significant CVD or cardiovascular event within the past 3 months

Phase II Bempedoic Acid Trials							
Ballantyne 2016[80]	134	U.S.	Phase IIB, DB, Parallel-Group RCT 12 weeks	- Percent change in LDL-C from baseline to week 12	1. Bempedoic Acid 120 mg once daily (n=44) 2. Bempedoic Acid 180 mg once daily (n=45) 3. Placebo once daily (n=45)	- Adults with hypercholesterolemia with a BMI from 18 to 45 kg/m2 on stable statin therapy (defined as use of atorvastatin (10 or 20mg), simvastatin (5,10, or 20 mg), rosuvastatin (5 or 10 mg), or pravastatin (10, 20, or 40 mg) for at least 3 months before screening - Fasting LDL-C levels from 115-220 mg/dl and fasting triglyceride level ≤ 400 mg/dl after washout of lipid-regulating agents other than the statins listed previously	- history of clinically significant cardiovascular disease within 12 months of screening - current clinically significant cardiovascular disease - type 1 diabetes or uncontrolled type 2 diabetes - liver or renal dysfunction - unexplained creatine kinase elevations; or use of anticoagulants, colchicine, systemic corticosteroids, digoxin, potent cytochrome P450 3A4 inhibitors or inducers, metformin, or thiazolidinediones within 4 weeks of screening.

Thompson 2016[83] NCT01941836	378	U.S.	Phase II DB, Parallel Group, Multicenter RCT 12 weeks 5-week single blind placebo run in	- Percent change in LDL-C from baseline to week 12	1. Bempedoic Acid 120 mg 2. Bempedoic Acid 180 mg 3. Active Comparator: Ezetimibe 10 mg 4. Bempedoic Acid 120 mg + Ezetimibe 10 mg 5. Bempedoic Acid 180 mg + Ezetimibe 10 mg	- Hypercholesterolemic adults (age 18 to 80 years) with a BMI from 18 to 45 kg/m2 - Fasting LDL-C between 130 and 220 mg/dL and fasting triglyceride ≤ 400 mg/dL after washout of lipid-regulating drugs - Included both statin tolerant and intolerant patients (intolerance defined as inability to tolerate more than 2 statins because of muscle-related symptoms. At least 1 statin must have been administered at the lowest approved daily dose	- Clinically significant cardiovascular disease - type 1 diabetes mellitus, uncontrolled type 2 diabetes mellitus, non–statin-related musculoskeletal complaints, uncorrected hypothyroidism, liver or renal dysfunction - Unexplained CK elevations off statin treatment >3 times the upper limit of normal; ingested <80% of drug during single-blind run-in
Gutierrez 2014[81]	60	U.S.	Phase II DB, Parallel Group, PC, RCT 4 weeks	- Percent change in LDL-C from baseline to day 29	1. Bempedoic Acid (n=30) 2. Placebo (n=30)	- Adults between 18-70 years old with T2DM, LDL-C greater than 100 mg/dL and a BMI between 25-35 kg/m2 -Stable dose of blood pressure medication if prescribed	- Uncontrolled blood pressure at screening - History of T1DM or diabetic ketoacidosis, history of diabetic complications with significant end-organ damage, - History or current clinically significant CVD

Lalwani 2019[82]	68	U.S.	Phase II DB, Parallel Group, PC RCT 4-week OL atorvastatin stabilization period 4-week treatment period	- Percent change in LDL-C from baseline to day 29	1. Bempedoic Acid 180 mg + Atorvastatin 80 mg 2. Placebo + Atorvastatin 80 mg	- Adults 18-70 with a BMI between 18 and 40 kg/m2 who were taking a stable, daily statin dose for at least 4 weeks before screening - Fasting LDL-C between 100 and 220 mg/dL for patients on daily high-intensity statin therapy and between 115 and 220 for patients on daily moderate or low intensity - Fasting triglyceride less than 400 mg/dL after washout of all lipid-regulating therapies or supplements (other than study-provided atorvastatin 80 mg) and before randomization	- History of significant CVD (including MI< coronary angioplasty, coronary artery bypass graft, unstable PAD, abdominal aortic aneurysm, or severe or unstable angina pectoris) within past 6 months of current significant CVD - History of statin-intolerance due to muscle-related pain or weakness - Uncontrolled hypothyroidism

AE: adverse event, ASCVD: atherosclerotic cardiovascular disease, BMI: body mass index, CHD: coronary heart disease, CVD: cardiovascular disease, DB: double blind, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, MACE: major adverse cardiovascular event, MedDRA: medical dictionary for regulatory activities, mg/dL: milligram per deciliter, n: number, N: total number, NYHA: New York Heart Association, OL: open label, PAD: peripheral artery disease, PC: placebo controlled, PCSK9: proprotein convertase subtilisin/kexin type 9, RCT: randomized controlled trial, T1/T2DM: type 1/2 diabetes mellitus, Tx: treatment

Table D2. Key Baseline Characteristics I

Trial	Arm	n	Age, years	Male	White	LDL-C, mg/dL	ASCVD	HeFH	ASCVD-Risk Equivalent	Current Smoker	Hyper-tension	Diabetes	Background Treatment: Overall %
			Mean (SD)	n (%)	n (%)	Mean (SD)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Inclisiran Trials[84-88]													
ORION 9	**Inclisiran**	242	Med: 56 (IQR 47-63)	112 (46.3)	226 (93.4)	151.4 (50.4)	59 (24.4)	242 (100)	NR	28 (11.6)	102 (42.1)	20 (8.3)	Statin: 91% High-intensity: 74% No Statin: 9% Ezetimibe: 53%
	Placebo	240	Med: 56 (IQR 46-64)	115 (47.9)	227 (94.6)	154.7 (58)	73 (30.4)	240 (100)	NR	28 (11.7)	101 (42.1)	28 (11.7)	
	Overall	482	Med: 56 (NR)	227 (47.1)	453 (94)	153.1 (54)	132 (27.4)	482 (100)	NR	56 (11.6)	203 (42.1)	48 (10)	
ORION 10	**Inclisiran**	781	66.4 (8.9)	535 (68.5)	653 (83.6)	104.5 (39.6)	781 (100)	8 (1)	0 (0)	123 (15.7)	714 (91.4)	371 (47.5)	Statin: 89%; High-intensity: 68% No Statin: 11% Ezetimibe: 10%
	Placebo	780	65.7 (8.9)	548 (70.3)	685 (87.8)	104.8 (37)	780 (100)	12 (1.5)	0 (0)	111 (14.2)	701 (89.9)	331 (42.4)	
	Overall	1561	66.1 (NR)	1083 (69.4)	1338 (85.7)	104.6 (NR)	1561 (100)	20 (1.3)	0 (0)	234 (15.0)	1415 (90.6)	702 (45.0)	
ORION 11	**Inclisiran**	810	64.8 (8.3)	579 (71.5)	791 (97.7)	107.2 (41.8)	712 (87.9)	14 (1.7)	98 (12.1)	160 (19.8)	640 (79.0)	296 (36.5)	Statin: 95% High-intensity: 79% No Statin: 5% Ezetimibe: 7%
	Placebo	807	64.8 (8.7)	581 (72)	796 (98.6)	103.7 (36.4)	702 (87)	14 (1.7)	105 (13)	132 (16.4)	661 (81.9)	272 (33.7)	
	Overall	1617	64.8 (NR)	1160 (71.7)	1587 (98.1)	105.5 (NR)	1414 (87.4)	28 (1.73)	203 (12.6)	292 (18.1)	1301 (80.5)	568 (35.1)	
ORION 1	**Inclisiran 300 mg (Two-Dose Regimen)**	61	64.1 (9.4)	45 (74.0)	58 (95.0)	131.3 (60.3)	43 (70.0)	3 (5.0)	NR	7 (12.0)	43 (70.0)	8 (13.0)	Statin: 73% High-intensity: 39% Ezetimibe: 31% Ezetimibe alone (statin-intolerant): 6.4% Statin + ezetimibe: 24%
	Placebo (Two-Dose Regimen)	62	62.8 (10.3)	33 (53)	58 (94)	125.2 (44.3)	46 (74.0)	3 (5.0)	NR	8 (13.0)	44 (72.0)	7 (11.0)	

Phase III Bempedoic Acid Trials[72,75-77 73]													
CLEAR Wisdom	**BA**	522	64.1 (8.8)	328 (62.8)	491 (94.1)	119.4 (37.7)	495 (94.8)	27 (5.2)	NR	NR	438 (83.9)	155 (29.7)	Statin: 90%; High-intensity: 53% Ezetimibe: 8% No LLT: 6%
	Placebo	257	64.7 (8.7)	168 (65.4)	244 (94.9)	122.4 (38.3)	241 (93.8)	16 (6.2)	NR	NR	224 (87.2)	81 (31.5)	
	Overall	779	64.3 (NR)	496 (63.7)	735 (94.4)	120.4 (NR)	736 (94.5)	43 (5.5)	NR	NR	662 (85.0)	236 (30.3)	
CLEAR Harmony	**BA**	1488	65.8 (9.1)	1099 (73.9)	1423 (95.6)	103.6 (29.1)	1449 (97.4)	56 (3.8)	NR	NR	1174 (78.9)	425 (28.6)	Statin: 99.9% High-intensity: 49.9% Ezetimibe: 7.7%
	Placebo	742	66.8 (8.6)	529 (71.3)	716 (96.5)	102.3 (30)	727 (98)	23 (3.1)	NR	NR	594 (80.1)	212 (28.6)	
	Overall	2230	66.1 (NR)	1628 (73.0)	2139 (95.9)	103.2 (NR)	2176 (97.6)	79 (3.5)	NR	NR	1768 (79.3)	637 (28.6)	
CLEAR Serenity	**BA**	234	65.2 (9.7)	101 (43.2)	211 (90.2)	158.5 (40.4)	90 (38.5)	4 (1.7)	144 (61.5)	NR	158 (67.5)	63 (26.9)	Low intensity statin: 8.4% Other LLT: 33.6% No LLT: 58%
	Placebo	111	65.1 (9.2)	50 (45)	96 (86.5)	155.6 (38.8)	44 (39.6)	3 (2.7)	67 (60.4)	NR	75 (67.6)	26 (23.4)	
	Overall	345	65.2 (NR)	151 (43.8)	307 (89)	157.6 (NR)	134 (38.8)	7 (2)	211 (61.2)	NR	233 (67.5)	89 (25.8)	
CLEAR Tranquility	**BA**	181	63.8 (10.8)	72 (39.8)	165 (91.2)	129.8 (30.9)	49 (27.1)	NR	NR	NR	111 (61.3)	35 (19.3)	Low intensity statin: 31% Ezetimibe: 100% Other LLT: 10%
	Placebo	88	63.7 (11.3)	32 (36.4)	75 (85.2)	123 (27.2)	22 (25)	NR	NR	NR	51 (58)	17 (19.3)	
	Overall	269	63.8 (NR)	104 (38.7)	240 (89.2)	127.6 (NR)	71 (26.4)	NR	NR	NR	162 (60.2)	52 (19.3)	
Ballantyne 2020	**BA + ezetimibe**	86	62.2 (9.5)	42 (48.8)	67 (77.9)	153.91 (40.7)	53 (61.6)	53 (61.6)	NR	NR	74 (86.0)	35 (40.7)	High-intensity statin: 34.6% Other-intensity statin: 30.2% No statin: 35.2%
	BA	88	65 (9.8)	40 (45.5)	70 (79.5)	145.01 (38.3)	55 (62.5)	55 (62.5)	NR	NR	77 (87.5)	45 (51.1)	
	Ezetimibe	86	65.1 (8.4)	43 (50)	72 (83.7)	148.9 (41.8)	54 (62.8)	54 (62.8)	NR	NR	71 (82.6)	43 (50.0)	
	Placebo	41	65.4 (10.8)	24 (58.5)	34 (82.9)	153.5 (46.8)	26 (63.4)	26 (63.4)	NR	NR	35 (85.4)	17 (41.5)	
	Overall	301	64.3 (NR)	149 (49.5)	243 (80.7)	149.8 (NR)	188 (62.5)	188 (62.5)	NR	NR	257 (85.4)	140 (46.5)	
Phase II Bempedoic Acid Trials[80-83]													

Ballantyne 2016	**BA 120 mg**	43	59 (9.0)	17 (39.0)	37 (86.0)	134 (20.0)	NR	NR	NR	NR	NR	NR	Statin: 90% No Statin: 10%
	BA 180 mg	45	57 (10.0)	14 (31.0)	37 (82.0)	142 (28.0)	NR	NR	NR	NR	NR	NR	
	Placebo	45	56 (10.0)	23 (51.0)	37 (82.0)	131 (22.0)	NR	NR	NR	NR	NR	NR	
	Overall	133	57.3 (NR)	54 (41.0)	111 (83.0)	135.7 (NR)	NR	NR	NR	NR	NR	NR	
Thompson 2016	**Statin Intolerant**	177	62 (9.0)	76 (43.0)	158 (89.0)	169 (25.0)	NR	NR	NR	NR	NR	NR	NR
	Statin Tolerant	171	57 (9.0)	91 (53.0)	156 (91.0)	160 (25.0)	NR	NR	NR	NR	NR	NR	
	Overall	348	59.5 (NR)	17 (44.0)	314 (83.0)	164.6 (NR)	NR	NR	NR	NR	NR	NR	
Gutierrez 2014	**BA**	30	55.3 (6.9)	17 (56.7)	29 (96.7)	125.2 (27.5)	NR	NR	NR	NR	8 (26.7)	NR	NR
	Placebo	30	56 (9.9)	20 (66.7)	28 (93.3)	128.4 (28.5)	NR	NR	NR	NR	8 (26.7)	NR	
	Overall	60	55.7 (NR)	37 (61.7)	57 (85)	126.8 (NR)	NR	NR	NR	NR	16 (26.7)	NR	
Lalwani 2019	**Atorva-statin + BA**	41	58 (10.0)	20 (48.8)	30 (73.2)	71 (19.0)	NR	NR	NR	NR	NR	NR	Statin: 100%
	Atorvastatin + Placebo	23	58 (8.0)	13 (56.6)	19 (82.6)	86 (26.0)	NR	NR	NR	NR	NR	NR	
	Overall	64	58 (NR)	33 (51.6)	49 (76.6)	76.4 (NR)	NR	NR	NR	NR	NR	NR	

ASCVD: atherosclerotic cardiovascular disease, BA: bempedoic acid, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, mg/dL: milligram per deciliter, N: total number

Table D3. Baseline Characteristics II

Trial	Arm	n	HDL-C, mg/dL	Non-HDL-C, mg/dL	Total Cholesterol, mg/dL	Triglycerides, mg/dL	ApoB, mg/dL	LpA, mg/dL	hsCRP, mg/dL	PCSK9, mcg/L
			Mean (SD)	Mean (SD)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Median (IQR)	Mean (SD)
Inclisiran Trials[84-88]										
ORION 9	**Inclisiran**	242	51.5 (15.1)	178.5 (55.4)	230 (54.6)	120 (82-167)	123.8 (33.2)	57 (22-180)	1.2 (0.5-2.9)	452.2 (131.2)
	Placebo	240	50.8 (13.1)	181.1 (62.5)	232.4 (62.8)	119 (85-166)	124.5 (34.8)	54 (20-185)	1.3 (0.6-3.2)	129.1 (135.2)
	Overall	482	51.2 (NR)	179.8 (NR)	231.2 (NR)	119.5 (NR)	124.1 (NR)	55.5 (NR)	1.2 (NR)	291.3 (NR)
ORION 10	**Inclisiran**	781	46.6 (14.3)	134 (44.5)	180.6 (46.1)	127 (92-181)	94.1 (25.6)	57 (18-181)	2.2 (0.9-4.8)	422.1 (176.9)
	Placebo	780	45.9 (14.4)	134.7 (43.5)	180.6 (43.6)	129 (96-182)	94.6 (25.1)	56 (20-189)	2 (1.0-5.5)	414.9 (145.7)
	Overall	1561	46.3 (NR)	134.3 (NR)	180.6 (NR)	128 (NR)	94.3 (NR)	56.5 (NR)	2.1 (NR)	418.5 (NR)
ORION 11	**Inclisiran**	810	49.7 (15.5)	137.6 (46.9)	187.3 (48.2)	135 (99-181)	97.1 (28)	42 (18-178)	1.5 (0.7-3.6)	355 (98.9)
	Placebo	807	49.3 (13.8)	133.9 (41)	183.3 (42.8)	135 (102-185)	95.1 (5.2)	35 (18-181)	1.6 (0.8-3.7)	353 (97.4)
	Overall	1617	49.5 (NR)	135.8 (NR)	185.3 (NR)	135 (NR)	96.1 (NR)	38.5 (NR)	1.5 (NR)	354 (NR)
ORION 1†	**Inclisiran 300 mg**	61	47.4 (13.6)	165.4 (61)	221.7 (65.5)	132 (105-185)	107.4 (32.1)	49 (12-161)	1.8 (0.7-3.8)	416.3 (127.3)
	Placebo	62	51.2 (16.1)	157.1 (53.7)	208.4 (54.7)	137 (103-187)	104.6 (31.5)	50 (11-154)	1.6 (0.8-4.4)	431.3 (132.3)
Phase III Bempedoic Acid Trials[72,75-77] [73]										
CLEAR Wisdom	**BA**	522	51.4 (12.9)	150.7 (42.7)	202.1 (42.7)	139 (103-190)	116.2 (29.6)	NR	1.61 (0.87-3.46)	NR
	Placebo	257	51.1 (13.1)	153.7 (44.4)	204.8 (46.1)	143 (106-189)	118.6 (30.5)	NR	1.88 (0.92-3.79)	NR
	Overall	779	51.3 (NR)	151.7 (NR)	203 (NR)	141 (NR)	117 (NR)	NR	1.7 (NR)	NR
CLEAR Harmony	**BA**	1488	48.7 (11.9)	130.9 (33.7)	179.7 (25.1)	126 (98-166)	88.5 (21.6)	NR	1.49 (0.74-3.28)	NR
	Placebo	742	49.3 (11.5)	129.4 (33.9)	178.6 (35.6)	123 (96-170)	86.8 (21.8)	NR	1.51 (0.79-3.33)	NR
	Overall	2230	48.9 (NR)	130.4 (NR)	179.3 (NR)	125 (NR)	87.9 (NR)	NR	1.5 (NR)	NR
CLEAR Serenity	**BA**	234	52.2 (14.5)	193.5 (45.1)	245.7 (47.3)	157 (115-219)	141 (31.6)	NR	2.92 (1.34-5.29)	NR

	Placebo	111	50.4 (14.4)	190.7 (43.8)	241.1 (44.3)	164 (120-226)	141.9 (30.4)	NR	2.78 (1.21-5.15)	NR
	Overall	345	51.6 (NR)	192.6 (NR)	244.2 (NR)	159 (NR)	141.3 (NR)	NR	2.9 (NR)	NR
CLEAR Tranquility	**BA**	181	55.8 (16.3)	162.4 (35.4)	218.2 (35.9)	153 (112-209)	123.3 (26.5)	NR	2.21 (1.1-4)	NR
	Placebo	88	57.1 (21.3)	151.6 (31.7)	208.6 (35.7)	136 (100-176)	115.8 (23.5)	NR	2.26 (1.06-4.5)	NR
	Overall	269	56.2 (NR)	158.9 (NR)	215.1 (NR)	147 (NR)	120.8 (NR)	NR	2.2 (NR)	NR
Ballantyne 2020	**BA + ezetimibe**	86	49.1 (14.7)	188.3 (46.8)	237.4 (48.7)	157 (106-209)	121.1 (30.9)	NR	3.1 (1.7-6.2)	NR
	BA	88	49.8 (12.4)	175.6 (40.6)	225.4 (43.3)	141 (108-190)	113.4 (26.4)	NR	2.9 (1.4-5)	NR
	Ezetimibe	86	51.4 (15.9)	180.2 (47.2)	231.2 (50.7)	143 (110-212)	115.5 (31.3)	NR	2.8 (1.3-5.9)	NR
	Placebo	41	50.2 (13.9)	180.9 (49.8)	231. 2 (50.2)	139 (105-168)	115.1 (32.5)	NR	3 (1.3-5.5)	NR
	Overall	301	50.2 (NR)	181.3 (NR)	231.3 (NR)	146 (NR)	116.4 (NR)	NR	2.9 (NR)	NR
Phase II Bempedoic Acid Trials[80-83]										
Ballantyne 2016	**BA 120 mg**	43	55 (15)	NR	216 (24)	112 (88-178)	NR	NR	1.8 (0.9-3.1)	NR
	BA 180 mg	45	55 (14)	NR	229 (29)	145 (122-196)	NR	NR	1.8 (1.2-4.0)	NR
	Placebo	45	54 (14)	NR	212 (24)	119 (82-159)	NR	NR	1.8 (1.1-4.6)	NR
	Overall	133	54.7 (NR)	NR	219 (NR)	125.5 (NR)	NR	NR	1.8 (NR)	NR
Thompson 2016	**Statin Intolerant**	177	53 (13)	NR	255 (33)	157 (52-365)	NR	NR	1.9 (0.2-31.7)	NR
	Statin Tolerant	171	51 (15)	NR	244 (31)	150 (38-434)	NR	NR	2.2 (0.1-22.5)	NR
	Overall	348	52 (NR)	NR	249.6 (NR)	153.6 (NR)	NR	NR	2 (NR)	NR
Gutierrez 2014	**BA**	30	43.7 (10.1)	NR	206.3 (36.1)	181.5 (86-572)*	NR	NR	2.3 (0.2-12.5)*	NR
	Placebo	30	47.4 (11.8)	NR	206.7 (34.1)	152 (81-248)*	NR	NR	2.2 (0.4-13.1)*	NR
	Overall	60	45.6 (NR)	NR	206.5 (NR)	166.8 (NR)	NR	NR	2.3 (NR)	NR
Lalwani 2019	**Atorvastatin + BA**	41	49 (16)	96 (24)	146 (27)	104 (52-331)*	70 (15)	NR	3.2 (0.1-14.8)*	NR
	Atorvastatin + Placebo	23	47 (9)	114 (28)	161 (28)	124 (74-286)*	82 (21)	NR	2.5 (0.1-17.0)*	NR

	Overall	64	48.3 (NR)	102.5 (NR)	151.4 (NR)	111.2 (NR)	74.3 (NR)	NR	2.9 (NR)	NR

ApoB: apolipoprotein B, BA: bempedoic acid, HDL-C: high-density lipoprotein cholesterol, IQR: interquartile range, LpA: lipoprotein A cholesterol, hsCRP: high sensitivity c-reactive protein, mcg/L: micrograms per liter, mg/dL: milligram per deciliter, NR: not reported, PCSK9: proprotein convertase subtilisin/kexin type 9, SD: standard deviation

* Median (Min - Max)

† Two-Dose Regimen

Table D4. Key Efficacy Outcomes I

Trial	Arm	n	Time-point	Percent Change in LDL-C, mg/dL		Absolute Change in LDL-C, mg/dL	
				% Change	Between group Diff	Absolute Change	Between group Diff
				Mean (95% CI)	Mean (95%CI), p-value	Mean (95%CI)	Mean (95%CI), p-value
Inclisiran Trials[84-88]							
ORION 9	**Inclisiran**	242	Day 510	-39.7 (-43.7, -35.7)	-47.9 (-53.5, -42.3), <0.001	-59 (-64.8, -53.2)	-68.9 (-77.1, -60.7), <0.001
	Placebo	240		8.2 (4.3, 12.2)		9.9 (4.1, 15.8)	
ORION 10	**Inclisiran**	781	Day 510	-51.3 (NR)	-52.3 (-55.7, -48.8), <0.001	-56.2 (NR)	-54.1 (-57.4, -50.9), <0.001
	Placebo	780		1 (NR)		-2.1 (NR)	
ORION 11	**Inclisiran**	810	Day 510	-45.8 (NR)	-49.9 (-53.1, -46.6), <0.001	-50.9 (NR)	-51.9 (-55.0, -48.7), <0.001
	Placebo	807		4 (NR)		1 (NR)	
ORION 1	**Inclisiran 300 mg, two-dose regimen**	59	Day 180	-52.6 (-57.1, -48.1)	NR	-64.2 (SD: 20.7)	NR
	Placebo, two dose regimen	61		1.8 (-2.6, 6.3)		-0.7 (SD: 25.6)	NR
	Inclisiran 300 mg, two-dose regimen	59	Day 360	-31.9 (-34.1, -29.0)	NR	NR	NR
	Placebo, two dose regimen	61		0.4 (-1.8, 2.8)		NR	NR
Phase III Bempedoic Acid Trials[72,75-77] [73]							
CLEAR Wisdom	**Bempedoic acid**	498	Week 12	-15.1 (NR)	-17.4 (-21.0, -13.9), <0.001	NR	NR
	Placebo	253		2.4 (NR)		NR	
	Bempedoic acid	485	Week 24	-12.1 (NR)	-14.8 (-19.5, -10.0) <0.001	NR	NR
	Placebo	247		2.7 (NR)		NR	
	Bempedoic acid	467	Week 52	NR	NR	NR	NR

	Placebo	237		NR		NR	
CLEAR Harmony	**Bempedoic acid**	1424	Week 12	-16.5 (SE: 0.52)	-18.1 (-20.0, -16.1), <0.001	-19.2 (SD: 24.0)	NR
	Placebo	725		1.6 (SE: 0.86)		0.4 (SD: 27.0)	
	Bempedoic acid	1397	Week 24	-14.9 (NR)	-16.1 (-18.2, -14.0), <0.001	NR	NR
	Placebo	707		1.2 (NR)		NR	
	Bempedoic acid	1364	Week 52	-12.6 (NR)	NR	NR	NR
	Placebo	685		1 (NR)		NR	
CLEAR Serenity	**Bempedoic acid**	234	Week 12	-23.6 (SE: 1.4)	-21.4 (-25.1, -17.7), <0.001	39.3 (NR)	NR
	Placebo	111		-1.3 (SE: 1.4)		-3.1 (NR)	
	Bempedoic acid	107	Week 24	-21.2 (SE: 1.4)	-18.9 (-23.0, -14.9), <0.001	-37 (NR)	NR
	Placebo	224		-2.3 (SE: 1.6)		-5.1 (NR)	
CLEAR Tranquility	**Bempedoic acid**	175	Week 12	-23.5 (SE: 2)	-28.5 (-34.4, -22.5), <0.001	-32 (SE: 2.5)	NR
	Placebo	82		5 (SE: 2.2)		4 (SE: 2.6)	NR (NR), <0.001
Ballantyne 2020 (Post-hoc analysis)	**BA + EZE FDC**	86	Week 12	-36.2 (SE: 2.6)	--	NR	NR
	Bempedoic acid	88		-17.2 (SE: 2.6)	-19 (-26.1, -11.9), <0.001	NR	NR
	Ezetimibe	86		-23.2 (SE: 2.2)	-13 (-19.7, -6.5), <0.001	NR	NR
	Placebo	41		1.8 (SE: 3.4)	-38 (-46.5, -29.6), <0.001	NR	NR
Ballantyne 2020 (ITT analysis)	**BA + EZE FDC**	108	Week 12	-31.5 (SE: 2.5)	--	NR	NR
	Bempedoic acid	110		-17.7 (SE: 2.2)	-13.8 (-20.4, -7.1), <0.001	NR	NR
	Ezetimibe	109		-21 (SE: 2)	-10.5 (-16.8, -4.2), 0.001	NR	NR
	Placebo	55		-2.5 (SE: 3.1)	-29 (-36.8, -21.3), <0.001	NR	NR

Phase II Bempedoic Acid Trials[80-83]							
Ballantyne 2016	**Bempedoic Acid 120 mg**	41	Week 12	-17.3 (SE: 4.0)	7 (NR), <0.01	NR	NR
	Bempedoic Acid 180 mg	43		-24.3 (SE: 4.2)	NR (NR), <0.0001	NR	NR
	Placebo	43		-4.2 (SE: 4.2)	--	NR	NR
Thompson 2016	**Bempedoic Acid 180mg**	99	Week 12	-30.1 (SE: 1.3)	NR (NR), <0.0001	NR	NR
	Bempedoic Acid 180 mg + Ezetimibe 10 mg	22		-47.7 (SE: 2.8)	NR (NR), <0.0001	NR	NR
	Ezetimibe 10 mg	98		-21.2 (SE: 1.3)	--	NR	NR
Gutierrez 2014	**Bempedoic Acid, 120 mg**	30	Week 4	-42.9 (SE: 2.9)	-39 (-46.2, -31.7), <0.0001	NR	NR
	Placebo	30		-4 (SE: 2.5)		NR	
Lalwani 2019	**Atorvastatin + Bempedoic Acid**	41	Week 4	-13 (SE: 4.12)	-22.2 (-36.4, -8.0), 0.003	-8.25 (NR)	NR
	Atorvastatin + Placebo	23		9.2 (SE: 5.58)		1 (NR)	

LDL-C: low-density lipoprotein cholesterol, mg/dL: milligram per deciliter, NR: not reported, SE: standard error, 95%CI: 95% confidence interval

Table D5. Key Efficacy Outcomes II

Trial	Arm	n	Time-adjusted Percent Change in LDL-C, mg/dL			Time-adjusted Absolute Change in LDL-C, mg/dL		
			Time Range	% Change	Between group Diff	Time Range	Absolute Change	Between group Diff
				Mean (95% CI)	Mean (95%CI), p-value		Mean (95%CI)	Mean (95%CI), p-value
Inclisiran Trials[84-88]								
ORION 9	**Inclisiran**	242	Day 90 to 540	-38.1 (-41.1, -35.1)	-47.9 (-48.5, -40.1), <0.001	Day 90 to 540	-56.9 (NR)	-62.6 (NR), <0.001
	Placebo	240		6.2 (3.3, 9.2)			5.8 (NR)	
ORION 10	**Inclisiran**	781	Day 90 to 540	-51.3 (NR)	-53.8 (-56.2, -51.3), <0.001	Day 90 to 540	-53.7 (NR)	-53.3 (-55.8, -50.8), <0.001
	Placebo	780		2.5 (NR)			-0.4 (NR)	
ORION 11	**Inclisiran**	810	Day 90 to 540	-45.8 (NR)	-49.2 (-51.6, -46.8), <0.001	Day 90 to 540	-48.6 (NR)	-48.9 (-51.4, -46.5), <0.001
	Placebo	807		3.4 (NR)			0.3 (NR)	
ORION 1	**Inclisiran 300 mg, two-dose regimen**	59	NR	NR	NR	NR	NR	NR
	Placebo, two dose regimen	61	NR	NR	NR	NR	NR	NR
	Inclisiran 300 mg, two-dose regimen	59	Day 30 to 360	-46.7 (-50.3, -42.5)	NR	NR	NR	NR
	Placebo, two dose regimen	61		NR	NR	NR	NR	NR
Phase III Bempedoic Acid Trials[72,75-77 73]								
CLEAR Wisdom	**Bempedoic acid**	498	NR	NR	NR	NR	NR	NR
	Placebo	253	NR	NR		NR	NR	NR
	Bempedoic acid	485	NR	NR	NR	NR	NR	NR

	Placebo	247	NR	NR		NR	NR	NR
	Bempedoic acid	467	NR	NR	NR	NR	NR	NR
	Placebo	237	NR	NR		NR	NR	NR
CLEAR Harmony	**Bempedoic acid**	1424	NR	NR	NR	NR	NR	NR
	Placebo	725	NR	NR		NR	NR	NR
	Bempedoic acid	1397	NR	NR	NR	NR	NR	NR
	Placebo	707	NR	NR		NR	NR	NR
	Bempedoic acid	1364	NR	NR	NR	NR	NR	NR
	Placebo	685	NR	NR		NR	NR	NR
CLEAR Serenity	**Bempedoic acid**	234	NR	NR	NR	NR	NR	NR
	Placebo	111	NR	NR		NR	NR	NR
	Bempedoic acid	107	NR	NR	NR	NR	NR	NR
	Placebo	224	NR	NR		NR	NR	NR
CLEAR Tranquility	**Bempedoic acid**	175	NR	NR	NR	NR	NR	NR
	Placebo	82	NR	NR		NR	NR	NR
Ballantyne 2020 (Post-hoc analysis)	**BA + EZE FDC**	86	NR	NR	NR	NR	NR	NR
	Bempedoic acid	88	NR	NR	NR	NR	NR	NR
	Ezetimibe	86	NR	NR	NR	NR	NR	NR
	Placebo	41	NR	NR	NR	NR	NR	NR
	BA + EZE FDC	108	NR	NR	NR	NR	NR	NR

Ballantyne 2020 (ITT analysis)	**Bempedoic acid**	110	NR	NR	NR	NR	NR	NR
	Ezetimibe	109	NR	NR	NR	NR	NR	NR
	Placebo	55	NR	NR	NR	NR	NR	NR
Phase II Bempedoic Acid Trials[80-83]								
Ballantyne 2016	**Bempedoic Acid 120 mg**	41	NR	NR	NR	NR	NR	NR
	Bempedoic Acid 180 mg	43	NR	NR	NR	NR	NR	NR
	Placebo	43	NR	NR	NR	NR	NR	NR
Thompson 2016	**Bempedoic Acid 180mg**	99	NR	NR	NR	NR	NR	NR
	Bempedoic Acid 180 mg + Ezetimibe 10 mg	22	NR	NR	NR	NR	NR	NR
	Ezetimibe 10 mg	98	NR	NR	NR	NR	NR	NR
Gutierrez 2014	**Bempedoic Acid, 120 mg**	30	NR	NR	NR	NR	NR	NR
	Placebo	30	NR	NR		NR	NR	NR
Lalwani 2019	**Atorvastatin + Bempedoic Acid**	41	NR	NR	NR	NR	NR	NR
	Atorvastatin + Placebo	23	NR	NR		NR	NR	NR

LDL-C: low-density lipoprotein cholesterol, mg/dL: milligram per deciliter, NR: not reported, SE: standard error, 95%CI: 95% confidence interval

Table D6. Key Efficacy Outcomes III

Trial	Arm	n	Timepoint	Percent Change in HDL-C, mg/dL		Percent Change in Total Cholesterol, mg/dL	
				% Change	Between group Diff	% Change	Between group Diff
				Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value
Inclisiran Trials[84-88]							
ORION 9	**Inclisiran**	242	Day 510	8.6 (NR)	2.6 (NR), NR	-26.1 (NR)	-32.9 (NR), NR
	Placebo	240		6 (NR)		6.8 (NR)	
ORION 10	**Inclisiran**	781	Day 510	7.5 (NR)	5.1 (NR), NR	-33.6 (NR)	-33.1 (NR), <0.001
	Placebo	780		2.4 (NR)		0.4 (NR)	
ORION 11	**Inclisiran**	810	Day 510	10.2 (NR)	6.1 (NR), NR	-28 (NR)	-29.8 (NR), <0.001
	Placebo	807		4.4 (NR)		1.8 (NR)	
ORION 1	**Inclisiran 300 mg, two-dose regimen**	59	Day 180	8.6 (SD: 14.9)	NR (NR), <0.01	-33.2 (SD: 11.3)	NR (NR), <0.001
	Placebo, two dose regimen	61		0.5 (SD: 12.5)		0.7 (SD: 12.3)	
Phase III Bempedoic Acid Trials[72,75-77 73]							
CLEAR Wisdom	**Bempedoic acid**	498	Week 12	-6.4 (SE: 0.7)	-6.1 (-8.4, -3.9), <0.001	-9.9 (SE: 0.7)	-11.2 (-13.6, -8.8), <0.001
	Placebo	253		-0.2 (SE: 0.9)		1.3 (SE: 1.0)	
	Bempedoic acid	485	Week 24	-4.7 (SE: 0.8)	-5.2 (-7.6, -2.9), <0.001	-9.3 (SE: 0.9)	-10.8 (-13.7, -7.8), <0.001
	Placebo	247		0.5 (SE: 0.9)		1.5 (SE: 1.2)	
	Bempedoic acid	467	Week 52	-7.4 (SE: 0.8)	-4 (-6.3, -1.7), <0.001	-10.3 (SE: 0.8)	-8.4 (-11.2, -5.5), <0.001
	Placebo	237		-3.4 (SE: 0.8)		-1.9 (SE: 1.2)	
CLEAR Harmony	**Bempedoic acid**	1424	Week 12	NR	NR	-10.3 (SE: 0.37)	-11.1 (-12.5, -9.8), <0.001
	Placebo	725		NR		0.8 (SE: 0.57)	
	Bempedoic acid	1397	Week 24	NR	NR	-9.8 (NR)	NR
	Placebo	707		NR		1.1 (NR)	
	Bempedoic acid	1364	Week 52	NR	NR	-8.9 (NR)	NR

	Placebo	685		NR		0.3 (NR)	
CLEAR Serenity	**Bempedoic acid**	234	Week 12	NR	NR	-16.1 (SE: 1.0)	-14.8 (-17.3, -12.2), <0.001
	Placebo	111		NR		-0.6 (SE: 1.0)	
	Bempedoic acid	107	Week 24	-5.2 (SE: 1.1)	-4.5 (-7.5, -1.6), 0.003	-15.5 (SE: 1.0)	-14.5 (-17.2, -11.8), <0.001
	Placebo	224		0.6 (SE: 1.0)		-1 (SE:1.0)	
CLEAR Tranquility	**Bempedoic acid**	175	Week 12	-7.3 (SE: 1.2)	NR (NR), 0.002	-15.1 (SE: 1.3)	-18 (SE: 2), <0.001
	Placebo	82		-1.4 (SE: 1.4)	--	2.9 (SE: 1.5)	
Ballantyne 2020 (Post-hoc analysis)	**BA + EZE FDC**	86	Week 12	NR	NR	-26.4 (SE: 1.9)	--
	Bempedoic acid	88		NR	NR	-12.1 (SE: 1.8)	-14.2 (-20.4, -8.1), <0.001
	Ezetimibe	86		NR	NR	-16 (SE: 1.6)	-10.4 (-16.1, 4.6), <0.001
	Placebo	41		NR	NR	0.7 (SE: 2.5)	-27.1 (-35.1, 19.1), <0.001
Ballantyne 2020 (ITT analysis)	**BA + EZE FDC**	108	Week 12	NR	NR	-22.6 (SE: 1.9)	--
	Bempedoic acid	110		NR	NR	-12.8 (SE: 1.7)	-9.8 (-15.7, -3.9), <0.001
	Ezetimibe	109		NR	NR	-13.5 (SE: 1.5)	-9.1 (-14.8, -3.4), <0.001
	Placebo	55		NR	NR	-2 (SE: 2.2)	-20.6 (-28, -13.2), <0.001
Phase II Bempedoic Acid Trials[80-83]							
Ballantyne 2016	**Bempedoic Acid 120 mg**	41	Week 12	-6.1 (SE: 2.6)	NR (NR), NS)	-12.8 (SE: 2.7)	NR (NR), <0.01
	Bempedoic Acid 180 mg	43		-4 (SE: 2.7)	NR (NR), NS)	-15.3 (SE: 2.9)	NR (NR), <0.01
	Placebo	43		-2 (SE: 2.7)	--	-3.2 (SE: 2.9)	--
Thompson 2016	**Bempedoic Acid 180mg**	99	Week 12	-4.8 (SE: 1.4)	NR (NR), <0.0001	-20.7 (SE: 0.9)	NR (NR), <0.001
	Bempedoic Acid 180 mg + Ezetimibe 10 mg	22		-3.7 (SE: 3.0)	NR (NR), <0.01	-34.3 (SE: 2.0)	NR (NR), <0.001

	Ezetimibe 10 mg	98		5 (SE: 1.4)	--	-14.3 (SE: 0.9)	--
Gutierrez 2014	**Bempedoic Acid, 120 mg**	30	Week 4	-1.2 (SE: 1.8)	-1.8 (-6.9, 3.4), 0.4965	-25.1 (SE: 1.9)	-24.6 (-29.9, -19.4), <0.0001
	Placebo	30		0.5 (SE: 1.8)		-0.5 (SE: 1.9)	
Lalwani 2019	**Atorvastatin + Bempedoic Acid**	41	Week 4	-1.6 (SE: 2.3_	-6.31 (-14.1, 1.5), 0.109	-5.7 (SE: 2.3)	-9.81 (-17.6, -2.1), 0.014
	Atorvastatin + Placebo	23		4.7 (SE: 3.1)		4.1 (SE: 3.1)	

BA: bempedoic acid, EZE: ezetimibe, HDL-C: high-density lipoprotein cholesterol, IQR: interquartile range, Med: median, mg: milligram, NR: not reported, SD: standard deviation, SE: standard error, 95%CI: 95% confidence interval

Table D7. Key Efficacy Outcomes IV

Trial	Arm	n	Timepoint	Percent Change in Non-HDL-C, mg/dL		Percent Change in Triglyceride, mg/dL	
				% Change	Between group Diff	% Change	Between group Diff
				Mean (95% CI)	Mean (95%CI), p-value	Median (95% CI)	Mean (95%CI), p-value
Inclisiran Trials[84-88]							
ORION 9	**Inclisiran**	242	Day 510	-36.1 (NR)	-43.6 (NR), NR	11.1 (NR)	-11.8 (NR), NR
	Placebo	240		7.5 (NR)		-0.7 (NR)	
ORION 10	**Inclisiran**	781	Day 510	-47.4 (NR)	-47.4 (NR), <0.001	-14.9 (NR)	-12.6 (NR), NR
	Placebo	780		-0.1 (NR)		-2.3 (NR)	
ORION 11	**Inclisiran**	810	Day 510	-41.2 (NR)	-43.3 (NR), <0.001	-12 (NR)	-7 (NR), NR
	Placebo	807		2.2 (NR)		-5 (NR)	
ORION 1	**Inclisiran 300 mg, two-dose regimen**	59	Day 180	-40.6 (SD: 14.6)	NR (NR), <0.001	-14.2 (-26.4, 5.4)	NR (NR), <0.05
	Placebo, two dose regimen	61		1.3 (SD: 16.9)		-3 (-17.2, 22.6)	
Phase III Bempedoic Acid Trials[72,75-77 73]							
CLEAR Wisdom	**Bempedoic acid**	498	Week 12	-10.8 (SE: 1.0)	-13, (-16.3, -9.8), <0.001	11 (SE: 2.3)	4.9 (-1.5, 11.3), 0.13
	Placebo	253		2.3 (SE: 1.4)		6.1 (SE: 2.3)	
	Bempedoic acid	485	Week 24	-10.2 (SE: 1.2)	-12.6 (-16.6, -8.7), <0.001	6.4 (SE: 2.1)	1.7 (-4.4, 7.8), 0.59
	Placebo	247		2.4 (SE: 1.6)		4.7 (SE: 2.2)	
	Bempedoic acid	467	Week 52	-10.3 (SE: 1.2)	-9.9 (-13.8, -6.0), <0.001	6 (SE: 1.9)	1.2 (-5.0, 7.4), 0.71
	Placebo	237		-0.4 (SE: 1.6)		4.8 (SE: 2.5)	
CLEAR Harmony	**Bempedoic acid**	1424	Week 12	-11.9 (SE: 0.5)	-13.3 (-15.1, -11.6), <0.001	NR	NR
	Placebo	725		1.5 (SE: 0.76)		NR	NR
	Bempedoic acid	1397	Week 24	-11.6 (NR)	NR	NR	NR
	Placebo	707		1.5 (NR)		NR	NR

	Bempedoic acid	1364	Week 52	-10 (NR)	NR	NR	NR
	Placebo	685		0.5 (NR)		NR	NR
CLEAR Serenity	**Bempedoic acid**	234	Week 12	-19 (SE: 1.3)	-17.9 (-21.1, -14.8), <0.001	NR	NR
	Placebo	111		-0.4 (SE: 1.0)		NR	NR
	Bempedoic acid	107	Week 24	-18 (SE: 1.2)	-17.1 (-20.5, -13.7), <0.001	7.9 (SE: 2.7)	0.4 (-8.2, 9.0), 0.921
	Placebo	224		0.9 (SE: 1.3)		7.4 (SE: 3.5)	
CLEAR Tranquility	**Bempedoic acid**	175	Week 12	-18.4 (SE: 1.7)	-23.6 (SE: 2.8), <0.001	-1.4 (NR)	NR
	Placebo	82		5.2 (SE: 2.3)		7.8 (NR)	NR
Ballantyne 2020 (Post-hoc analysis)	**BA + EZE FDC**	86	Week 12	-31.9 (SE: 2.2)	--	NR	NR
	Bempedoic acid	88		-14.1 (SE: 2.2)	-17.8 (-25.1, -10.5), <0.001	NR	NR
	Ezetimibe	86		-19.9 (SE: 2.1)	-12.1 (-19.1, -5), <0.001	NR	NR
	Placebo	41		1.8 (SE: 3.3)	-33.7 (-43.9, -23.4), <0.001	NR	NR
Ballantyne 2020 (ITT analysis)	**BA + EZE FDC**	108	Week 12	-27.2 (SE: 2.2)	--	NR	NR
	Bempedoic acid	110		-14.9 (SE: 2)	-12.3 (-19.3, -5.3), <0.001	NR	NR
	Ezetimibe	109		-16.3 (SE: 2)	-10.9 (-17.9, -3.9), <0.001	NR	NR
	Placebo	55		-1.8 (SE: 2.8)	-25.4 (-34.6, 16.1), <0.001	NR	NR
Phase II Bempedoic Acid Trials[80-83]							
Ballantyne 2016	**Bempedoic Acid 120 mg**	41	Week 12	-14.3 (SE: 3.7)	NR (NR), <0.01	-4.8 (IQR: 28)	NR (NR), NS
	Bempedoic Acid 180 mg	43		-16.6 (SE: 3.9)	NR (NR), <0.01	-9.1 (IQR: 47)	NR (NR), NS
	Placebo	43		-1.8 (SE: 3.9)	--	-3 (IQR: 37)	NR
Thompson 2016	**Bempedoic Acid 180mg**	99	Week 12	-25.4 (SE: 1.1)	NR (NR), <0.0001	-2.7 (IQR: 46.2)	NR

	Bempedoic Acid 180 mg + Ezetimibe 10 mg	22		-42.4 (SE: 2.4)	NR (NR), <0.0001	-12.2 (IQR: 36.5)	NR
	Ezetimibe 10 mg	98		-18.7 (SE: 1.2)	--	-7 (IQR: 32.9)	NR
Gutierrez 2014	**Bempedoic Acid, 120 mg**	30	Week 4	-32 (SE: 2.3)	-31.4 (-38.0, 24.8), <0.0001	-1 (NR)	NR (NR), 0.1219
	Placebo	30		-0.5 (SE: 2.3)		8 (NR)	
Lalwani 2019	**Atorvastatin + Bempedoic Acid**	41	Week 4	-7.4 (SE: 3.1)	-13.4 (-24.1, -2.7), 0.015	-1.04 (SD: 37.5)	9.31 (-7.5, 27.3), 0.251
	Atorvastatin + Placebo	23		6.1 (SE: 4.2)		-9.31 (SD: 38.9)	

BA: bempedoic acid, EZE: ezetimibe, HDL-C: high-density lipoprotein cholesterol, IQR: interquartile range, Med: median, mg: milligram, NR: not reported, SD: standard deviation, SE: standard error, 95%CI: 95% confidence interval

Table D8. Key Efficacy Outcomes V

Trial	Arm	n	Time-point	Percent Change in hsCRP		Percent Change in ApoB		Percent Change in Lp(a)		Percent Change in PCSK9		Absolute Change in PCSK9, mcg/L	
				% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff
				Median (95% CI)	Median (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value
Inclisiran Trials[84-88]													
ORION 9	**Inclisiran**	242	Day 510	0 (NR)	4 (NR), NR	-34 (NR)	-36.9 (NR), NR	Med: -13.5 (NR)	-17.2 (NR), NR	-60.7 (-64.4, -57.0)	-78.4 (-83.7, -73.0), <0.001	-282.6 (-297.6, -267.2)	-337.1 (-358.9, -315.3), <0.001
	Placebo	240		4 (NR)		2.9 (NR)		Med: 3.7 (NR)		17.7 (13.9, 21.4)		54.5 (39.1, 70.0)	
ORION 10	**Inclisiran**	781	Day 510	0 (NR)	8.8 (NR), NR	-44.8 (NR)	-43.1 (NR), <0.001	Med: -21.9 (NR)	-25.6 (NR), NR	-69.8 (NR)	-83.3 (-89.3, 77.3), <0.001	NR	NR
	Placebo	780		-8.8 (NR)		-1.7 (NR)		Med: 3.7 (NR)		13.5 (NR)		NR	
ORION 11	**Inclisiran**	810	Day 510	0 (NR)	8.9 (NR), NR	-32.8 (NR)	-38.9 (NR), <0.001	Med: -18.6 (NR)	-18.6 (NR), NR	-63.6 (NR)	-79.3 (-82, -76.6), <0.001	NR	NR
	Placebo	807		-8.9 (NR)		0.8 (NR)		Med: 0 (NR)		15.6 (NR)		NR	
ORION 1	**Inclisiran 300 mg, two-dose regimen**	59	Day 180	-16.7 (-50.9, 33.3)	NR (NR), <0.05	-40.9 (SD: 14.8)	NR (NR), <0.001	-25.6 (-38.5, 15.2)	NR (NR), NS	-69.1 (SD: 12.1)	NR (NR), <0.001	NR	NR
	Placebo, two dose regimen	61		-20 (-50, 30)		0.9 (SD: 13.0)		0 (-10.0, 12.4)		-1.2 (SD: 20.7)		NR	

	Inclisiran 300 mg, two-dose regimen	59	Day 360	NR	NR	NR	NR	NR	NR	-38.4 (-41.6, -34.6)	NR (NR), <0.001	-60.4 (-64.5, -56.7)	NR
	Placebo, two dose regimen	61		NR		NR		NR		-1.4 (-4.9, 1.9)		NR	
Phase III Bempedoic Acid Trials[72,75-77] [73]													
CLEAR Wisdom	**BA**	498	Week 12	-18.7 (-46.1, 23.9)	-8.7 (-17.2, -0.4), 0.04	-9.3 (SE: 0.9)	-13 (-16.1, -9.9), <0.001	NR	NR	NR	NR	NR	NR
	Placebo	253		-9.4 (-36.3, 35.2)		3.7 (SE: 1.3)		NR	NR	NR	NR	NR	
	BA	485	Week 24	-24.1 (-51.5, 14.0)	-21.3 (-32.3, -10.0), <0.001	-8.6 (SE: 1.3)	-13 (-17.8, -8.2), <0.001	NR	NR	NR	NR	NR	NR
	Placebo	247		1.6 (-32.2, 47.5)		4.4 (SE: 2.1)		NR	NR	NR	NR	NR	
	BA	467	Week 52	-16.7 (-50.9, 31.4)	-7.6 (-17.0, 1.7), 0.1	-6.6 (SE: 1.0)	-9.6 (-13.1, 6.0), <0.001	NR	NR	NR	NR	NR	NR
	Placebo	237		-6.3 (-39.3, 41.8)		3 (SE: 1.5)		NR	NR	NR	NR	NR	
CLEAR Harmony	**BA**	1424	Week 12	-22.4 (IQR: 72.5)	-21.5 (-27.0, -16.0), <0.001	-8.6 (SE: 0.5)	-11.9 (-13.6, -10.2), <0.001	NR	NR	NR	NR	NR	NR
	Placebo	725		2.6 (IQR: 91.9)		3.3 (SE: 0.7)		NR	NR	NR	NR	NR	
	BA	1397	Week 24	-16.4 (NR)	NR	-7 (NR)	NR	NR	NR	NR	NR	NR	NR
	Placebo	707		2.7 (NR)		4.4 (NR)		NR	NR	NR	NR	NR	

	BA	1364	Week 52	-14.4 (NR)	NR	-5.9 (NR)	NR	NR	NR	NR	NR	NR	NR
	Placebo	685		1.8 (NR)		3.1 (NR)		NR	NR	NR	NR	NR	
CLEAR Serenity	**BA**	234	Week 12	-25.4 (NR)	-24.3 (-35.9, -12.7), <0.001	-15.5 (SE: 1.2)	-15 (-18.1, -11.0), <0.001	NR	NR	NR	NR	NR	NR
	Placebo	111		2.7 (NR)		-0.2 (SE: 1.3)		NR	NR	NR	NR	NR	
	BA	107	Week 24	-25.1 (IQR: 73.7)	-27.1 (-40.5, -13.7), <0.001	-15 (SE: 1.1)	-15.5 (-18.8, -12.2), <0.001	NR	NR	NR	NR	NR	NR
	Placebo	224		4.4 (IQR: 67.8)		0.5 (SE: 1.3)		NR	NR	NR	NR	NR	
CLEAR Tranq-uility	**BA**	175	Week 12	-32.5 (NR)	-31 (NR), <0.001	-14.6 (SE: 1.5)	-19.3 (SE: 2.3), <0.001	NR	NR	NR	NR	NR	NR
	Placebo	82		2.1 (NR)		4.7 (SE: 1.8)		NR	NR	NR	NR	NR	
Ballan-tyne 2020 (Post-hoc analysis)	**BA + EZE FDC**	86	Week 12	-35.1 (NR)	--	-24.6 (SE: 2.4)	--	NR	NR	NR	NR	NR	NR
	BA	88		-31.9 (NR)	NS	-11.8 (SE: 2.2)	-12.8 (-20.3, -5.3), <0.001	NR	NR	NR	NR	NR	NR
	EZE	86		-8.2 (NR)	-25.6 (-45, -7.2), 0.002	-15.3 (SE: 2)	-9.3 (-16.5, -2.1), <0.003	NR	NR	NR	NR	NR	NR
	Placebo	41		21.6 (NR)	-46.1 (-78.8, -15.8), <0.001	5.5 (SE: 3)	-30.1 (-39.9, -20.3), <0.001	NR	NR	NR	NR	NR	NR
Ballan-tyne 2020 (ITT analysis)	**BA + EZE FDC**	108	Week 12	-34 (NR)	--	-20.1 (SE: 2.3)	--	NR	NR	NR	NR	NR	NR
	BA	110		-20 (NR)	NS	-11.7 (SE: 2.2)	-8.4 (-15.6, -1.1), 0.008	NR	NR	NR	NR	NR	NR

	EZE	109		-8.5 (NR)	-19 (-36.6, -2), 0.01	-13.1 (SE: 1.8)	-6.9 (-13.6, -0.2), 0.016	NR	NR	NR	NR	NR	NR
	Placebo	55		4 (NR)	-37.2 (-64.5, -13.3), <0.001	1.6 (SE: 2.8)	-21.7 (-30.9, -12.5), <0.001	NR	NR	NR	NR	NR	NR
Phase II Bempedoic Acid Trials[80-83]													
Ballan-tyne 2016	**BA 120 mg**	41	Week 12	21.8 (IQR:44)	NR (NR), NS	-15 (SE: 3.3)	NR (NR), <0.05	NR	NR	NR	NR	NR	NR
	BA 180 mg	43		-29.8 (IQR:50)	NR (NR), NS	-17.2 (SE: 3.4)	NR (NR), <0.01	NR	NR	NR	NR	NR	NR
	Placebo	43		0 (IQR: 0)	--	-5.5 (SE: 3.4)	--	NR	NR	NR	NR	NR	NR
Thomp-son 2016	**BA 180mg**	99	Week 12	-40.2 (IQR: 53.3)	NR (NR), <0.01	-21.3 (SE: 1.3)	NR	NR	NR	NR	NR	NR	NR
	BA 180 mg + EZE 10 mg	22		-25.6 (IQR: 37.2)	NR (NR), <0.05	-35.2 (SE: 2.6)	NR (NR), <0.0001	NR	NR	NR	NR	NR	NR
	EZE 10 mg	98		-10.5 (IQR:59)	NR	-15.2 (SE: 1.2)	NR	NR	NR	NR	NR	NR	NR
Gutierrez 2014	**BA, 120 mg**	30	Week 4	-40.1 (NR)	NR (NR), 0.0011	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	30		-10.8 (NR)		NR		NR	NR	NR	NR	NR	
Lalwani 2019	**Atorvast atin + BA**	41	Week 4	-34.6 (SD: 96.5)	-44.2 (-69.9, -16.2), 0.002	-9.04 (SE: 2.9)	-14.9 (-24.9, -4.9), 0.004	NR	NR	NR	NR	NR	NR
	Atorvast atin + Placebo	23		0.74 (SD: 50.9)		5.88 (SE: 3.9)		NR	NR	NR	NR	NR	NR

ApoB: apolipoprotein B, BA: bempedoic acid, EZE: ezetimibe, HDL-C: high-density lipoprotein cholesterol, IQR: interquartile range, LpA: lipoprotein A cholesterol, hsCRP: high sensitivity c-reactive protein, mcg/L: micrograms per liter, Med: median, mg/dL: milligram per deciliter, NR: not reported, NS: not significant, PCSK9: proprotein convertase subtilisin/kexin type 9, SD: standard deviation, SE: standard error, 95%CI: 95% confidence interval

Table D9. Percent Change in LDL-C – Subgroups

Trial	Population	Arm	n	Timepoint	Percent Change in LDL-C			
					% Change		Difference	
					Mean	(95% CI)	Mean	(95% CI)
ORION 9[84]	**Overall (HeFH)**	**Inclisiran**	242	Day 510	-39.7	(-43.7, -35.7)	-47.9	(-53.5, -42.3)
		Placebo	240		8.2	(4.3, 12.2)	--	--
ORION 10[88]	**Overall (ASCVD)**	**Inclisiran**	781	Day 510	-51.3	NR	-52.3	(-55.7, -48.8)
		Placebo	780		1	NR	--	--
	Statin at BL	**Inclisiran**	701		NR		-57.3	(-60.7, -54.0)
		Placebo	692				--	--
	No statin at BL	**Inclisiran**	80				-54.8	(-62.0, -47.6)
		Placebo	88				--	--
ORION 11[88]	**Overall (ASCVD or RE)**	**Inclisiran**	810	Day 510	-45.8	NR	-49.9	(-53.1, -46.6)
		Placebo	807		4	NR	--	--
	Statin at BL	**Inclisiran**	766		NR		-53.3	(-56.5, -50.1)
		Placebo	766				--	--
	No statin at BL	**Inclisiran**	44				-41.6	(-51.1, -32.1)
		Placebo	41				--	--
	ASCVD	**Inclisiran**	712				-53.3	(-56.6, -50.1)
		Placebo	702				--	--
	ASCVD-risk equivalent	**Inclisiran**	98				-47.2	(-56.1, -38.3)
		Placebo	105				--	--
ORION 1[85]	**Overall**	**Inclisiran**	59	Day 180	-52.6	(-57.1, -48.1)	NR	NR
		Placebo	61		1.8	(-2.6, 6.3)	--	--
CLEAR Wisdom[75]	**Overall (ASCVD, HeFH, or both)**	**Bempedoic acid**	498	Week 12	-15.1	NR	-17.4	(-21.0, -13.9)
		Placebo	253		2.4	NR	--	--

	HeFH ± ASCVD	**Bempedoic acid**	17		NR	NR	-28.3	(-42.2, -14.3)
		Placebo	13		NR	NR	--	--
	ASCVD Only	**Bempedoic acid**	474		NR	NR	-17.3	(-21.1, -13.7)
		Placebo	237		NR	NR	--	--
	High intensity statin	**Bempedoic acid**	271		-14.4	SE: 1.5	-17.2	(-22.3, -12.1)
		Placebo	135		2.8	SE: 2.1	--	--
	Low/mod intensity statin	**Bempedoic acid**	179		-14.9	SE: 1.6	-18.1	(-23.4, -12.8)
		Placebo	89		3.2	SE: 2.1	--	--
	No statin	**Bempedoic acid**	48		-24.6	SE: 3.6	-22	(-33.4, -10.6)
		Placebo	29		-2.6	SE: 4.4	--	--
CLEAR Harmony[77]	**Overall (ASCVD, HeFH, or both)**	**Bempedoic acid**	1424	Week 12	-16.5	SE: 0.52	-18.1	(-20.0, -16.1)
		Placebo	725		1.6	SE: 0.86	--	--
	ASCVD	**Bempedoic acid**	1388		NR		-18.6	(-20.6, -16.7)
		Placebo	710				--	--
	HeFH	**Bempedoic acid**	54				-20.6	(-35.7, -5.4)
		Placebo	23				--	--
	Low/mod intensity statin	**Bempedoic acid**	706				-20	(-22.8, -17.3)
		Placebo	362				--	--
	High intensity statin	**Bempedoic acid**	718				-17.5	(-20.2, -14.7)
		Placebo	363				--	--
	Background Ezetimibe	**Bempedoic acid**	112				-15.8	(-23.5, -8.2)
		Placebo	53				--	--
	Background Fibrate	**Bempedoic acid**	51				-23.8	(-34.1, -13.5)
		Placebo	25				--	--
CLEAR Harmony & Wisdom	**Overall (ASCVD, HeFH, or both)**	**Bempedoic acid**	2010	Week 12	-16	NR	-17.8	(-19.5, -16.0)
		Placebo	999		1.8	NR	--	--

Pooled[74]	**With ASCVD**	**Bempedoic acid**	1869		NR		-18.4	(-20.1, -16.7)
		Placebo	953				--	--
	Without ASCVD	**Bempedoic acid**	53				-21.8	(-36.5, -7.1)
		Placebo	25				--	--
	With HeFH	**Bempedoic acid**	71				-22.3	(-33.3, -11.4)
		Placebo	36				--	--
	Without HeFH	**Bempedoic acid**	1851				-18.3	(-20.1, -16.6)
		Placebo	942				--	--
	Low/mod intensity statin	**Bempedoic acid**	882				-19.7	(-22.2, -17.3)
		Placebo	451				--	--
	High intensity statin	**Bempedoic acid**	989				-17.3	(-19.7, -14.9)
		Placebo	498				--	--
	No statin	**Bempedoic acid**	51				-22	(-33.5, -10.5)
		Placebo	29				--	--
	Ezetimibe	**Bempedoic acid**	144				-13.4	(-20.5, -6.2)
		Placebo	73				--	--
	No Ezetimibe	**Bempedoic acid**	1778				-18.8	(-20.6, -17.1)
		Placebo	905				--	--
CLEAR Serenity[76]	**Overall (statin intolerant)**	**Bempedoic acid**	234	Week 12	-23.6	SE: 1.4	-21.4	(-25.1, -17.7)
		Placebo	111		-1.3	SE: 1.4	--	--
	Statin	**Bempedoic acid**	18		NR		-17.5	(-30.1, -4.7)
		Placebo	10				--	--
	Nonstatin	**Bempedoic acid**	79				-23.6	(-29.9, -17.3)
		Placebo	33				--	--
	No LLT	**Bempedoic acid**	127				-22.5	(-26.8, -17.5)
		Placebo	64				--	--

	Primary Prevention	**Bempedoic acid**	140				-23.8	(-27.9, -19.5)
		Placebo	64				--	--
	Secondary Prevention/HeFH	**Bempedoic acid**	84				-19.7	(-26.6, -12.9)
		Placebo	43				--	--
CLEAR Tranquility[72]	**Overall (statin intolerant)**	**Bempedoic acid**	175	Week 12	-23.5	SE: 2	-28.5	(-34.4, -22.5)
		Placebo	82		5	SE: 2.2	--	--
	Statin	**Bempedoic acid**	56		NR	NR	-20.5	(-33.44, -7.58)
		Placebo	22		NR	NR	--	--
	Other LLT	**Bempedoic acid**	119		NR	NR	-34.7	(-40.82, -28.66)
		Placebo	60		NR	NR	--	--
Ballantyne 2016[80]	**Overall**	**Bempedoic Acid 120 mg**	41	Week 12	-17.3	SE: 4.0	NR	NR
		Bempedoic Acid 180 mg	43		-24.3	SE: 4.2	--	--
		Placebo	43		-4.2	SE: 4.2	NR	NR
Thompson 2016[83]	**Overall**	**Bempedoic Acid 180mg**	99	Week 12	-30.1	SE: 1.3	NR	NR
		Bempedoic Acid 180 mg + Ezetimibe 10 mg	22		-47.7	SE: 2.8	NR	NR
		Ezetimibe 10 mg	98		-21.2	SE: 1.3	NR	NR
	Statin Tolerant	**Bempedoic Acid 180mg**	49		-30.2	SE: 1.9	NR	NR
		Bempedoic Acid 180 mg + Ezetimibe 10 mg	12		-47.5	SE: 4.2	NR	NR
		Ezetimibe 10 mg	47		-24.2	SE: 2.1	NR	NR
	Statin Intolerant	**Bempedoic Acid 180mg**	50		-31.2	SE: 1.4	NR	NR

		Bempedoic Acid 180 mg + Ezetimibe 10 mg	10		-50.8	SE: 3.6	NR	NR
		Ezetimibe 10 mg	51		-20.3	SE: 1.6	NR	NR
Ballantyne 2020[73]	**Overall**	**BA + EZE FDC**	86	Week 12	-36.2	SE: 2.6	--	--
		Bempedoic acid	88		-17.2	SE: 2.6	-19	(-26.1, -11.9)
		Ezetimibe	86		-23.2	SE: 2.2	-13.1	(-19.7, -6.5)
		Placebo	41		1.8	SE: 3.4	-38	(-46.5, -29.6)
	ASCVD ± HeFH	**BA + EZE FDC**	50		NR		--	--
		Bempedoic acid	54				-23	(-31, -14.1)
		Ezetimibe	49				-15.2	(-23.6, -6.6)
		Placebo	26				-40	(-51.7, -29)
	Multiple CV Risk Factors	**BA + EZE FDC**	33				--	--
		Bempedoic acid	28				-13.3	(-26.6, -2.8)
		Ezetimibe	31				-10.4	(-21.5, 1.2)
		Placebo	14				-37.2	(-51.7, -23)
	High Intensity Statin at BL	**BA + EZE FDC**	30				--	--
		Bempedoic acid	26				-25.6	(-39.6, -11.6)
		Ezetimibe	26				-12.3	(-23.6, -1.2)
		Placebo	16				-45.2	(-63, -27.8)
	Other Intensity Statin at BL	**BA + EZE FDC**	20				--	--
		Bempedoic acid	29				-12.8	(-25.8, -0.2)
		Ezetimibe	24				-8.9	(-23.4, -5.6)
		Placebo	11				-31.2	(-45.5, -16.2)
	No statin at BL	**BA + EZE FDC**	33				--	--
		Bempedoic acid	27				-19.2	(-31.2, -7)
		Ezetimibe	30				-16	(-26, -5.6)

		Placebo	13			-39.2	(-52, -26.6)

ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, BA: bempedoic acid, BL: baseline, EZE: ezetimibe, HeFH: heterozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein cholesterol, NR: not reported, SE: standard error, 95%CI: 95% confidence interval

Table D10. Safety Outcomes I

Trial	Arm	n	Time-point	Any AE n (%)	TEAE n (%)	Study Drug-Related AEs n (%)	D/C due to AE n (%)	Serious AE n (%)	Fatal TEAE n (%)	Uric Acid Increase n (%)	Gout n (%)	Myal-gia n (%)	Injection -Site Rxn n (%)
Inclisiran Trials[84-88]													
ORION 9	**Inclisiran**	241	Day 510	185 (76.8)	185 (76.8)	NR	3 (1.2)	18 (7.5)	NR	NR	NR	8 (3.3)	41 (17)
	Placebo	240		172 (71.7)	172 (71.7)	NR	0 (0)	33 (13.8)	NR	NR	NR	5 (2.1)	4 (1.7)
ORION 10	**Inclisiran**	781	Day 510	574 (73.5)	574 (73.5)	NR	19 (2.4)	175 (22.4)	NR	NR	NR	NR	20 (2.6)
	Placebo	778		582 (74.8)	582 (74.8)	NR	17 (2.2)	205 (26.3)	NR	NR	NR	NR	7 (0.9)
ORION 11	**Inclisiran**	811	Day 510	671 (82.7)	671 (82.7)	NR	23 (2.8)	181 (22.3)	NR	NR	NR	21 (2.6)	38 (4.7)
	Placebo	804		655 (81.5)	655 (81.5)	NR	18 (2.2)	181 (22.5)	NR	NR	NR	23 (2.9)	4 (0.5)
ORION 1*	**Inclisiran 300 mg**	62	Day 210	47 (77.0)	NR	NR	0 (0)	7 (11)	NR	NR	NR	5 (8)	4 (7)
	Placebo	62		50 (81.0)	NR	NR	1 (2)	6 (10	NR	NR	NR	3 (5)	0 (0)
Phase III Bempedoic Acid Trials[72,75-77 73]													
CLEAR Wisdom	**BA**	522	Week 52	366 (70.1)	366 (70.1)	91 (17.4)	57 (10.9)	106 (20.3)	6 (1.1)	36 (6.9)	11 (2.1)	15 (2.9)	NA
	Placebo	257		182 (70.8)	182 (70.8)	32 (12.5)	22 (8.6)	48 (18.7)	2 (0.8)	6 (2.3)	2 (0.8)	8 (3.1)	
CLEAR Harmony	**BA**	1487	Week 52	1167 (78.5)	1167 (78.5)	NR	162 (10.9)	216 (14.5)	8 (0.5)	34 (2.3)	18 (1.2)	89 (6)	
	Placebo	742		584 (78.7)	584 (78.7)	NR	53 (7.1)	104 (14)	2 (0.3)	5 (0.7)	2 (0.3)	45 (6.1)	
CLEAR Serenity	**BA**	234	Week 24	150 (64.1)	150 (64.1)	51 (21.8)	43 (18.4)	14 (6)	0 (0)	6 (2.6)	4 (1.7)	8 (7.2)	

	Placebo	111		63 (56.8)	63 (56.8)	20 (18)	13 (11.7)	4 (3.6)	0 (0)	0 (0)	1 (0.9)	11 (4.7)	
CLEAR Tranquility	**BA**	181	Week 12	88 (48.6)	88 (48.6)	39 (21.5)	11 (6.1)	5 (2.8)	0 (0)	14 (7.7)	0 (0)	3 (1.7)	
	Placebo	87		39 (44.8)	39 (44.8)	8 (9.2)	5 (5.7)	3 (3.4)	0 (0)	2 (2.3)	0 (0)	2 (2.3)	
Ballantyne 2020	**BA + EZE**	85	Week 12	NR	53 (62.4)	13 (15.3)	7 (8.2)	8 (9.4)	0 (0)	3 (3.5)	0 (0)	2 (2.4)	
	BA	88		NR	58 (65.9)	12 (13.6)	9 (10.2)	7 (8)	0 (0)	1 (1.1)	0 (0)	5 (5.7)	
	EZE	86		NR	47 (54.7)	9 (10.5)	10 (11.6)	9 (10.5)	0 (0)	0 (0)	0 (0)	2 (2.3)	
	Placebo	41		NR	18 (43.9)	4 (9.8)	2 (4.9)	1 (2.4)	0 (0)	0 (0)	0 (0)	1 (2.4)	
Ballantyne 2016	**BA 120 mg**	43	Week 12	15 (35)	15 (35)	4 (9)	0 (0)	0 (0)	NR	NR	NR	1 (2)	
	BA 180 mg	45		28 (62)	28 (62)	8 (18)	2 (4)	1 (2)	NR	NR	NR	0 (0)	
	Placebo	45		28 (62)	28 (62)	9 (20)	3 (7)	2 (4)	NR	NR	NR	2 (4)	
Phase II Bempedoic Acid Trials[80-83]													
Thompson 2016	**BA 180mg**	100	Week 12	55 (55)	55 (55)	18 (18)	6 (6)	1 (1)	0 (0)	NR	NR	1 (1)	NA
	BA 180 mg + EZE 10 mg	24		17 (71)	17 (71)	10 (42)	1 (4)	0 (0)	0 (0)	NR	NR	1 (4)	
	EZE 10 mg	99		53 (54)	53 (54)	19 (19)	8 (8)	1 (1)	0 (0)	NR	NR	6 (6)	
Gutierrez 2014	**BA**	30	Week 4	14 (47)	NR	NR	0 (0)	NR	NR	NR	NR	0 (0)	
	Placebo	30		21 (70)	NR	NR	1 (3)	NR	NR	NR	NR	0 (0)	
Lalwani 2019	**Atorva-statin + BA**	45	Week 4	16 (35.6)	NR	7 (15.6)	1 (2.2)	0 (0)	NR	NR	0 (0)	2 (4.4)	
	Atorva-statin + Placebo	23		5 (21.7)	NR	1 (4.3)	0 (0)	0 (0)	NR	NR	1 (4.3)	0 (0)	

AE: adverse event, BA: bempedoic acid, D/C: discontinuation, EZE: ezetimibe, mg: milligram, n: number, NA: not applicable, NR: not reported, Rxn: reaction, TEAE: treatment-emergent adverse event

*Two-Dose Regimen

Table D11. Safety Outcomes II

Trial	Arm	n	Time-point	Diabetes Mellitus	Death		CV Death		Cancer-Related Death		Myocardial Infarction (Fatal or Nonfatal)		Stroke (Fatal or Nonfatal)	
				n (%)	n (%)	RR (95%CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Inclisiran Trials[84-88]														
ORION 9	**Inclisiran**	241	Day 510	NR	1 (0.4)	1.0 (0.1, 15.8)	1 (0.4)	NA	NR	NR	3 (1.2)	3.0 (0.3, 28.5)	0 (0)	NA
	Placebo	240		NR	1 (0.4)		0 (0)		NR		1 (0.4)		0 (0)	
ORION 10	**Inclisiran**	781	Day 510	120 (15.4)	12 (1.5)	1.1 (0.5, 2.4)	7 (0.9)	1.4 (0.4, 4.4)	1 (0.1)	0.3 (0.0, 3.2)	20 (2.6)	1.1 (0.6, 2.1)	11 (1.4)	1.6 (0.6, 4.0)
	Placebo	778		108 (13.9)	11 (1.4)		5 (0.6)		3 (0.4)		18 (2.3)		7 (0.9)	
ORION 11	**Inclisiran**	811	Day 510	88 (10.9)	14 (1.7)	0.9 (0.4, 1.9)	9 (1.1)	0.9 (0.4, 2.2)	3 (0.4)	1.0 (0.2, 4.9)	10 (1.2)	0.5 (0.2, 0.9)	2 (0.2)	0.2 (0.1, 1.2)
	Placebo	804		94 (11.7)	15 (1.9)		10 (1.2)		3 (0.4)		22 (2.7)		8 (1)	
ORION 1	**Inclisiran 300 mg, two-dose regimen**	62	Day 210	NR	0 (0)	NA	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo, two dose regimen	62		NR	0 (0)		NR		NR		NR		NR	
Phase III Bempedoic Acid Trials[72,75-77 73]														
CLEAR Wisdom	**BA**	522	52 weeks	36 (6.9)	6 (1.1)	NR	4 (0.8)	0.98 (0.18, 5.34)	0 (0)	NA	6 (1.1)	0.33 (0.12, 0.91)	4 (0.8)	0.98 (0.18, 5.34)
	Placebo	257		19 (7.4)	2 (0.8)		2 (0.8)		0 (0)		9 (3.5)		2 (0.8)	
CLEAR Harmony	**BA**	1487	52 weeks	49 (3.3)	13 (0.9)	3.24 (0.73, 14.34)	6 (0.4)	2.99 (0.36, 24.82)	NR	NR	19 (1.3)	0.73 (0.36, 24.82)	5 (0.3)	1.25 (0.24, 6.41)
	Placebo	742		40 (5.4)	2 (0.3)		1 (0.1)		NR	NR	13 (1.8)		2 (0.3)	

CLEAR Serenity	**BA**	234	24 weeks	5 (2.1)	0 (0)	NA	0 (0)	NA	NR	NR	1 (0.4)	NR	2 (0.9)	NR
	Placebo	111		5 (4.5)	0 (0)		0 (0)		NR	NR	0 (0)		0 (0)	
CLEAR Tranquility	**BA**	181	Week 12	2 (1.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	87		2 (2.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ballantyne 2020	**BA + EZE**	85	Week 12	NR	NR	NR	NR	NR	NR	NR	1 (1.2)	NR	NR	NR
	BA	88		NR	NR	NR	NR	NR	NR	NR	2 (2.3)	NR	NR	NR
	EZE	86		NR	NR	NR	NR	NR	NR	NR	3 (3.5)	NR	NR	NR
	Placebo	41		NR	NR	NR	NR	NR	NR	NR	0 (0)	NR	NR	NR
Phase II Bempedoic Acid Trials[80-83]														
Ballantyne 2016	**BA 120 mg**	**43**	Week 12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BA 180 mg	**45**		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	**45**		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thompson 2016	**BA 180mg**	**100**	Week 12	NR	0 (0)	NA	NR	NR	NR	NR	NR	NR	NR	NR
	BA 180 mg + EZE 10 mg	**24**		NR	0 (0)	NA	NR	NR	NR	NR	NR	NR	NR	NR
	EZE 10 mg	**99**		NR	0 (0)	NA	NR	NR	NR	NR	NR	NR	NR	NR
Gutierrez 2014	**BA**	**30**	Week 4	NR	NR	NR	NR	NR	NR	NR	0 (0)	NR	NR	NR
	Placebo	**30**		NR	NR	NR	NR	NR	NR	NR	1 (3.3)		NR	
Lalwani 2019	**Atorvastatin + BA**	**45**	Week 4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Atorvastatin + Placebo	**23**		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

BA: bempedoic acid, EZE: ezetimibe, n: number, NA: not applicable, NR: not reported, RR: risk ratio, 95%CI: 95% confidence interval

Table D12. Safety Outcomes III

Trial	Arm	n	Timepoint	Composite CV Event*		New or Worsening Cancer		ALT >3x ULN	AST >3x ULN	Creatine kinase >5x ULN
				n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	n (%)	n (%)
Inclisiran Trials[84-88]										
ORION 9	**Inclisiran**	241	Day 510	10 (4.1)	1.0 (0.4, 2.3)	2 (0.8)	0.7 (0.1, 3.9)	3 (1.2)	2 (0.8)	4 (1.7)
	Placebo	240		10 (4.2)		3 (1.2)		1 (0.4)	1 (0.4)	3 (1.2)
ORION 10	**Inclisiran**	781	Day 510	58 (7.4)	0.7 (0.5, 1.0)	26 (3.3)	1.0 (0.6, 1.7)	2 (0.3)	4 (0.5)	10 (1.3)
	Placebo	778		79 (10.2)		26 (3.3)		2 (0.3)	5 (0.6)	8 (1)
ORION 11	**Inclisiran**	811	Day 510	63 (7.8)	0.8 (0.6, 1.0)	16 (2)	0.8 (0.1, 1.5)	4 (0.5)	2 (0.2)	10 (1.2)
	Placebo	804		83 (10.3)		20 (2.5)		4 (0.5)	4 (0.5)	9 (1.1)
ORION 1	**Inclisiran 300 mg, two-dose regimen**	62	Day 210	NR	NR	NR	NR	1 (2)	0 (0)	0 (0)
	Placebo, two dose regimen	62		NR		NR		0 (0)	0 (0)	0 (0)
Phase III Bempedoic Acid Trials[72,75-77 73]										
CLEAR Wisdom	**Bempedoic acid**	522	52 weeks	32 (6.1)	0.75 (0.44, 1.27)	NR	NR	6 (1.1)		0 (0)
	Placebo	257		21 (8.2)		NR		2 (0.8)		1 (0.4)
CLEAR Harmony	**Bempedoic acid**	1487	52 weeks	68 (4.6)	0.81 (0.56, 1.17)	NR	NR	7 (0.5)		7 (0.5)
	Placebo	742		42 (5.7)		NR		1 (0.1)		1 (0.1)
CLEAR Serenity	**Bempedoic acid**	234	24 weeks	NR	NR	NR	NR	NR	NR	NR
	Placebo	111		NR	NR	NR	NR	NR	NR	NR
CLEAR Tranquility	**Bempedoic acid**	181	Week 12	NR	NR	NR	NR	Liver function test increased: 7 (3.9)		NR
	Placebo	87		NR	NR	NR	NR	Liver function test increased: 0 (0)		NR
Ballantyne 2020	**Bempedoic acid + ezetimibe**	85	Week 12	NR	NR	NR	NR	1 (1.2)		0 (0)
	Bempedoic acid	88		NR	NR	NR	NR	0 (0)		0 (0)
	Ezetimibe	86		NR	NR	NR	NR	0 (0)		0 (0)
	Placebo	41		NR	NR	NR	NR	0 (0)		0 (0)

Phase II Bempedoic Acid Trials[80-83]										
Ballantyne 2016	**Bempedoic Acid 120 mg**	43	Week 12	NR	NR	NR	NR	0 (0)	0 (0)	0 (0)
	Bempedoic Acid 180 mg	45		NR	NR	NR	NR	0 (0)	1 (2)	0 (0)
	Placebo	45		NR	NR	NR	NR	0 (0)	0 (0)	0 (0)
Thompson 2016	**Bempedoic Acid 180mg**	100	Week 12	NR	NR	NR	NR	NR	NR	NR
	Bempedoic Acid 180 mg + Ezetimibe 10 mg	24		NR	NR	NR	NR	NR	NR	NR
	Ezetimibe 10 mg	99		NR	NR	NR	NR	NR	NR	NR
Gutierrez 2014	**Bempedoic Acid**	30	Week 4	NR	NR	NR	NR	NR	NR	NR
	Placebo	30		NR	NR	NR	NR	NR	NR	NR
Lalwani 2019	**Atorvastatin + Bempedoic Acid**	45	Week 4	NR	NR	NR	NR	0 (0)	0 (0)	1 (2)
	Atorvastatin + Placebo	23		NR	NR	NR	NR	0 (0)	0 (0)	0 (0)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CV: cardiovascular, n: number, NA: not applicable, NR: not reported, RR: risk ratio, ULN: upper limit of normal, 95%CI: 95% confidence interval

* Composite CV event defined in ORION 9, 10, and 11 as exploratory cardiovascular events (cardiovascular basket of non-adjudicated terms), including those classified in the *Medical Dictionary for Regulatory Activities* as cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or nonfatal stroke. CLEAR Wisdom and Harmony defined the composite CV event endpoint as 5-point MACE including CV death, myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization. All other trials abstracted did not report a composite CV event endpoint.

Table D13. Study Quality

Trial	Comp. Groups	Non-differential Follow-up	Patient/Investigator Blinding (Double-Blind)	Clear Definition of Intervention	Clear Definition of Outcomes	Selective Outcome Reporting	Measurements Valid	Intention to Treat Analysis	Approach to Missing Data	USPSTF Rating
Inclisiran Trials[84-88]										
ORION-9	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple imputation	Good
ORION-10	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple imputation	Good
ORION-11	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple imputation	Good
ORION-1	Yes	Not Reported	Yes	Yes	Yes	No	Yes	Yes	ITT analysis with imputation	Good
Phase III Bempedoic Acid Trials[72,75-77 73]										
CLEAR Wisdom	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Pattern Mixture Imputation	Fair
CLEAR Harmony	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Pattern Mixture Imputation	Good
CLEAR Serenity	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Pattern Mixture Imputation	Good
CLEAR Tranquility	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple imputation	Good
Ballantyne 2020	Yes	No	Yes	Yes	Yes	No	Yes	No	Multiple imputation	Fair

Comp.: comparable, ITT: intent to treat, USPSTF: United States Preventive Services Task Force

Appendix E. Comparative Value Supplemental Information

Table E1. 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)
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[149]

Description of 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.

3. 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.[150]

4. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

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

6. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

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

8. 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.

Table E2. Results for the Base Case for Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin*

	Statin + Ezetimibe	Bempedoic acid + Ezetimibe + Statin
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07 (13.87-16.19)	15.35 (14.11-16.53)
Mean survival (discounted)	11.48 (10.74-12.16)	11.66 (10.90-12.37)
Incremental survival (discounted)	Comparator	0.18 (0.11-0.25)
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.57 (9.89-11.22)	10.74 (10.02-11.40)
Incremental QALYs (discounted)	Comparator	0.17 (0.11-0.23)
Lifetime MACE, mean number	1.01	0.95
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.65	2.37
Stroke	0.87	0.79
Death from cardiovascular causes	2.51	2.32
Composite MACE	5.06	4.75
Direct Health Care Costs		
Lifetime health care Costs, 2020 USD (discounted)	$185,000 ($159,000-$209,000)	$216,000 ($190,000-$241,000)
Spending on lipid-lowering therapies	$4,000 ($3,000-$4,000)	$35,000 ($33,000-$37,000)
Spending on cardiovascular care	$106,000 ($87,000-$119,000)	$105,000 ($86,000-$119,000)
Background Health Care Costs	$75,000 ($61,000-$93,000)	$76,000 ($61,000-$94,000)
Incremental health care costs, 2020 USD (discounted)	Comparator	$31,000 (429,000-$34,000)
ICER, $ per MACE averted	Comparator	$535,000
ICER, $ per life-year gained	Comparator	$175,000 ($132,000-$277,000)
ICER, $ per QALY gained	Comparator	$186,000 ($140,000-$293,000)
ICER, $ per evLYG	Comparator	$168,000 ($128,000-$260,000)

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)
Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.
*The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin
†Rates of adverse events are estimated from the first five years of the model run.

Table E3. Results for the Base Case for Inclisiran + Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin*

	Statin + Ezetimibe	Inclisiran + Statin + Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07 (13.87-16.19)	15.80 (14.50-17.10)
Mean survival (discounted)	11.48 (10.74-12.16)	11.94 (11.15-12.72)
Incremental survival (discounted)	Comparator	0.46 (0.29-0.66)
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.57 (9.89-11.22)	11.01 (10.25-11.72)
Incremental QALYs (discounted)	Comparator	0.44 (0.27-0.61)
Lifetime MACE, mean number	1.01	0.86
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.65	1.81
Stroke	0.87	0.70
Death from cardiovascular causes	2.51	2.00
Composite MACE	5.06	4.34
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD (discounted)	$185,000 ($159,000-$209,000)	$253,000 ($225,000-$281,000)
Spending on lipid-lowering therapies	$4,000 ($3,000-$4,000)	$73,000 ($68,000-$$77,000)
Spending on cardiovascular care	$106,000 ($87,000-$119,000)	$103,000 ($85,000 - $118,000)
Background Health Care Costs	$75,000 ($61,000-$93,000)	$78,000 ($63,000-$96,000)
Incremental Health Care Costs, 2020 USD (discounted)	Comparator	$68,000 ($63,000-$74,000)
ICER, $ per MACE averted	Comparator	$451,000
ICER, $ per life-year gained	Comparator	$147,000 ($112,000-$221,000)
ICER, $ per QALY gained	Comparator	$157,000 ($119,000-$232,000)
ICER, $ per evLYG	Comparator	$142,000 ($109,000-$208,000)

evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020) Costs and ICERs rounded to the nearest thousand. Numbers may not sum due to rounding.

*Using assumed placeholder price. The base case assumed that 10% of the population is statin-intolerant and therefore not on a statin.

†Rates of adverse events are estimated from the first five years of the model run.

Table E4. Threshold Unit Prices in Individuals with Established ASCVD

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	11.00	7.82	2.52	4.51	6.50	8.50
evLYG	11.00	7.82	2.73	4.93	7.14	9.35
Inclisiran						
QALYs Gained	N/A*	2,822.00**	931.50	1,836.00	2,740.50	3,644.50
evLYG	N/A*	2,822.00**	1,025.50	2,023.50	3,022.00	4,020.00

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Table E5. Threshold Unit Prices in Individuals with Established ASCVD and Heterozygous FH

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	11.00	7.82	4.11	7.71	11.31	14.91
evLYG	11.00	7.82	4.49	8.47	12.45	16.43
Inclisiran						
QALYs Gained	N/A*	2,822.00**	1,862.00	3,718.00	5,573.50	7,429.50
evLYG	N/A*	2,822.00**	3,724	7,436	11,147	14,859

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Table E6. Threshold Unit Prices in Statin-Intolerant Individuals with Established ASCVD

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	11.00	7.82	4.98	9.22	13.45	17.69
evLYG	11.00	7.82	5.45	10.14	14.84	19.54
Inclisiran						
QALYs Gained	N/A*	2,822.00**	1,535.00	2,985.50	4,436.00	5,886.50
evLYG	N/A*	2,822.00**	1,689.00	3,293.00	4,897.50	6,502.00

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Table E7. Threshold Unit Prices in Individuals with Established ASCD and Recent ACS

Outcome	WAC	Net price (Base-case price, derived from Federal Supply Schedule, Aug 2020)	Price to Achieve $50,000 Threshold	Price to Achieve $100,000 Threshold	Price to Achieve $150,000 Threshold	Price to Achieve $200,000 Threshold
Bempedoic Acid/Ezetimibe						
QALYs Gained	11.00	7.82	2.74	4.82	6.89	8.96
evLYG	11.00	7.82	2.94	5.20	7.47	9.74
Inclisiran						
QALYs Gained	N/A*	2,822.00**	1,030.50	1,970.00	2,909.50	3,849.00
evLYG	N/A*	2,822.00**	1,115.50	2,140.00	3,164.50	4,189.00

evLYG: equal value of life-year gained, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Inclisiran is not available in the US market and therefore does not have a WAC or net price.

**The base case assumed a net price equal to the Federal Supply Schedule price for the PCSK9 inhibitors evolocumab and alirocumab in August 2020. The annual price is equal to the cost of two six-monthly doses (the first year requires an additional loading dose at 90 days).

Table E8. Cumulative Net Cost Per Patient Treated with Bempedoic Acid (in Combination with Ezetimibe) at Net Price and Inclisiran at Assumed Placeholder Price Over a Five-Year Time Horizon

	Bempedoic Acid/Ezetimibe		Inclisiran	
Year	Cumulative Cost	Additional Costs per Year (Non-Cumulative)	Cumulative Cost	Additional Costs per Year (Non-Cumulative)
Year 1	$2,508	$2,508	$8,004	$8,004
Year 2	$4,940	$2,432	$13,046	$5,042
Year 3	$7,316	$2,376	$17,994	$4,948
Year 4	$9,636	$2,320	$22,847	$4,853
Year 5	$11,900	$2,264	$27,603	$4,756

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on February 5, 2021. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

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Disclosures: Joaquim Cristino is a full-time employee of Novartis.

Cardiovascular disease (CVD) is the number one killer in the United States and deaths are increasing.[1-3] Atherosclerotic cardiovascular disease (ASCVD) accounts for a majority of CVD deaths and contributes to the economic burden of cardiovascular disease, which is projected to reach $1.1 trillion by 2035.[3,4] Up to 80% of patients with ASCVD on lipid-lowering therapies are not meeting their LDL-C target because current standard of care and suggested lifestyle changes have limitations.5 LDL-C is the most readily modifiable risk factor of ASCVD and there is a significant unmet need for an effective and long-lasting cholesterol-lowering option.[6] Novartis is confident in the value that inclisiran may bring to patients, the health care system and society. We are committed to pricing our drugs responsibly and if approved, the price will reflect the value of inclisiran as an innovative treatment with the potential to lower LDL-C in indicated patients.

Novartis appreciates the perspective shared by the Institute for Clinical and Economic Review (ICER) in its report; however, we believe there are two assumptions that ICER should revisit. Firstly, the cost-effectiveness model assumes the usage of inclisiran only on top of ezetimibe and statins in ASCVD patients. This concern was also raised by other stakeholders (expert clinicians, patient advocacy groups, patients and Esperion) at the public meeting. Some stakeholders felt such an assumption could perpetuate the access barriers for new innovative therapies, thus leading to high proportions of patients failing to meet their guideline-recommended LDL-C goals.

- This is an idealized scenario, and it is inconsistent with real-world practice (where only approximately 4.2% of ASCVD patients receive ezetimibe) and also the way inclisiran was studied.[7-9]

- In the ORION 10 and 11 clinical trials, inclisiran was studied on top of maximum tolerated statin dose and, although ezetimibe was allowed in the trial, it was not required.[8,9]

- Only 9.9% of the patients in ORION-10 and 7.1% of the patients in ORION-11 were receiving ezetimibe.[8]

- Consequently, the model assumes a lower LDL-C level in the real-world at baseline (a reduction from 104.97 mg/dL to 88.8 mg/dL).[7]

- This assumption implies an underestimation of the total number of CV events avoided by inclisiran in the ICER model.

- It is mentioned in the reply to the Novartis comments, the baseline LDL level is varied in sensitivity analysis, but the report offers no in-depth discussion of the implications of this assumption.

- In the cost-effectiveness analysis developed by Novartis, increasing the baseline LDL-C value from the 88.8 mg/dL assumed in the ICER model to the 104.97 mg/dL observed in real life, resulted in an approximately 30% decrease in the incremental cost- effectiveness ratio. The assumption of having inclisiran used only after ezetimibe undervalues the assessment of inclisiran.

- We strongly urge ICER to accept the feedback provided by multiple key stakeholders regarding the ezetimibe assumptions of the model in order to improve the external validity and utility of this effort for future decision-making.

Secondly, on a response to Novartis comments on the draft report, ICER stated that differential adherence between treatments is not assumed. Omitting the role and impact of treatment discontinuation in the analysis neglects real-life patient behavior, and can have a large impact on results.

- High medication burden (i.e., the frequency of administration) associated with statins has a negative impact on adherence and average LDL-C reduction over time, which will likely diminish the CV risk reduction benefits associated with statins. Therapeutics that reduce medication burden have the potential to improve adherence.[10]

- The biannual administration of inclisiran given by a healthcare professional (HCP) may potentially have an advantage over current therapies by mitigating typical adherence issues associated with patient self-administration (e.g., self-injection anxiety, delayed doses). For example, patients with osteoporosis (an asymptomatic and chronic condition) showed improved persistence and adherence with longer-acting HCP-administered regimens compared to weekly self-administered medications.[11-14]

- Different discontinuation rates between treatment regimens should be incorporated into the cost-effectiveness model, accounting for the expected improved adherence associated with the inclisiran administration. Novartis recommends the use of 11.5% as the annual discontinuation rate for inclisiran and 23% for statins.[11,15] The recommendation on the use of 11.5% as the discontinuation rate for inclisiran is derived by applying a rate ratio of 0.5 vs. statin discontinuation rates. This method is based on research published in osteoporosis, comparing the discontinuation rates observed by mode and frequency of administration. Research has shown similar discontinuation rates when adding ezetimibe to statin therapy (vs. statin monotherapy); thus, it is recommended to also to use a discontinuation rate of 23% for statins and ezetimibe.[16,17]

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Bempedoic acid (BA) (Nexletol®) and the fixed-dose combination with ezetimibe (Nexlizet®) were the first oral LDL-C-lowering medications approved for patients with ASCVD and HeFH in nearly twenty years. The Phase 3 program consisted of five trials involving almost 4,000 high risk patients and demonstrated mean placebo-corrected LDL-C reductions of 17.8%-24.5% with Nexletol and 38.0% with Nexlizet.[1,2,3,4,5,6] BA works in the same cholesterol synthesis pathway as statins, and its LDL-C lowering efficacy is more pronounced in the absence of statins.

Additionally, treatment with BA and with Nexlizet was associated with significant decreases in the inflammatory biomarker hsCRP, ranging from 19%-35% compared to baseline.[1] Both treatments were well-tolerated with an overall safety profile generally comparable to placebo. Unlike statins, BA is not active in skeletal muscle and is not associated with increased muscle pain and weakness, common symptoms of statin intolerance, compared to placebo. BA was associated with small mean increases in uric acid levels which were reversible after treatment cessation. Across all five Phase 3 trials, only one serious adverse event of gout was reported and only one patient discontinued treatment due to gout.[7] In addition, despite the fact that the majority of patients in the BA Phase 3 trials had either prediabetes (51.6%) or diabetes (31.3%) at baseline, treatment with BA did not worsen measures of glycemic control or increase new onset diabetes, and in fact was associated with a statistically significant improvement in HbA1c.[8] The CLEAR Cardiovascular Outcomes Trial, which has enrolled over 14,000 patients, is underway to evaluate the impact of BA on cardiovascular events in patients with or at high risk for cardiovascular disease who are statin intolerant.[9]

We would like to comment on three topics related to the ICER evaluation of Nexlizet:

1. As pointed out in several public comments, **maximally tolerated statins (MTS) plus 100% ezetimibe use is not the appropriate comparator.** Multiple recent large clinical trials, real world data and ICER's own NHANES analysis show that current ezetimibe usage ranges from 2-7% in the US, indicating physicians do not routinely prescribe it on top of MTS.[6,10,11,12,13] An analysis based on a comparator assuming 100% ezetimibe use does not reflect real-world practice and is only relevant for a small proportion of hypercholesterolemic ASCVD patients. If the comparator arm in ICER's analysis is changed to consist of MTS plus 10% ezetimibe use, Nexlizet is cost-effective in the overall ASCVD population (ICER<$100,000/QALY), and even more so in statin intolerant ASCVD patients (ICER<$50,000/QALY). This analysis, which is more reflective of real-world practice, demonstrates that current pricing for Nexlizet falls within an acceptable range to achieve moderate to high value for the overall ASCVD population and

statin intolerant ASCVD patients, respectively. Both treatments currently have favorable formulary coverage with the majority of commercial health plans.

There are approximately 10-15 million US patients with ASCVD/HeFH receiving MTS who are not at LDL-C goal.[14] While ICER notes that it is not recommending ezetimibe step therapy, ICER's assumption that all patients receive ezetimibe prior to additional non-statin treatments in fact assumes a mandatory step edit, which if implemented in clinical practice, would delay many patients reaching LDL-C goal promptly, resulting in unnecessary cardiovascular events.[15,16] ICER's model should account for the fact that an ezetimibe step edit is not appropriate for patients who require more LDL-C reduction than provided by ezetimibe.

2. **The hypothetical model assumption that ASCVD patients have a mean baseline LDL-C of 88.8mg/dl is not representative of the real-world ASCVD population**. In six recent Phase 3 trials involving over 7000 ASCVD patients with LDL-C>70mg/dL, mean baseline LDL-C ranged from 102mg/dL-120mg/dL.[2,6,17,18,19] Cardiovascular risk reduction with lipid lowering therapy is proportional to the absolute decrease in LDL-C achieved. The inappropriately low mean baseline LDL-C in ICER's analysis underestimates Nexlizet's absolute LDL-C reduction, and therefore underestimates its potential cardiovascular risk reduction and its cost-effectiveness.

3. **Since ICER's value for money assessment evaluated Nexlizet, the voting questions should have focused on Nexlizet rather than Nexletol**, especially since the two medicines are priced at parity. There is no rationale for ICER's assertion that only the value of BA should be considered, when in fact, Nexlizet allows patients to avoid taking two separate pills and paying two copays. Such an approach is not patient centric and inappropriately limits patient access to this innovative treatment.

Esperion is passionately committed to developing affordable, non-statin, oral, once-daily medicines to lower elevated LDL-C. We strongly believe that value assessments of new treatments should reflect real-world population characteristics and treatment patterns and not inappropriately limit patient access to innovative treatments.

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Andrea Baer, MS, BCPA
Executive Director, The Mended Hearts, Inc.

Disclosures: The Mended Hearts, Inc. receives > 25% of their funding from health care companies, including Novartis.

I am Andrea Baer, Executive Director of The Mended Hearts, Inc. and I appreciate your time. I would like to begin by letting you know that I come to you today on behalf of the 102 million Americans with high cholesterol, their families, caregivers, employers, and friends. My comments today are designed to bring the patient voice to the table and present to you the real-world impact on the decisions that will be made here today. You have heard the scientists speak and listened to the data being crunched, all to determine the cost effectiveness of these medications. My job is to bring the patient to life for you.

Innovation means nothing without access. If a patient cannot access the treatment that could save their life, they could die. We've seen today how data is studied and how numbers are crunched to come up with the perfect formula to make a decision of whether a medication is "cost effective" or not. Unfortunately, just because something looks good on paper, doesn't mean it is good for the real-world patient. There is a high burden of hidden costs to not treating. When innovation isn't accessible, this is what happens - Patients have critical and costly events, such as a stroke, they become debilitated by the disease, their caretakers struggle and have to quit their jobs to care for them. Their families are burdened by a preventable illness. Employers lose employees and the healthcare costs of those patients rise. When one patient gets sick, he or she is not the only one affected. Prevention is always less expensive than treatment: To the patient, the family, and the healthcare system.

A patient trusts their health care provider, and together they should have the ability to make a shared decision about a treatment regimen without worry that the best treatment for them isn't accessible because their life isn't worth the money, and honestly, with all due respect, this is what we are talking about today. Is the cost of a medication worth it.

A flaw in the model that is being used is that individual patients are not reflected in the model. Not everyone can fit into a pre-determined box on paper. Every patient is different, and treatments that may work for one, does not work for others. The beauty of having choices is that doctors and patients can work together to find what works for them. It would be ideal if all treatments were the most cost-effective, but sometimes they aren't. But, always, that decision should be made by the patient and their health care provider.

Let's be clear, ICER has an impact on how payors structure and approve medications. ICER can literally be a deciding factor of whether patients have access to their treatment – this was noted

after the PCSK9 and Vascepa reviews. Payors will use the information that ICER puts out to deny treatment, treatment that could be lifesaving, to patients, strictly based on cost effectiveness. Doctors aren't not prescribing the medication because it doesn't work, they aren't prescribing the medication because they know their patients can't access it. This is not only sad, it's harmful. If a medication has been deemed scientifically effective, it's been proven safe, and has been granted FDA approval, the medication should be available for use when deemed appropriate by a health care provider and the patient, in a shared decision-making capacity.

Seth Baum, MD, FACC, FAHA, FNLA, FASPC
Founder & CEO, Excel Medical Clinical Trials
Clinical Affiliate Professor of Cardiology, Florida Atlantic University

Disclosures: Dr. Seth Baum has served as PI on numerous studies of bempedoic acid and inclisiran. He has served as a consultant and speaker for Esperion and as a consultant for Novartis.

I am a Past President of the American Society for Preventive Cardiology and although I am speaking today on my own – and not the Society's behalf – this leadership position is relevant. The Society's Mission has been my own goal for the last 20 years. I spent the first part of my career exclusively treating, not preventing CV disease. In cardiac catheterization laboratories, I managed atherosclerosis long after its inception, often during the throes of life-threatening and permanently devasting events. Recognizing the futility of this Band-Aid approach, I later turned my full attention to cardiovascular disease prevention, believing that with more strategic efforts on the part of clinicians and patients, combined with successful innovations by pharmaceutical companies, there would come a time when we would truly prevent the events that I had battled during my early years as a physician.

Consistent with the tenets of ASPC, I have maintained that heart disease can be reduced or even prevented. Rigorous research and development has indeed produced effective therapeutics. Unfortunately, cost has become an unprecedented barrier to access for scientifically validated, FDA approved therapies.

This year in the US 800,000 people will suffer a stroke with 90% of these being considered avertable had proper preventive strategies been in place. When preventive drugs do become available, in order for them to work, patients must be able to get them. Many of us are concerned that another PCSK9 inhibitor debacle might be in our future. Your voice is very powerful, and I am hopeful that your final document will reflect and fairly apply to real world patients. After all, they are the ones who will be at the receiving end of either easy and appropriate access to these medications or the opposite.

I am most concerned about some of your assumptions as they will clearly influence your findings. In your model, 100% of patients are on both a high intensity statin and ezetimibe. Most real-world studies show quite a different picture. A 2019 American Heart Association poster by Nehar Desai, MD revealed that only 44% of patients one year out from an MI were taking high intensity statins. We must remember that this is our highest risk cohort, patients within a year of an Acute Coronary Syndrome. If these individuals are not using high intensity statins, imagine how the rest of the secondary prevention population is doing. Further, assuming that 100% of very high-risk patients are taking ezetimibe appears almost to be a typographical error. In FOURIER, a 27,564 patient CVOT of very high-risk patients, only 5.2% were taking ezetimibe! We know that our best-managed

patients are in trials such as this. How then can we posit that 100% of real-world patients are treated so much better?

Making matters worse, in the real-world payers paid only about 65% of claims for ezetimibe in patients with FH and LDL-C >190 mg/dL on maximally tolerated statins. Getting payers to approve and then pay for such medications is a real issue that must be included in any honest cost-effectiveness model. Further, regarding the assumption that real world very high-risk patients have an average LDL-C 88.8 mg/dL we only need look again at FOURIER to see this cannot be so. The superbly treated patients in this study had a baseline median LDL-C of 92 mg/dL. Finally, there is ample evidence that your assumptions that MACE is only 5.06/100 patient years and statin intolerance prevalence is only 10%, are also gross underestimates among real world patients.

The crux of this matter is that your findings will ultimately greatly influence the care of real patients. Personally, I have treated high-risk patients who experienced strokes and MIs after being wrongfully denied PCSK9 inhibitors. We have published that 63% of patients with Familial Hypercholesterolemia and established ASCVD – an undeniably extremely high-risk group - were denied coverage for PCSK9i! Additionally, we demonstrated that adverse outcomes do indeed occur more frequently among such high-risk patients who are denied PCSK9i. In 2015 and beyond, payers ran with your PCSK9i findings and left no holds barred in constructing obstacles for patient access to these vital drugs. Even after the drugs' 60% price decrease, we still find ourselves battling to get our high-risk patients on treatment. I am afraid we will have similar matters to confront if your current assumptions are used when you model cost effectiveness of these 2 excellent novel lipid-lowering therapies. I beseech you to reconsider your estimates and make them more consistent with real world data. Thank you for your consideration.

John Clymer
Executive Director, National Forum for Heart Disease & Stroke Prevention

Disclosures: National Forum for Heart Disease & Stroke Prevention receives >25% of its funding from health care companies.

Thank you for this opportunity to address you. I speak on behalf of the National Forum for Heart Disease & Stroke Prevention, a nonprofit hub for public-private collaboration to improve cardiovascular health, and the Value & Access Steering Committee. Committee members represent patients, providers, public health, payers, purchasers, and pharma and biotech companies. The Committee provides consensus input to ICER on various reviews.

The first point I would like to address is ezetimibe as a comparator. The analytic model should accurately reflect what happens in the real world. This is not the case with use of ezetimibe. For example, NHANES data show that only 4.2 percent of people with prior ASCVD and LDL-C greater than 70 on statin therapy take ezetimibe. Yet ICER's model assumes that all patients take ezetimibe.

The National Forum and Value & Access Steering Committee support evidence-based medicine. We recognize that the ACC/AHA guidelines for management of blood cholesterol call for ezetimibe to be used before more aggressive therapies. However, two significant factors should affect the weight that current modeling gives to the guidelines.

1. The guidelines added ezetimibe as a step-through for PCSK9 inhibitors because of the high cost of those therapies. The guidelines explicitly refer to "mid-2018 list prices," before the manufacturers cut the cost of PCSK9 inhibitors by about half. The price cut significantly affected cost-effectiveness.

2. The data tell all of us that real-world use of ezetimibe is low (less than 7%).

We understand that clinicians ICER consulted said they would likely consider ezetimibe as the first treatment. However, clinicians consulted by the National Forum said that because many patients with high residual CV risk and / or high LDL-C will need more than ezetimibe, many physicians will bypass that and go to a more potent therapy.

Therefore, ezetimibe is not a realistic comparator for either treatment being considered. Furthermore, if more people benefit from ezetimibe's lipid-lowering power when it is combined with bempedoic acid, either because more clinicians will prescribe it in the combination pill, or because patients are more likely to take a combination pill, LDL-C reduction is achieved, and it benefits cardiovascular health. This is sound justification for the value-based price of bempedoic acid to include the lipid-lowering benefit of ezetimibe.

The second point is the baseline LDL-C level among patients on maximally tolerated statin and ezetimibe used in the model. For the reasons I have just covered, this is not grounded in real world practice. The value of 88.8 mg/dL (milligrams per deciliter) is significantly lower than

baseline LDL-C levels in Phase III trials. The more accurate, or realistic baseline to use would be the population average without applying the effect of ezetimibe to the entire population. Using the lower LDL-C level of 88.8 negatively impacts the cost-effectiveness analysis. As the primary goal of high cholesterol treatment is absolute lowering of LDL-C, starting at an artificially lower number in effect, lowers the ceiling on the impact that can be achieved with both inclisiran and bempedoic acid.

One option ICER might consider is an additional stratified analysis by base LDL-C. Many clinicians are used to LDL-based thresholds. Looking at cost effectiveness in those with LDL-C 70-99 vs 100-129 vs 130+ would be useful. The other challenge is that ICER uses LDL-C reduction to estimate treatment efficacy. These estimates should be updated after cardiovascular outcome trial (CVOT) data are released.

Finally, high-risk patients need effective therapeutic options. As ICER's review and Dr. Lin's presentation show, bempedoic acid and inclisiran are effective in reducing LDL-C in high-risk populations. They provide alternative treatment options to patients and society to address the most prevalent and costly chronic conditions impacting Americans today.

Payers who are on the Value & Access Steering Committee have reported that multiple payers currently have bempedoic acid on Tier 2 formularies without restrictions. They have determined it is cost effective. There is concern that were ICER to judge its cost effectiveness based on modeling assumptions that do not obtain in the real world, it could open the door for formulary changes that would have the effect of reducing treatment options for patients.

Pat Meredith
Patient Expert

Disclosures: No financial conflicts to disclose.

I was raised in a family where watching one's health was not a primary focus. My mother was a heavy smoker, moderate drinker and rarely exercised. Her father and she had high cholesterol and high blood pressure. My father died due to alcoholism. My two older brothers have high cholesterol and have had issues on and off with their blood pressure, depending on their lifestyle choices. Cholesterol is an issue for both of them, and I believe neither are taking statins due to their concerns about the medication. Because of my family history and parent's lifestyle, I realized I needed to live my life differently.

My journey of health started early in school, being active in team sports and running. After college, I moved to Vermont to ski. I worked to play as a lot of young people do when they move to a resort town. However, I chose to stay because I did not want to give up the lifestyle. As I got older, I quit drinking alcohol, stopped smoking and increased my cardiovascular activities. My passions are hiking, backpacking, running, biking, and kayaking. Vermont is the perfect playground for me to do all I can for my health and have fun doing it. In my 60's, I added functional strength training and yoga to my physical routine. I eat mostly a plant-based diet and am careful about what I eat. Despite taking these precautions to maintain my health, my cholesterol was extremely high and could not be controlled by my careful diet and by exercise. I was prescribed statins to lower my cholesterol but did not tolerate the statin medication. I had knee pain, severe leg cramps and/or muscle weakness to the point where I felt I could not exercise as I wanted.

However, very alarming was the brain fog I experienced. Having a mother, grandfather and husband who lived with and died from Alzheimer's Disease, I found this side effect very disturbing. I was in a dilemma in that what do I chose, my cognition or my cardiovascular health? Statins took away from what I loved to do, which is being active and clear headed. Having spoken to my PCP about the side effects I experienced, I was dismissed. In regard to the brain fog, he indicated that metal fog wasn't a side effect and "not to worry". In regard to the leg muscle issues, I was told "it wasn't a big deal". There had to be a better way to deal with my high cholesterol.

These negative experiences lead me to Dartmouth-Hitchcock Medical Center in New Hampshire where I found a lipid specialist. I felt an immediate kinship with my doctor for she indicated that I had familial hyperlipidemia and though I was doing everything I could, my lifestyle would not be enough to change my cholesterol numbers. I tried statins once again under her care and found I could still not tolerate the medication. We spoke of alternatives and possible side effects and agreed together upon a different course of treatment. My total cholesterol, HDL and LDL numbers are now within normal limits and with no side effects. With my current medication.

My past experience highlights the need for a thorough review of side effects and adverse reactions of medication with the patient. When I asked questions about the medication, side effects were glossed over, and the provider talked only about the effectiveness of statins. Second, patient care is not a one size fits all approach. It takes conversation and cooperation between provider and patient to build trust and find a workable solution to the cholesterol problem. I worked with my lipid specialist to find alternatives to statins and appreciated her ability to hear and acknowledge my concerns.

Lea Parker
Patient Expert

Disclosures: No financial conflicts to disclose.

My name is Lea Parker, and I am a heart patient. In 2003, I was diagnosed with Aortic Stenosis as a result of a congenital heart defect. In 2016, I had open heart surgery to replace my aortic valve. Following my surgery, I began statin therapy because my LDL was over 100.

Everyone in my family takes a statin – my mom, dad, brother, and sister. As with my family, my LDL improved when I started taking Atorvastatin. But, by the end of 2016, my liver enzymes were elevated, and I was sent to a liver specialist. Over the course of the year, my liver numbers continued to be a problem. They wanted to do a liver biopsy. I felt increasing muscle stiffness and pain in my legs. I had difficulty standing up from a chair. My doctor offered a referral to a Rheumatologist. We decided I should consult my cardiologist first. He suggested I stop taking the statin to see what would happen. Right away, my liver enzymes returned to normal, and my energy and activity level soared because I no longer experienced the muscle pain. I could enjoy exercise. I was able to sleep through the night and do all the things I loved.

So, while I felt great, my LDL went up. My doctor does my blood work quarterly. She suggested I talk to my cardiologist about trying a different medication. My cardiologist prescribed Ezetimibe. My liver numbers stayed good, but my cholesterol remained high. Since then, I tried 3 other statin brands. I've tried taking the statin 3 times a week. I tried reduced dosages. My cholesterol went down, but the pain came back. I was ashamed to go out with friends because I didn't have the strength to stand up from the dinner table. I shortened my daily walks because they hurt. I took Tylenol and used a heating pad often. I wondered if the medication was causing long-term damage. Pain means something is wrong. But high cholesterol isn't good either.

I planned a Disney World trip with our kids and grandkids last February and I decided I was not going to be physically limited. I stopped taking my statin in January in preparation for the trip. My son-in-law says, "the way to navigate Disney, is to simply tie a rope around Grammy and hang on tight." I am the one with the energy to wear out the kids and I was determined to be able to climb out of the rides without embarrassing my granddaughters. Without the statin, I easily led the family on 25,000 step days and I was pretty graceful climbing out of the rocket ship at Space Mountain.

I walk every single day, rain, or shine – never missing a day for the past 5 years- and I have been a vegetarian for over 20 years. I love living my life. I love my daily walk and I love being able to run up and down the stairs doing things in my house. I love jumping on the trampoline with my eight-year-old granddaughter and dancing in the living room with my twelve-year-old granddaughter. I also want to reduce my cholesterol. It feels as though I have three choices: 1) take a statin and live

a painful, sedentary life 2) NOT take a statin and increase my risk for heart disease or 3) keep looking for something new. It's been 5 years, and I am still searching for the answer. I am grateful that I have doctors who know me, who focus on patient-centered care, and who are willing to keep looking for a treatment that will work for me.

I can't imagine that going on and off statins is a very good way to manage this condition. My grandmother died of a heart attack and she was very fit and active, and my dad, who is now 80 suffered a heart attack and a stroke, so I know my family history. I can't ignore my cholesterol. I also want to live life to the fullest. I don't want to choose between a long life and a good life – I want both. Please consider new therapies for patients. I am asking you to consider offering new medication options. I know people just stop taking statins when they feel pain. We need a solution that will work for those of us who experience statin intolerance but still have a lot of active years left. Thank you.

Katherine Wilemon
Founder and Chief Executive Officer, FH Foundation

***Disclosures: The FH Foundation receives funding for its programs from health care companies, including Esperion and Novartis*.**

The FH Foundation is pleased that ICER has recognized the important public health need for additional treatment options to improve outcomes for high-risk individuals. The FH Foundation, a non-profit research and advocacy organization, is dedicated to improving the diagnosis and treatment of those born with familial hypercholesterolemia and other inherited lipid disorders that face premature cardiovascular disease.

Lowering LDL-C is the single most modifiable risk factor for cardiovascular disease. Even now as we live through a pandemic- cardiovascular disease kills and sickens more people than any other disease.

Assessing the value of therapies that can further reduce LDL-C burden on individuals at high risk is a complicated question with significant implications for people living with familial hypercholesterolemia and established heart disease.

We would like to thank ICER for making substantive efforts to improve accuracy of the inputs and the quality of the assumptions in the model. We are grateful for the opportunity to work with your stellar team, and to have had real opportunity to share data, medical expertise, the experiences of people living with ASCVD, and FH in this most recent report.

The FH Foundation would like to comment on several assumptions in the model.

Specifically, that all patients are taking both statins and ezetimibe. This is a gross overestimation of the real-world uptake for both medications for which there is data to support a more realistic estimate.

Another assumption that is misleading is that quality of life goes back to perfect or almost perfect health after a heart attack.

I have FH and heart disease. I survived a heart attack at the age of 39. Contrary to the assumptions made in the report about quality of life after a heart attack, I can attest from personal experience and from the experiences of thousands of men and women who are members of the FH Foundation, that life does not return to its former state. Becoming a cardiovascular disease patient in whatever form – heart attacks, bypass surgery, multiple stents and stroke – changes your life.

Science has clearly elucidated the role of LDL cholesterol management in preventing cardiovascular disease. The sooner we lower someone's high cholesterol and the more we lower someone's

cholesterol, the further we take them out of harm's way. We must recognize that for some people, including those with FH, multiple therapies are required to reach recommended safe levels for LDL-C. In fact, published data from the FH Foundation's CASCADE FH Registry showed that those individuals with FH and heart disease who met guideline-based targets were on 3-6 lipid lowering therapies.[1]

As the report calls out, the FH population is an extremely high-risk population that crosses the threshold of cardiovascular disease on average two decades earlier than the rest of the population.

There are approximately 1.3 million men, women, and children in the US who have familial hypercholesterolemia. Much of the scientific understanding of how LDL-cholesterol drives the disease process of atherosclerosis has come from studying this population. LDL-C runs on average twice the normal levels, and the toxic impact on the vessels is measurable in the FH population before puberty.

When you consider both the need and uptake of therapies, bear in mind that 9 out of 10 people with FH remain undiagnosed. Because we are undiagnosed, those of us who make it to the other side of the first heart attack become members of the ASCVD population and still remain "undiagnosed" in the system.

This ICER report highlights the evidence that people with both FH and ASCVD are a higher-risk subpopulation for which there is a greater benefit from cholesterol lowering treatment for secondary prevention, and recognizes that that the FH population will also benefit from primary prevention.

It would be unforgivable to suggest that people can only have access to safe and effective medications to lower their risk for cardiovascular events after they have had a first cardiovascular event.

This ICER report recognizes that there are people who will benefit from these new treatments, and by extension, from the LDL lowering treatments that are already available but are underutilized. We know that there is a significant unmet need for LDL lowering in high-risk populations.

We also know that past utilization management practices intended to limit the use of treatment and manage healthcare dollars have had the unintended consequence of denying, delaying, or

[1] Duell PB, Gidding SS, Andersen RL, Knickelbine T, Anderson L, Gianos E, Shrader P, Kindt I, O'Brien EC, McCann D, Hemphill LC, Ahmed CD, Martin SS, Larry JA, Ahmad ZS, Kullo IJ, Underberg JA, Guyton J, Thompson P, Wilemon K, Roe MT, Rader DJ, Cuchel M, Linton MF, Shapiro MD, Moriarty PM, Knowles JW. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry. Atherosclerosis. 2019 Oct;289:85-93. doi: 10.1016/j.atherosclerosis.2019.08.007. Epub 2019 Aug 19. PMID: 31487564.

making treatment unaffordable to people who would benefit. In 2019, the FH Foundation published research that showed that people who were prescribed a PCSK9 inhibitor by their physician, but who did not get treatment because it was denied by insurance or they did not fill the prescription, were significantly more likely to have a cardiac event within 12 months (16% and 21% respectively)[2]. Many of the individuals impacted were Medicare patients who had high out of pocket costs. These are devastating events that could be prevented. Sadly, women, Blacks, Asians, and Hispanics were more likely to be denied by insurers; an inequity that we cannot perpetuate.

I implore insurance plans, manufacturers and others to find a way to make all cholesterol lowering treatments both affordable and accessible and to work together with patients and healthcare professionals to facilitate better care, rather than create undue burdens that stand in the way of better outcomes.

The results of this report will matter to families across the United States, because we have created a system that is hard for Americans who are sick to navigate. Today you have an opportunity to earn the trust of the American people and invest in prevention of the immense burden of cardiovascular disease.

[2] Myers KD, Farboodi N, Mwamburi M, Howard W, Staszak D, Gidding S, Baum SJ, Wilemon K, Rader DJ. Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular Outcomes. Circ Cardiovasc Qual Outcomes. 2019 Aug;12(8):e005404. doi: 10.1161/CIRCOUTCOMES.118.005404. Epub 2019 Jul 23. PMID: 31331194; PMCID: PMC7665275.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the February 5, 2021 Public meeting of the Midwest CEPAC.

Table G1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Foluso Agboola, MBBS, MPH Director, Evidence Synthesis ICER Grace A. Lin, MD, MAS Associate Professor of Medicine and Health Policy University of California, San Francisco	**Dhruv S. Kazi, MD, MSc, MS** Associate Director, Smith Center for Outcomes Research in Cardiology Director, Cardiac Critical Care Unit Beth Israel Deaconess Medical Center Associate Professor, Harvard Medical School
Rick Chapman, PhD, MS, (Former) Director of Health Economics, ICER	**Grace A. Lin, MD, MAS**, Associate Professor of Medicine and Health Policy, University of California, San Francisco
Monica Frederick, Program and Event Coordinator, ICER	**Avery McKenna,** Research Assistant, ICER
Jane Jih, MD, MPH Assistant Professor, Division of General Internal Medicine University of California, San Francisco	**Maggie O'Grady,** Program Manager, ICER
	Steven D. Pearson, MD, MSc, President, ICER

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table G2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of Midwest CEPAC	
Alan Balch, PhD* Chief Executive Officer, Patient Advocate Foundation, National Patient Advocate Foundation	**Yngve Falck-Ytter, MD, AGAF*** Professor of Medicine, Case Western Reserve University; Chief, Gastroenterology and Hepatology VA Northeast Ohio Healthcare System, Cleveland
Nick Bagley, JD* Professor of Law, the University of Michigan Law School	**Elbert Huang, MD, MPH, FACP*** Professor of Medicine, Director, Center for Chronic Disease Research and Policy, University of Chicago Associate Director of the Chicago Center for Diabetes Translation Research, University of Chicago
Bijan Borah, PhD* Professor of Health Services Research, Mayo Clinic College of Medicine and Science	**Jill Johnson, PharmD*** Professor, Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy
Angela Brown, MPH* Chief Executive Officer, St. Louis Regional Health Commission (RHC)	**Bradley Martin, PharmD, PhD*** Professor, Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences College of Pharmacy
Aaron Carroll, MD, MS* Professor of Pediatrics; Associate Dean for Research Mentoring; Director, Center for Health Policy and Professionalism Research, Indiana University School of Medicine	**Scott Micek, PharmD*** Associate Professor, Pharmacy Practice, St. Louis College of Pharmacy
Donald Casey, MD, MPH, MBA* President, American College of Medicine (ACMQ)	**Reem Mustafa, MD, MPH, PhD* (Chair)** Associate Professor of Medicine, Division of Nephrology and Hypertension, and Director, Outcomes and Implementation Research, University of Kansas Medical Center
Stacie B. Dusetzina, PhD* Associate Professor of Health Policy, Ingram Associate Professor of Cancer Research, Vanderbilt University School of Medicine	**Rachel Sachs, JD, MPH*** Associate Professor of Law, Washington University in St. Louis

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Member	Conflicts of Interest
Cat Davis Ahmed, MBA Vice President, Policy and Outreach, FH Foundation	The FH Foundation receives funding for its programs from health care companies, including Esperion and Novartis.
Andrea Baer, MS, BCPA Executive Director, The Mended Hearts, Inc.	Mended Hearts receives > 25% of their funding from health care companies, including Novartis.
Dave Busch, MS Vice President Pharmacy, HealthPartners	Dave Busch is a full-time employee of HealthPartners.
Keith C. Ferdinand, MD Gerald S. Berenson Endowed Chair in Preventive Cardiology and Professor of Medicine, John W. Deming Department of Medicine, Tulane School of Medicine	Dr. Ferdinand has served as a consultant for Novartis Pharmaceuticals.
Michael Louie, MD, MPH, MSc Head of Clinical Development, Medical Affairs, and Pharmacovigilance, Esperion Therapeutics	Dr. Louie is a full-time employee of Esperion Therapeutics.
David Platt, MD Vice President and Head, Cardiovascular, Renal & Metabolism Medical Unit, US Clinical Development and Medical Affairs, Novartis Pharmaceuticals	Dr. Platt is a full-time employee of Novartis Pharmaceuticals.
Erik Schindler, PharmD, BCPS Director, Emerging Therapeutics and Outcome-Based Contracting, UnitedHealthcare Pharmacy	Dr. Schindler is a full-time employee of UnitedHealthcare Pharmacy.
Salim S. Virani, MD, PhD Professor in Cardiology and Cardiovascular Research Sections, Baylor College of Medicine	Dr. Virani receives grant support from the Department of Veterans Affairs, World Heart Federation, Tahir and Jooma Family. In addition, Dr. Virani receives honorarium from the American College of Cardiology; Associate Editor for Innovations, acc.org.