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

Draft Evidence Report

November 12, 2020

Prepared for

MIDWEST CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

ICER Staff and Consultants	Modeling Team
Grace A. Lin, MD, MAS Associate Professor of Medicine and Health Policy University of California, San Francisco **Jane Jih, MD, MPH** Assistant Professor, Division of General Internal Medicine University of California, San Francisco **Foluso Agboola, MBBS, MPH** Director, Evidence Synthesis ICER **Rick Chapman, PhD, MS** Director of Health Economics ICER **Steven D. Pearson, MD, MSc** President ICER	**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 *Dr. Kazi was responsible for the development of the cost-effectiveness model, interpretation of results, and drafting of the economic sections of this report; the resulting ICER reports do not necessarily represent the views of Beth Israel Deaconess Medical Center or Harvard Medical School.*

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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-review.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 http://www.icer-review.org/about/support/.

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-review.org/programs/midwest-cepac/.

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 draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/high-cholesterol-update-stakeholder-list/.

Expert Reviewers

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.

Keith C. Ferdinand, MD
Gerald S. Berenson Endowed Chair in Preventive Cardiology and Professor of Medicine
John W. Deming Department of Medicine
Tulane University School of Medicine
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.

Salim Virani, MD, PhD
Professor in Cardiology and Cardiovascular Research Sections
Baylor College of Medicine
Dr. Salim 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.

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List of Acronyms and Abbreviations Used in this Report

ACS	Acute coronary syndrome
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
CI	Confidence Interval
CTAF	California Technology Assessment Forum
CV	Cardiovascular
CVD	Cardiovascular Disease
CTTC	Cholesterol Treatment Trialists Collaboration
FDA	Food and Drug Administration
FH	Familial Hypercholesterolemia
FSS	Federal Supply Schedule
HDL-C	High-density Lipoprotein Cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
ITT	Intention to treat
LDL-C	Low-density Lipoprotein Cholesterol
MACE	Major Adverse Cardiovascular Event
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
ULN	Upper limit of normal
US	United States
USPSTF	US Preventive Services Task Force
WAC	Wholesale Acquisition Cost

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, 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.[1] 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[2] persons worldwide; patients with HoFH typically develop severe atherosclerosis and cardiovascular events during childhood.[3] Heterozygous FH (HeFH), in which one copy of a gene affecting cholesterol metabolism is defective, is the most common form of FH, affecting approximately 1 in 250 people in the 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).[4-7] 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 a myocardial infarction (MI) before age 50 meet clinical criteria for FH.[8] 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.[9]

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.[10,11] The financial burden of ASCVD is also substantial, with total costs expected to reach $1.1 trillion by 2035.[12] Between 2007 and 2013, death rates from ASCVD decreased for all racial/ethnic groups in the United States 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.[11]

Treatment of all patients with FH and patients with established ASCVD includes risk factor modification, medical therapy, and when necessary, percutaneous or surgical revascularization.[13] Risk factor modification includes management of other chronic conditions that contribute to ASCVD risk such as hypertension and diabetes, along with lifestyle changes such as dietary modification, weight reduction, physical activity, and smoking cessation. Medical therapy includes antiplatelet agents such as low-dose aspirin, which has been shown to decrease mortality in patients with established ASCVD,[14] and therefore is recommended in all patients who can tolerate it.[13] 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.[15,16] Finally, medical therapy includes intensive lipid-lowering therapy, which is recommended for primary prevention of 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 ASCVD, ideally with high dose or maximally tolerated statin.[13,17] 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, 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 such as bile acid sequestrants and Lipoprotein Apheresis may be considered to reach treatment goals.[18] Throughout this report, we will use “statin intolerance”, consistent with descriptions in the clinical trials reviewed.

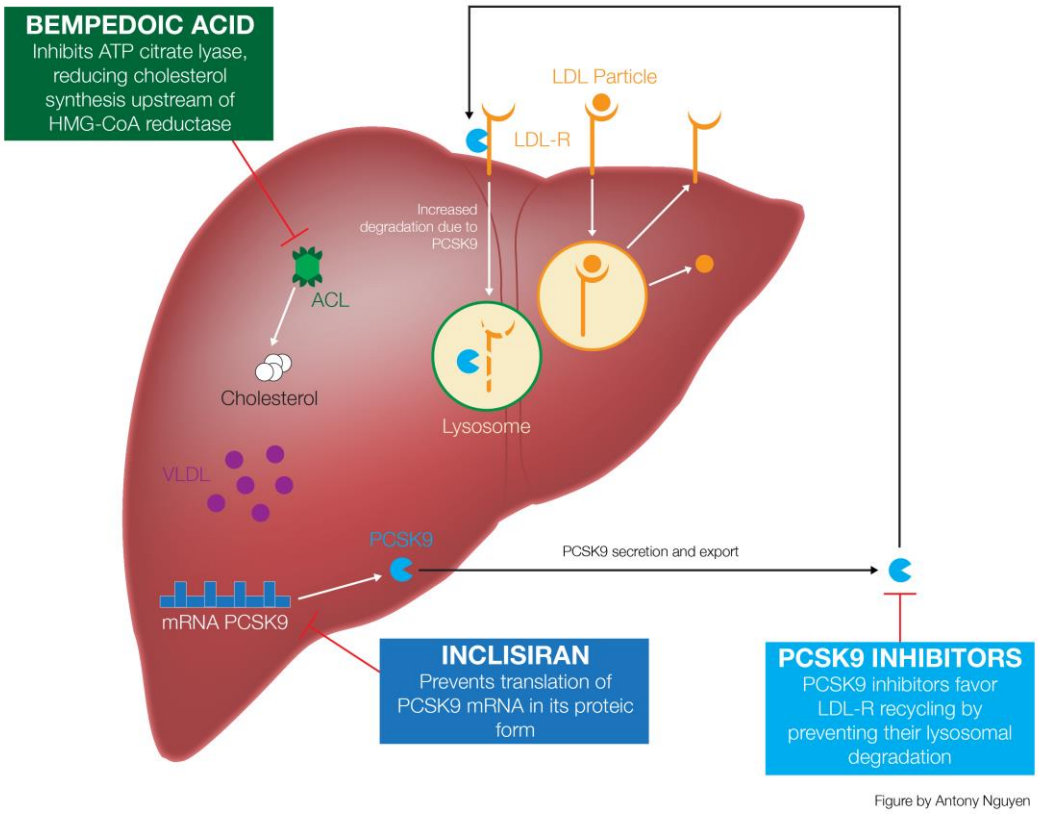
Even with the wide range of aforementioned options for risk factor modification and treatment, patients with HeFH and established ASCVD, who are the focus of this review, remain at high residual risk for further MACE, particularly if LDL-C levels are not adequately controlled. Thus, there is an important public health need for additional treatment options to improve outcomes for patients who remain at higher risk for cardiovascular events. 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.[19] It works upstream from HMG-CoA, which is the target for statins (Figure 1.1). 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.[20] 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. This agent 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).[21] It is delivered as a subcutaneously administered prefilled injection stored at room temperature, and 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 with a regulatory decision expected in the latter half of 2020.

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
    - Myocardial infarction
    - 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 effects (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.[17]

- Primary prevention of ASCVD: Prevention of a first cardiovascular event such as myocardial infarction (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, stroke and all-cause mortality.[22]

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. In this report, this corresponds to the placebo arms in clinical trials, and may also include ezetimibe and other cholesterol-lowering drugs as allowed by the trial protocols.

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.[23] 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-review.org/material/2020-value-assessment-framework-final-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 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, 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,[24] new evidence update in 2017 of evolocumab[25] and subsequent new evidence update in 2019 of alirocumab.[26]

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

Input received during the Open Input period informed the initial selection of population, interventions, comparators, and outcomes measures for which we sought evidence described in a draft scoping document that 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.

2.2 Impact on Patients

Patient groups highlighted that FH is underdiagnosed 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, 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 often-cumbersome insurance prior authorization process for newer cholesterol-lowering drugs like PCSK9-inhibitors and has resulted in delayed or denial of access to therapy for some patients. 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 or achieve LDL goals. Patient groups and clinicians 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. 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 concerns regarding bempedoic acid side effects such as increased uric acid levels and the risk of gout, a negative feature in comparison to ezetimibe, which is considered to be essentially free of side effects. 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 but without confirmatory trial data on CVD outcomes until ongoing outcomes trials are completed. 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 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 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). 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

Because it has not yet been approved by the FDA, we were not able to find publicly available coverage policies for inclisiran. We anticipate inclisiran to 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 and evolocumab current as of October 2020.[27] 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 decisions from representative commercial payers. We were unable to locate publicly available coverage policies for alirocumab from BCBS New Jersey, BCBS Tennessee, Emblem, or Health Care Service Corporation; and for evolocumab from BCBS New Jersey, BCBS Tennessee, Emblem, Health Care Service Corporation, or Highmark.

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 3.1. Coverage Decisions for Alirocumab by Health Plan[27]

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

The following health plan(s) did not issue a coverage decision for the selected drug and indication: BCBS New Jersey, BCBS Tennessee, Emblem, Health Care Service Corporation

Table 3.2. Coverage Decisions for Evolocumab by Health Plan[27]

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

The following health plan(s) did not issue a coverage decision for the selected drug and indication: BCBS New Jersey, BCBS Tennessee, Emblem, Health Care Service Corporation, Highmark

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

	Step Therapy Protocol	Prescriber Requirement	Patient Subgroup Restriction	Other Restriction
Aetna[28]	Yes	No	No	Yes
Anthem[29]	Yes	No	Yes	Yes
BCBS Massachusetts[30]	Yes	Yes	No	Yes
BCBS Michigan[31]	Yes	No	No	Yes
BCBS New Jersey[32]	Yes	No	No	Yes
BCBS North Carolina*[33]	Yes	NA	NA	NA
Centene[34]	Yes	No	Yes	Yes
Cigna[35]	Yes	No	No	Yes
Highmark[36]	Yes	No	Yes	Yes
Humana[37]	Yes	No	No	Yes
UnitedHealthcare[38]	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[39]

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 may be 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[40]

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. 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. 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 a lack of data on their effects on key clinical outcomes, such as stroke, MI, and cardiovascular death. 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.[41,42] 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.[43] 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-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/). 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-review.org/use-of-in-confidence-data/).

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).[44]

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 I2 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 a lack of data on their effects on key clinical outcomes, such as stroke, MI, and cardiovascular death.

4.3 Results

Study Selection

Our literature search identified 1,833 potentially relevant references (see Appendix Figure A1), of which 18 references (15 publications, 1 conference presentations, and 2 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[45-52], and four represented four Phase II trials.[53-56] 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).[53-56] The six remaining references present data on four RCTs (three Phase III trials and one Phase II trial) of inclisiran.[57-62] We did not identify any high-quality observational studies. Details of all included studies are summarized in Appendix Table D.1 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).[48] 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, 64% were male, 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%).[52] 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).[50] 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, 73% were male, 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 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.[46] 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 male, 81% were white, 63% had HeFH, and

63% had established ASCVD. 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.[49] 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, 44% were male, 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.[45] The trial enrolled patients requiring additional lipid-lowering therapy (LDL-C level ≥100 mg/dL). Patients with known 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, 39% were male, 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: 62.5% HeFH: NR
Other Trials			
CLEAR Serenity (N=345)	ASCVD, HeFH, or hypercholesterolemia with statin intolerance	1. Bempedoic acid 180 mg 2. Placebo	Age: 65% 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 4-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 Inclisiran vs. Placebo					**-19.5 (-22.7, -16.4); p<0.0001; I^2 =69%**

ASCVD: atherosclerotic cardiovascular disease, BA: bempedoic acid, Eze: ezetimibe, 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% versus 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% versus 13%). These differences are further explored below.

Bempedoic acid also improved other lipid parameters. There were significant reductions in total cholesterol (9% -18%), non-HDL-C (11% -23%), apolipoprotein B (7% -25%), and hsCRP (9% -31%) with bempedoic acid compared with control.[45,46,48-50] 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).[47]

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, I2: I-squared

Bempedoic Acid/Ezetimibe Combination

As described above, we identified one trial that evaluated the efficacy and safety of 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 5-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.[63]

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.

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.[64]

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)	O.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[52]

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 (3 Phase III and 1 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).[61] 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, 69% were male, 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, 72% were male, 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 284 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.[57] 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, 47% were male, 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 284 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).[58] 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, 64% were male, 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 versus 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 versus 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 284 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 284 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 284 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).[62]

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.[57] 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.[57] Similarly, the time adjusted change in LDL-C after day 90 and up to day 540 was 44.3% (95% CI: -48.5, -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.[61] 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.[61] 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.[57,61] 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).[65]

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.

Harms

The majority of adverse events (AEs) observed in inclisiran trials were mild or moderate.[57,61] 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. Bempedoic acid's safety profile also 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.

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 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. 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, 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 mechanism of action of inclisiran suggests that the degree of LDL-C lowering it provides will translate into reduction in MACE rates that are more comparable to those seen with statins or with PCSK9 inhibitors, the latter of which showed lower than expected reduction in MACE rates in their clinical outcomes trials relative to their degree of LDL-C lowering, in part due to short follow-up duration. 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, it is unknown whether data from PCSK9-inhibitors on LDL-C translation into MACE prevention or on long-term safety can be extrapolated to inclisiran.

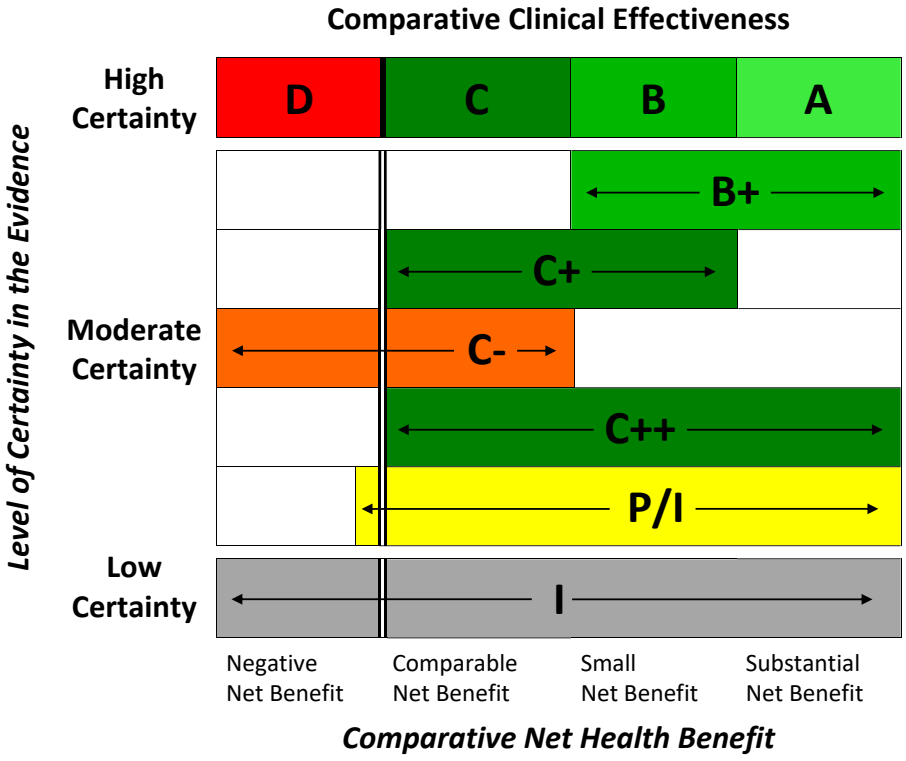
Trials of inclisiran enrolled relatively few patients with statin intolerance. Meta-analysis of LDL-C lowering in this patient population showed that statin intolerant patients had a slightly lower percentage of LDL-C lowering than patients on statins, although this difference was not statistically significant 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, perhaps delivered in the clinical setting, would translate into better real-world adherence and outcomes.

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.

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

All available data suggest that inclisiran substantially lowers LDL-C compared with placebo, though longer-term trials powered to examine its impact on cardiovascular events and mortality are needed. Inclisiran does not appear to have any significant safety concerns, as most of the reported adverse events were mild or moderate. Whether the dosing schedule is advantageous for improving adherence compared with PCSK9-inhibitors is currently theoretical; real-world data are required to confirm this benefit.

Despite the lack of true patient-centered outcomes, given the robust effect on LDL-C lowering and the minimal side effect profile, we have high certainty of at least a comparable net health benefit for inclisiran, with limitations in the evidence providing moderate certainty that the net health benefit will be comparable, small, or substantial. This equates to an ICER evidence rating of "Comparable or Better" (C++).

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 cardiovascular events (MACE, defined in this economic section as a composite of acute coronary syndrome [ACS], stroke, and cardiovascular 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.[66]

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.

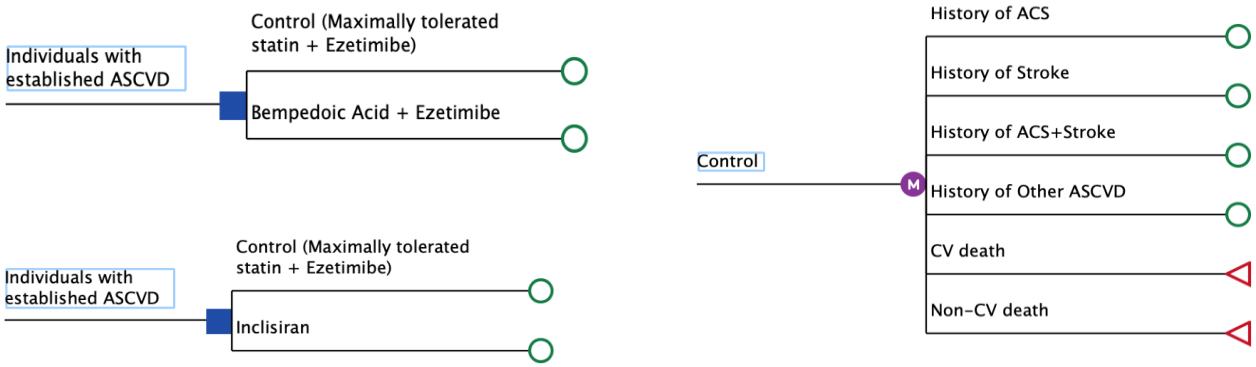
The Markov model contains the following states (Figure 5.1B):

- History of acute coronary syndrome (ACS, including MI and unstable angina)
- History of stroke
- History of ACS and stroke
- History of other ASCVD, such as stable angina or 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.

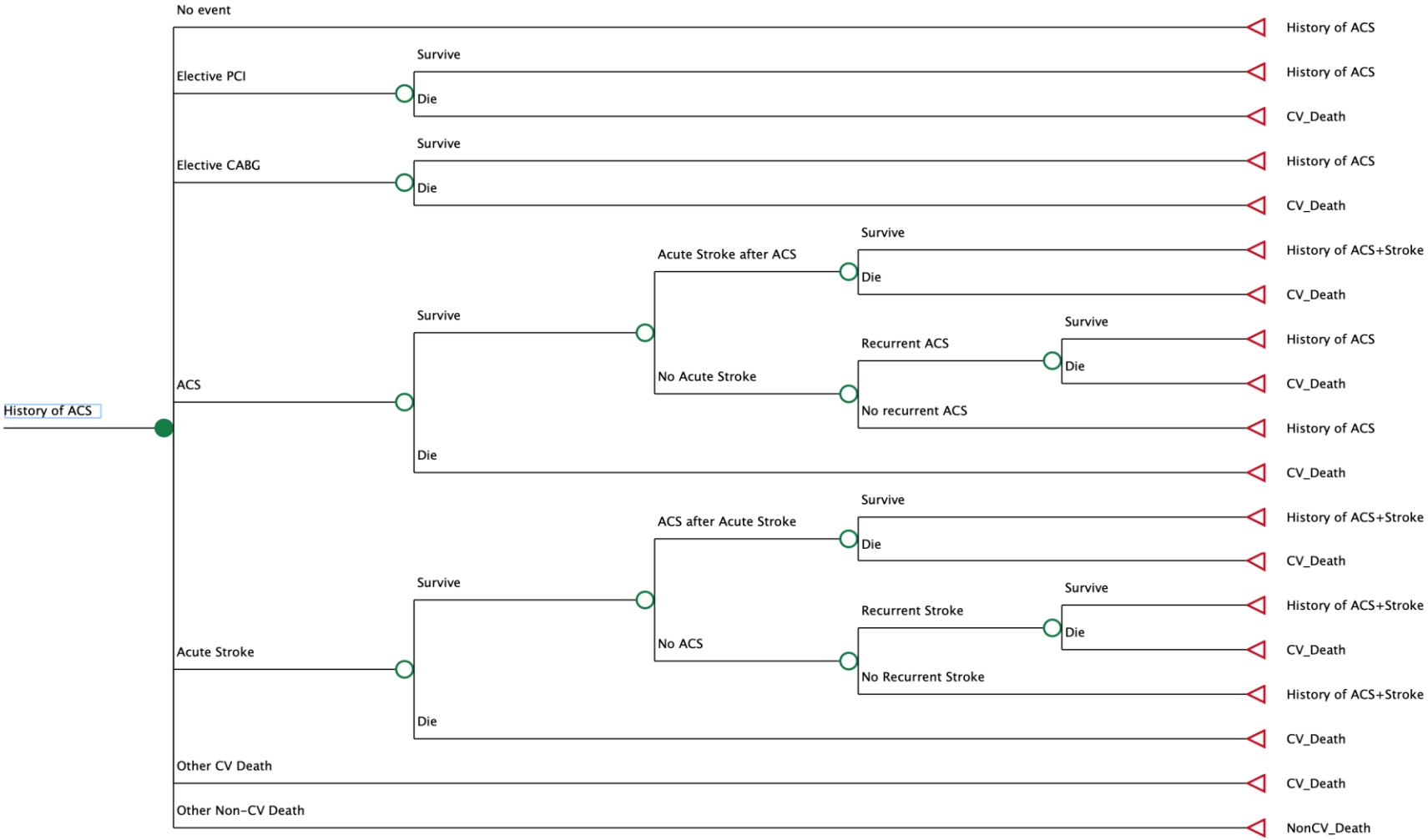
Figure 5.1. Model Framework

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.[24-26]

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.[67] 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%.[2]

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.[68]
  - 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. This yielded a mean±SE LDL-C level of 137.9±2.1 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.[66] Thus, with statin therapy (had they been able to tolerate it), the mean LDL-C level would have declined from 137.9 mg/dL to 89.6 mg/dL, a decline of 48.3 mg/dL or 1.25 mmol/L. As a result, the ACS rate would have declined to (1-0.24)^1.25 of the prior rate, i.e., to 71% 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 (=1/0.71 or 41% 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).[69] 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.[68,69]

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).

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

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, with the risk being particularly elevated 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. We may revisit this assumption prior to the final report as new data become available.
Patients with established ASCVD who statin-intolerant are 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).[1]
Patients with HeFH with established ASCVD have higher event rates than the general population with established ASCVD.	Lifetime exposure to high levels of LDL-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

Assumption	Rationale
	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 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, produces a permanent change in quality-of-life.	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. This assumption, however, undervalues the prevention of recurrent events in the secondary prevention population, and we are open to stakeholders providing evidence to support alternative assumptions.

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)
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[68-70]
Rate of Elective Coronary Revascularization, per 100 person-years	1.0768	0.8614-1.2922	Log normal	Estimated from the FOURIER trial;[71] 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[72-74]
Rate of Non-CV Death	Age-specific estimate	0.8x – 1.5x base-case value	N/A	CDC WONDER and US vital statistics;7 lower end of range assumed; upper end of range derived from

Parameter	Base-Case Value	Range for Sensitivity Analyses	Distribution if Included in Probabilistic Analysis	Source, Comment
				analysis of pooled epidemiological cohorts
Baseline Mean LDL-C in the Control Arm (mg/dL)	88.7mg/dL	86.34-91.1	Normal	NHANES (2009-2016)
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[9-13]
Relative Reduction in LDL-C Level with Inclisiran, %	50.5%	45.4% -55.5%	Beta	Randomized trials of inclisiran[14-17]
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)[66]
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)[66]
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)[66]
Rate Ratio for Elective Revascularization,	0.76	0.73-0.80	Log normal	Based on published meta-analyses of randomized trials of statin therapy (endpoint:

Parameter	Base-Case Value	Range for Sensitivity Analyses	Distribution if Included in Probabilistic Analysis	Source, Comment
per mmol/L Reduction in LDL-C				any coronary revascularization, statin v. control)[66]
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[75,76]

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).[77-84]

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.[85]

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)[86,87] Murray et al. (2012)[88]
History of ACS	0.9648	0.9513-0.9764	Beta	Moran et al. (2014)[86,87] Murray et al. (2012)[88]
History of Stroke	0.8835	0.8456-0.9133	Beta	Moran et al. (2014)[86,87] Murray et al. (2012)[88]
History of ACS and Stroke	0.8524	0.8083-0.8987	Beta	Moran et al. (2014)[86,87] Murray et al. (2012)[88]
Transient Utility Tolls (Disutilities) for Acute Events				
Percutaneous Coronary Revascularization	0.0096	0.0041-0.0192	Beta	Kazi et al. (2014)[74]
Surgical Revascularization	0.0192	0.0096-0.0396	Beta	Kazi et al. (2014)[74]
ACS	0.0961 for 1 month	0.0621-0.1363 for 1 month	Beta	Moran et al. (2014)[86,87] Murray et al. (2012)[88]
Acute Stroke	0.1375 for 1 month	0.1022-0.1874 for 1 month	Beta	Moran et al. (2014)[86,87] Murray et al. (2012)[88]

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[89,90]
Injection-Site Reactions (Inclisiran)	4.3	0.0003 (0.0000-0.0020) **	0	Prior economic evaluations of injectable therapies[91]

*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

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.[47]

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).[68,76,92]

Table 5.8. Other Costs (2020 U.S. 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)[29,30]
Hospitalization for ACS, non-fatal	$27,296	$21,837-$32,755	Log normal	National Inpatient Sample, Peterson et al. (2015)[29,30]
CV costs in the first year after an ACS event	$16,800	$13,440-$20,160	Log normal	Medical Expenditure Panel Survey[31]
Chronic CV care costs	Vary by age and clinical condition	±20% of base-case value	Log normal	Medical Expenditure Panel Survey[31]
Costs of Stroke Care, USD				
Stroke hospitalization, fatal	$21,284	$17,027-$25,541	Log normal	National Inpatient Sample, Peterson et al. (2015)[29,30]
Stroke hospitalization, non-fatal	$18,824	$15,059-$22,589	Log normal	National Inpatient Sample, Peterson et al. (2015)[29,30]
Post-Stroke Cost, First year after stroke	$18,855	$15,084-$22,626	Log normal	Medical Expenditure Panel Survey[31]
Background healthcare 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[31]

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 cardiovascular event, but no differences beyond the first year.[93] We assumed these first-year annualized hours, 163.2 hours, would apply to all individuals in the model who experienced a cardiovascular event. The average hourly wage of $29.47 was assumed to apply to all hours no matter the working status of the individual.[94]

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. Finally, in a 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 outcomes 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

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 cardiovascular events in this population. This included 2.65 fatal and non-fatal ACS, 0.88 fatal and non-fatal strokes, and 2.51 deaths from cardiovascular causes per 100 person-years (Tables 5.10 and 5.11). Additional lipid-lowering with bempedoic acid/ezetimibe or inclisiran lowered MACE rates and prolonged survival. This resulted in savings in downstream cardiovascular costs, but these savings were offset by increased costs of lipid-lowering therapy and background health care costs (due to additional years of life). 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 5.10. 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)	15.06 (13.87-16.19)	15.34 (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	0.88	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	$172,000 ($132,000-$277,000)
ICER, $ per QALY gained	Comparator	$183,000 ($140,000-$293,000)
ICER, $ per evLYG	Comparator	$165,000 ($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 5.11. 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)	15.06 (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	0.47 (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	0.88
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	2.57	1.81
Stroke	0.88	0.69
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	$548,000
ICER, $ per life-year gained	Comparator	$145,000 ($112,000-$221,000)
ICER, $ per QALY gained	Comparator	$155,000 ($119,000-$232,000)
ICER, $ per evLYG	Comparator	$140,000 ($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.
*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.

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 5.12. 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 5.13. 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.
*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.

Table 5.14. 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)	14.32	14.91
Mean survival (discounted)	11	11.38
Incremental survival (discounted)	Comparator	0.37
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.12	10.48
Incremental QALYs (discounted)	Comparator	0.35
Lifetime MACE, mean number	1.18	1.04
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	3.73	2.92
Stroke	1.09	0.91
Death from cardiovascular causes	2.99	2.68
Composite MACE	6.2	5.85
Direct Healthcare Costs		
Lifetime Healthcare Costs, 2020 USD (discounted)	$185,000	$214,000
Spending on lipid-lowering therapies	$2,000	$33,000
Spending on cardiovascular care	$110,000	$107,000
Background Healthcare Costs	$73,000	$75,000
Incremental healthcare costs, 2020 USD (discounted)	Comparator	$29,000
ICER, $ per MACE averted	Comparator	$213,000
ICER, $ per life-year gained	Comparator	$79,000
ICER, $ per QALY gained	Comparator	$83,000
ICER, $ per evLYG	Comparator	$75,000

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

	Ezetimibe	Inclisiran + Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	14.32	15.48
Mean survival (discounted)	11	11.74
Incremental survival (discounted)	Comparator	0.74
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.12	10.82
Incremental QALYs (discounted)	Comparator	0.70
Lifetime MACE, mean number	1.18	0.92
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	3.73	2.30
Stroke	1.09	0.77
Death from cardiovascular causes	2.99	2.24
Composite MACE	6.2	5.29
Direct Healthcare Costs		
Lifetime Healthcare Costs, 2020 USD (discounted)	$185,000	$250,000
Spending on lipid-lowering therapies	$2,000	$70,000
Spending on cardiovascular care	$110,000	$104,000
Background Healthcare Costs	$73,000	$77,000
Incremental healthcare costs, 2020 USD (discounted)	Comparator	$66,000
ICER, $ per MACE averted	Comparator	$257,000
ICER, $ per life-year gained	Comparator	$89,000
ICER, $ per QALY gained	Comparator	$94,000
ICER, $ per evLYG	Comparator	$85,000

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. 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)	15.04	15.33
Mean survival (discounted)	11.46	11.64
Incremental survival (discounted)	Comparator	0.18
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.77	10.94
Incremental QALYs (discounted)	Comparator	0.18
Lifetime MACE, mean number	1.14	1.06
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	5.09	4.41
Stroke	1	0.88
Death from cardiovascular causes	2.5	2.35
Composite MACE	7.54	7.34
Direct Healthcare Costs		
Lifetime Healthcare 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 Healthcare Costs	$72,000	$73,000
Incremental healthcare costs, 2020 USD (discounted)	Comparator	$30,000
ICER, $ per MACE averted	Comparator	$412,000
ICER, $ per life-year gained	Comparator	$167,000
ICER, $ per QALY gained	Comparator	$172,000
ICER, $ per evLYG	Comparator	$158,000

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 5.17. 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)	15.04	15.79
Mean survival (discounted)	11.46	11.93
Incremental survival (discounted)	Comparator	0.47
Quality-adjusted survival, QALYs		
Mean QALYs (discounted)	10.77	11.22
Incremental QALYs (discounted)	Comparator	0.46
Lifetime MACE, mean number	1.14	0.95
Rate of MACE, per 100 person-years†		
Acute coronary syndrome	5.09	3.36
Stroke	1	0.81
Death from cardiovascular causes	2.5	2.02
Composite MACE	7.54	6.93
Direct Health Care Costs		
Lifetime Healthcare 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	$350,000
ICER, $ per life-year gained	Comparator	$141,000
ICER, $ per QALY gained	Comparator	$145,000
ICER, $ per evLYG	Comparator	$133,000

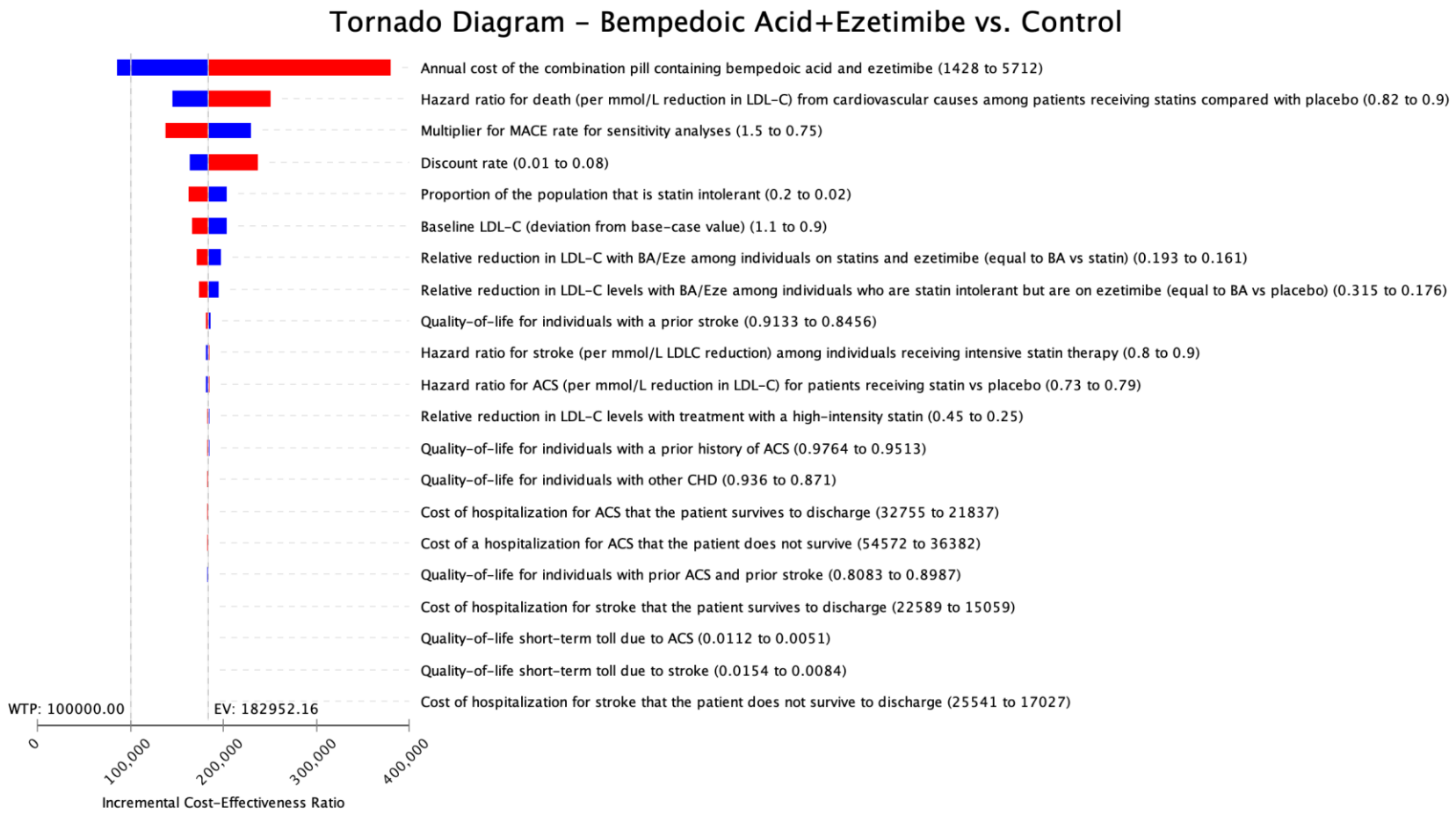
evLYG: equal value life-years gained, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal acute coronary syndrome, and non-fatal stroke), QALY: quality-adjusted life year, USD: US dollars (2020)
Costs and ICERs rounded to the nearest thousand. Numbers may not sum due 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.

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).

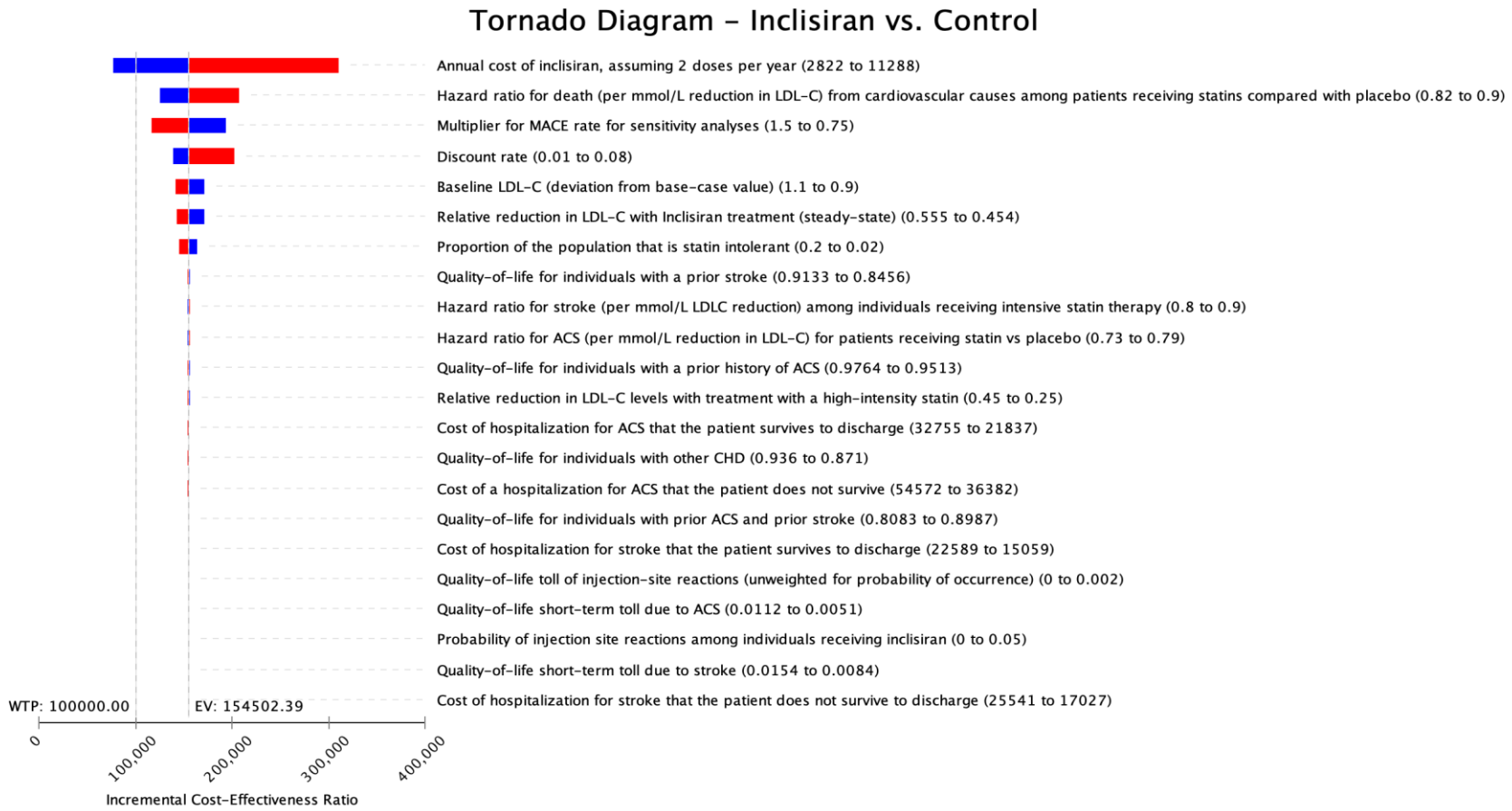
The incremental cost-effectiveness ratio was most sensitive to the cost of the drug, the relationship between LDL-C lowering and reduction in cardiovascular death, and the rate of MACE. In contrast, it was not very sensitive to assumptions about the magnitude of quality-of-life decrements from prior ASCVD events.

Figure 5.2. 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 cardiovascular 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



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.

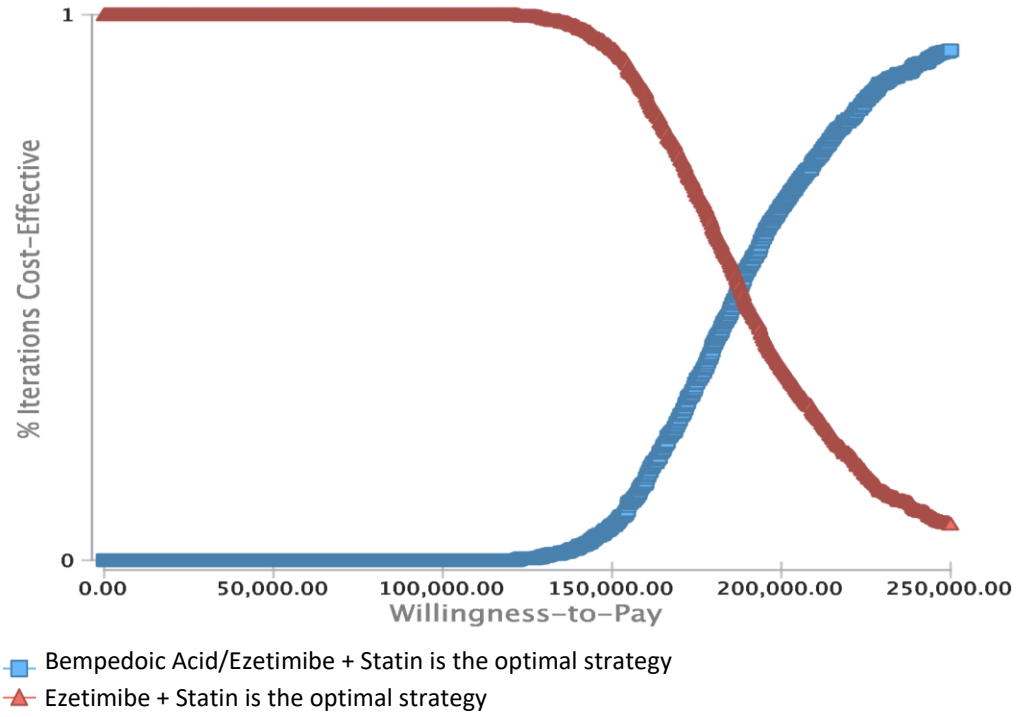
Table 5.18. Probabilistic Sensitivity Analysis Results: Bempedoic Acid/Ezetimibe + Maximally Tolerated Statin Compared with Ezetimibe + Maximally Tolerated Statin

	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



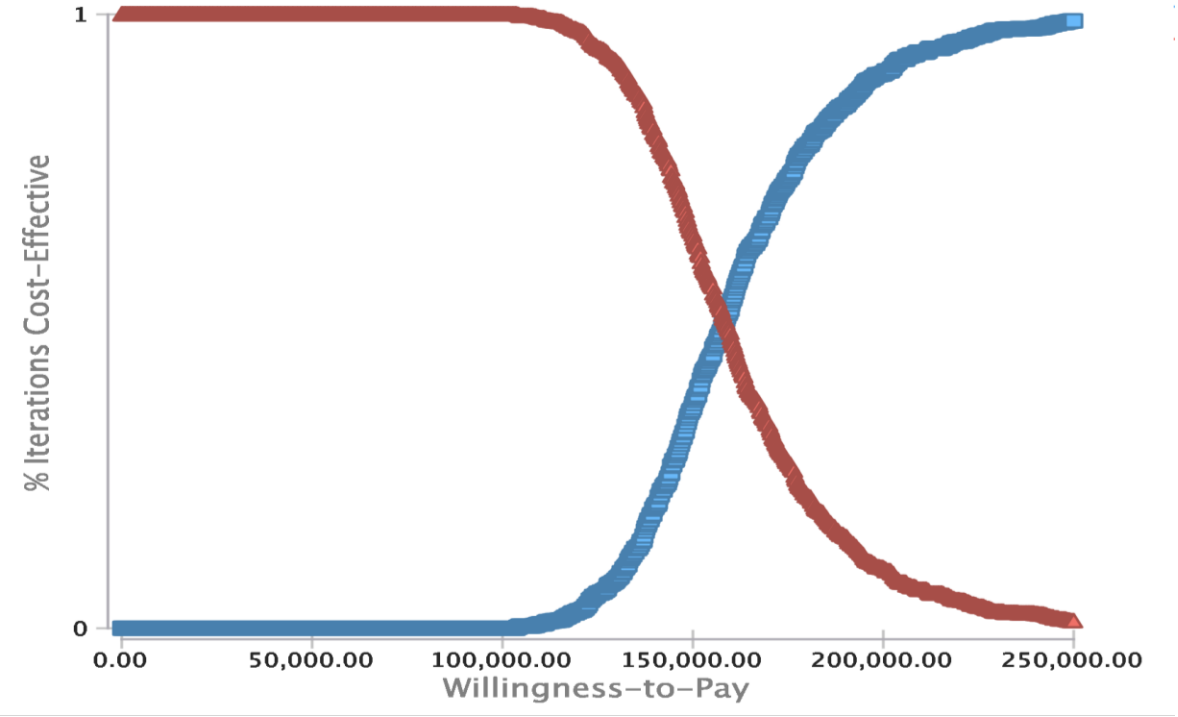
The use of inclisiran was cost-effective relative to the control arm in 0% of the simulations at a threshold of $100,000 per QALY gained and 35.9% of the simulations at a threshold of $150,000 per QALY gained.

Table 5.19. 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 5.20. Inclisiran 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)	15.06	15.25
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	0.88	0.67
Death from cardiovascular causes	2.51	2.35
Composite MACE	5.06	4.68
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	$595,000
ICER, $ per life-year gained	Comparator	$521,000
ICER, $ per QALY gained	Comparator	$515,000
ICER, $ per evLYG	Comparator	$457,000

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.

Modified Societal Perspective

We conducted a scenario analysis by assigning an annualized productivity-related cost of $4,810 to each acute cardiovascular 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 $183,000 to $182,000

per QALY gained for bempedoic acid/ezetimibe and from $155,000 to $153,000 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 5.21 below. We strongly caution readers against assuming that the values provided in this section will approximate the health benefit price benchmarks (HBPBs) that will be presented in the next version of this Report. Based on reviewer, manufacturer, and public input as well as internal model review, these results may change substantially. See appendix for additional methodological details regarding this approach. As expected, using an evLYG approach increases the threshold prices for the two lipid-lowering therapies, each compared with its own control.

Table 5.21. 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	919	1,647	2,375	3,104
evLYG	4,018	2,856	996	1,802	2,608	3,414
Inclisiran						
QALYs Gained	N/A*	5,644**	1,863	3,672	5,481	7,289
evLYG	N/A*	5,644**	2,051	4,047	6,044	8,040

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 5.22. 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	1,502	2,817	4,132	5,447
evLYG	4,018	2,856	1,641	3,095	4,548	6,002
Inclisiran						
QALYs Gained	N/A*	5,644**	3,381	6,749	10,117	13,485
evLYG	N/A*	5,644**	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 5.23. 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	1,820	3,367	4,914	6,461
evLYG	4,018	2,856	1,989	3,705	5,421	7,137
Inclisiran						
QALYs Gained	N/A*	5,644**	3,070	5,971	8,872	11,773
evLYG	N/A*	5,644**	3,378	6,586	9,795	13,004

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 5.24. 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	1,002	1,759	2,516	3,273
evLYG	4,018	2,856	1,073	1,901	2,730	3,558
Inclisiran						
QALYs Gained	N/A*	5,644**	2,061	3,940	5,819	7,698
evLYG	N/A*	5,644**	2,231	4,280	6,329	8,378

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.[71,75] 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 5.25). This is likely because real world populations have higher cardiovascular 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).[76]

Table 5.25. Comparison of Model Outputs with Event Rates Observed in Contemporary Randomized Trials

	FOURIER (patients with ASCVD)[71]	ODYSSEY OUTCOMES (patients with recent ACS)[75]	Model Output*
ACS (MI + Hospitalization for angina)	0.0292	N/A	0.0262
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 MI + Nonfatal stroke + CV Death	0.0349	N/A	0.0522
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).[74]

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.[95,96] 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. 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 $515,000 per QALY or $457,000 per evLYG) if its effect on cardiovascular outcomes is similar to evolocumab and alirocumab (as in our scenario analysis) rather than the effect of statins on cardiovascular outcomes (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. As bempedoic acid produces only a modest reduction in LDL-C, and because generic formulations of ezetimibe are now available, we find that a large reduction in the price of bempedoic acid/ezetimibe would be necessary to meet conventional cost-effectiveness thresholds. Although the price of inclisiran is not currently available, we assumed that its price would match that of the two monoclonal antibody PCSK9 inhibitors currently on the market. At that price, the incremental cost-effectiveness ratio for inclisiran would approach conventional cost-effectiveness thresholds, with a small price reduction possibly making it cost-effective in the secondary prevention population.

Alternatively, the cost effectiveness of either agent can be improved by restricting its use to a higher risk subgroup such as patients with established ASCVD who are also statin-intolerant or have HeFH. Doing so produces impressive improvements in our estimates of cost-effectiveness. For instance, the incremental cost-effectiveness ratio for bempedoic acid/ezetimibe compared with control improves from $183,000 per QALY gained to $101,000 per QALY gained among individuals who have established ASCVD and HeFH, and to $83,000 per QALY gained among individuals with established ASCVD who are statin-intolerant. There are similar improvements in the incremental cost-effectiveness ratio of inclisiran when it is used in subgroups of individuals with established ASCVD who are at higher risk of recurrent events. 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 lower-risk populations, such as for the primary prevention of ASCVD. Our findings should therefore not be extrapolated to the primary prevention population without adjustment for baseline risk of cardiovascular 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, systematic cost-effectiveness analyses, coupled with market pressure from unapproved or abandoned prescriptions, were instrumental in achieving an eventual 60% reduction in the WAC of evolocumab and alirocumab (with even deeper discounts in net price). 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.

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

Potential Other Benefit or Contextual Consideration	Relevant Information
Assumptions made in the base-case cost-effectiveness estimates rendering results overly optimistic or pessimistic.	• Reduction in MACE rates for bempedoic acid with or without ezetimibe and inclisiran have not yet been established. • Contemporary recurrent MACE rates for patients with established ASCVD, with and without HeFH, are not known. • It is uncertain whether patients with HeFH and established ASCVD have higher MACE rates than patients with established ASCVD in the general population.
Whether the intervention represents a similar or novel mechanism of action compared to that of other active treatments.	• Bempedoic acid acts along with cholesterol synthesis pathway like statins, but targets a novel molecule. • Inclisiran acts to reduce PCSK9 through inhibiting the translation of PCSK9 mRNA rather than blocking PCSK9 action via monoclonal antibodies (as is the mechanism of PCSK9-inhibitors).
Whether the delivery mechanism or relative complexity of the intervention under review is likely to lead to very different real-world outcomes relative to an active comparator than estimated from clinical trials.	N/A
Whether the intervention could reduce or preclude the potential effectiveness of future treatments.	N/A
Whether the intervention offers a special advantage for some patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.	• 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. • Bempedoic/ezetimibe combination is priced the same as bempedoic acid alone, so in cost-sensitive situations, use of the combination pill may be attractive compared with separate prescriptions for the two medications. • 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.
Whether the intervention differentially benefits a historically disadvantaged or underserved community.	• Clinical trials of both bempedoic acid and inclisiran lacked racial and ethnic diversity.
Whether there is a notably large or small health loss without this treatment as measured by absolute QALY shortfall.	Absolute shortfall was estimated to be 0.54 QALY for this population of adults with established ASCVD and 3.09 QALYs for adults with HeFH and established ASCVD; for comparison with other conditions, see Table 6.2.
Whether there is a notably large or small health loss without this treatment as measured by proportional QALY shortfall.	Proportional QALY shortfall was estimated to be 0.04 for this population of adults with established ASCVD and 0.18 for adults with HeFH and established ASCVD, representing a loss of 4% and 18% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition.
Whether the intervention will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.	• Additional lipid-lowering offered by bempedoic acid and inclisiran for patients with established ASCVD and HeFH may translate into fewer CV events and better quality of life, and reduce the caregiving burden.
Whether the intervention will have a significant impact on improving return to work and/or overall productivity vs. the comparator.	• Reduction of MACE may improve overall productivity and quality of life, particularly in working patients and patients with HeFH, who are at higher risk of events earlier in their life.

QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions,[97] 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.[98,99] 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.[100] 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.[101,102] 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.[99]

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

	From ICER Reports			From iDBC tool[103]	
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

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

8. Potential Budget Impact

8.1 Overview

Note that these results are preliminary and for reasons discussed in Section 6 should not be assumed to reflect the health-benefit price benchmarks that will be provided in the next version of this Report.

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of bempedoic acid (in combination with ezetimibe) and inclisiran for the adult population with established ASCVD 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 budget impact.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

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,[104] 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,[105] 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.[106] 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 20% of these patients would initiate treatment in each of the five years, or approximately 2,042,000 patients per year.

We evaluated whether the new treatments would take market share from one or more existing treatments to calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, we assumed that each drug is added on to optimal lipid-lowering therapy (i.e., maximally tolerated statin + ezetimibe). As bempedoic acid/ezetimibe, which was approved earlier this year, and inclisiran would be launched within two years of each other, we followed ICER's Reference Case guidance, assuming that equal proportions of the eligible population will be split among the two interventions. Using the estimate from above of approximately 2,042,000 eligible patients per year, this would equate to approximately 1,021,000 patients per year for each drug.

ICER's methods for estimating potential budget impact are described in detail elsewhere.[107] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $819 million per year for new drugs.

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

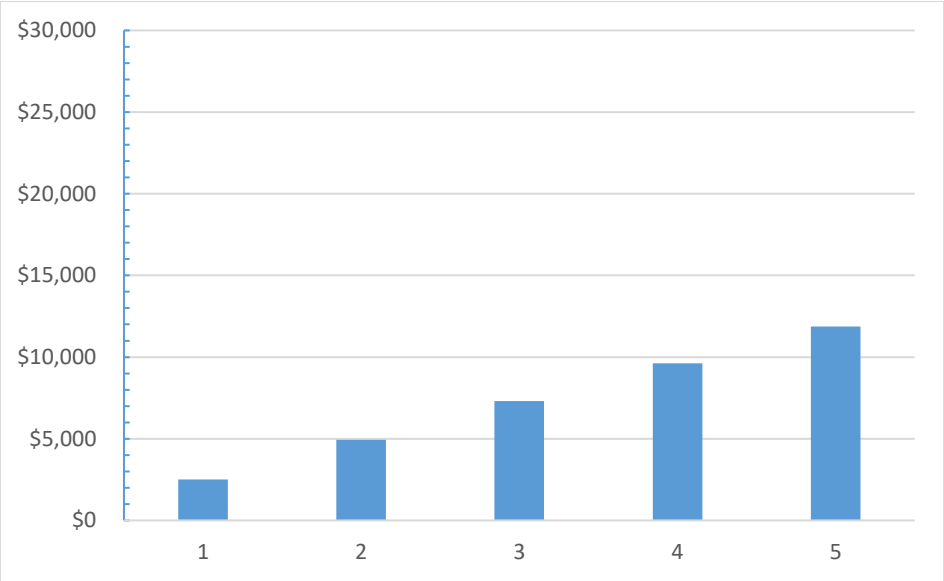


Figure 8.2 illustrates the cumulative per-patient budget impact calculations for inclisiran compared to ezetimibe + maximally tolerated statin, based on the assumed placeholder price of $5,644 per year for inclisiran. The average potential budgetary impact for inclisiran was an additional per-patient 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

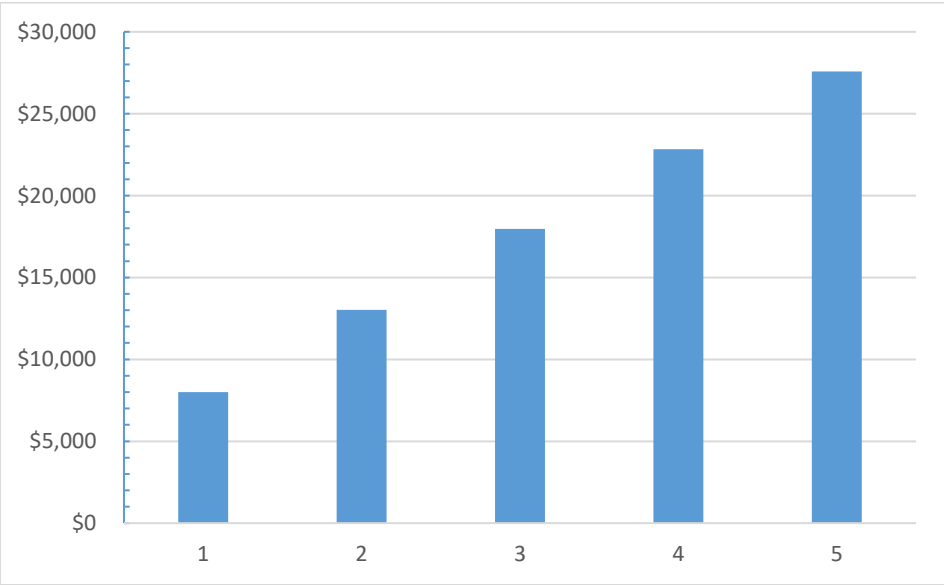


Figure 8.3 illustrates the potential budget impact of bempedoic acid treatment of the eligible population with bempedoic acid (in combination with ezetimibe), based on the WAC ($4,018 per year), net price ($2,856 per year), and the threshold prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $2,380, $1,650, and $920 per year of treatment, respectively) compared to ezetimibe + maximally tolerated statin. As shown in Figure 8.3, 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 net price. Approximately 14% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, approximately 21% at the $100,000 per QALY threshold price, and approximately 48% at the $50,000 per QALY threshold price.

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

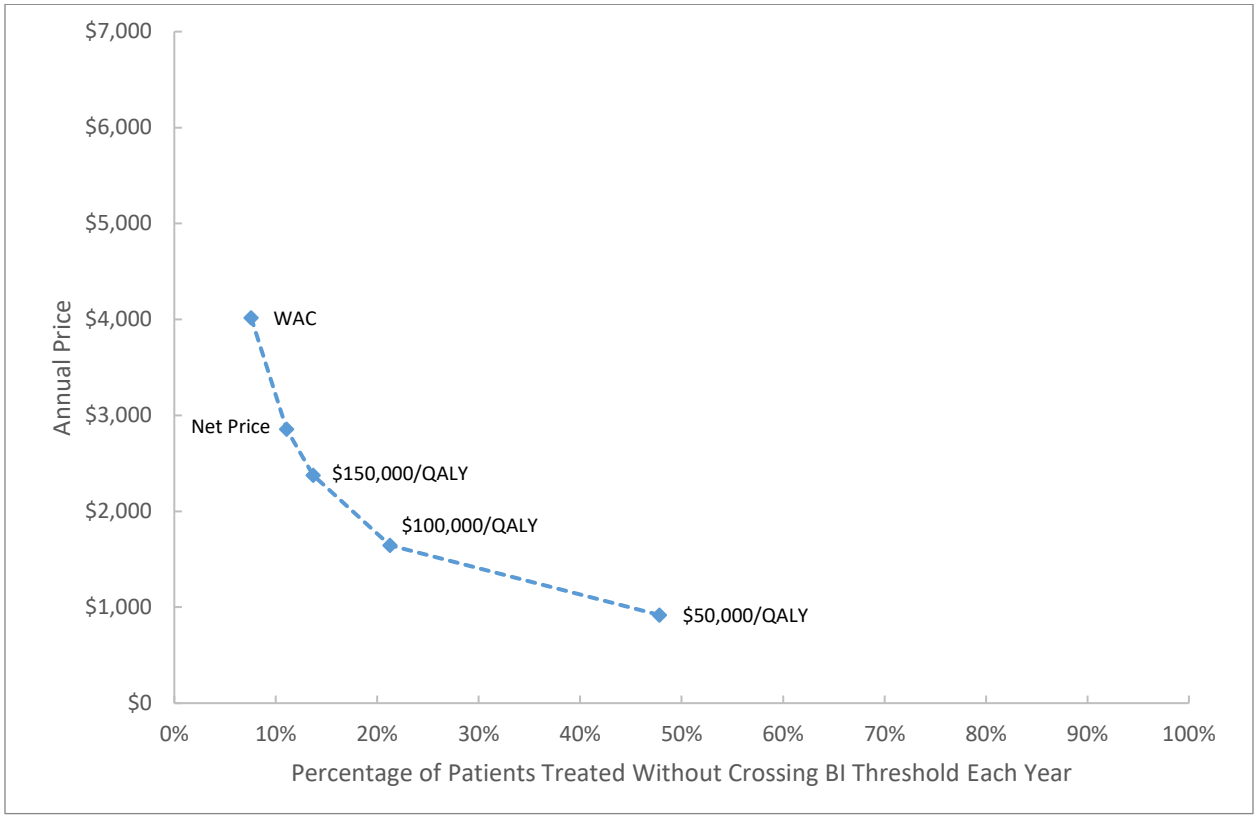
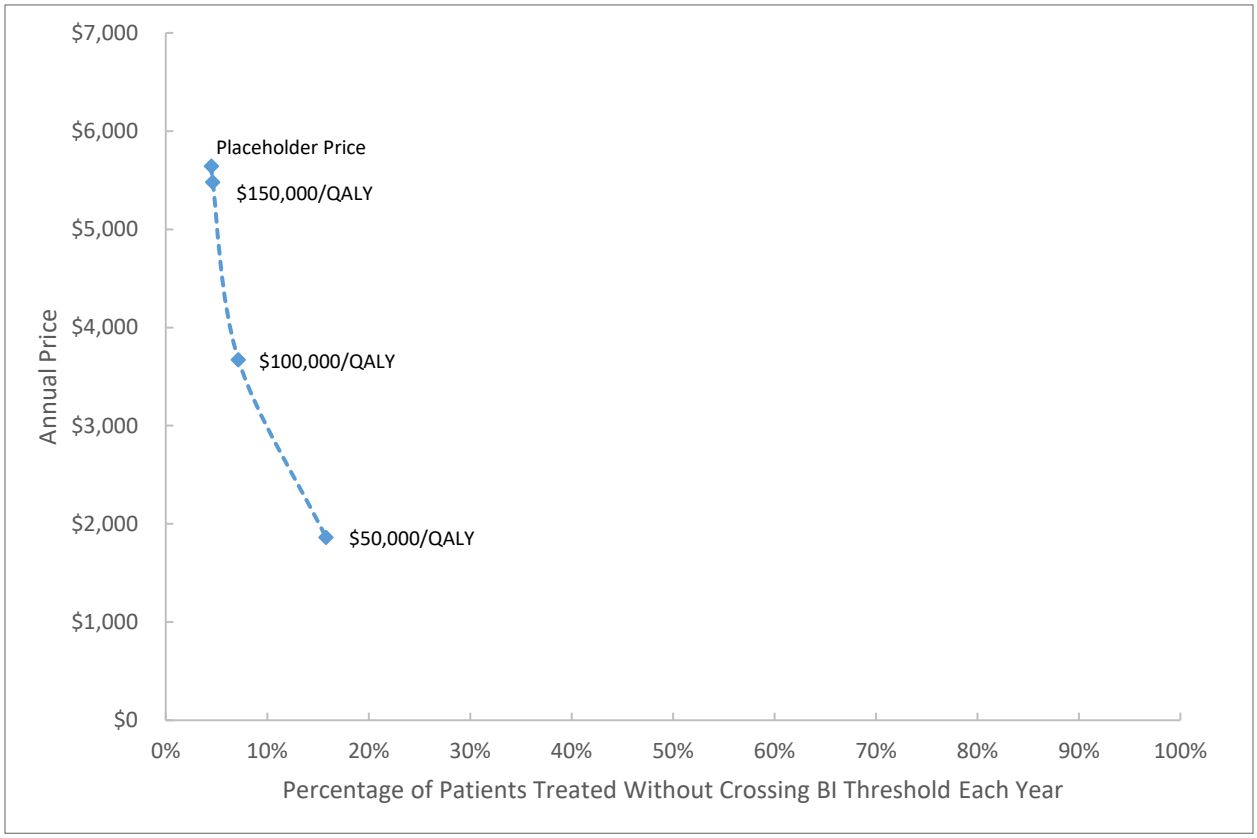


Figure 8.4 illustrates the potential budget impact of treatment with inclisiran of the eligible population, based on the assumed placeholder price ($5,644 per year), and the threshold prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $5,480, $3,670, and $1,860 per year, respectively) compared to ezetimibe + maximally tolerated statin. As shown in Figure 8.4, only 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 4.6% of patients could be treated in a given year without crossing the

budget impact threshold at the $150,000 per QALY threshold price. Approximately 7% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price, rising to approximately 16% at the $50,000 per QALY threshold price.

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



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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.

		Checklist Items
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., healthcare 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

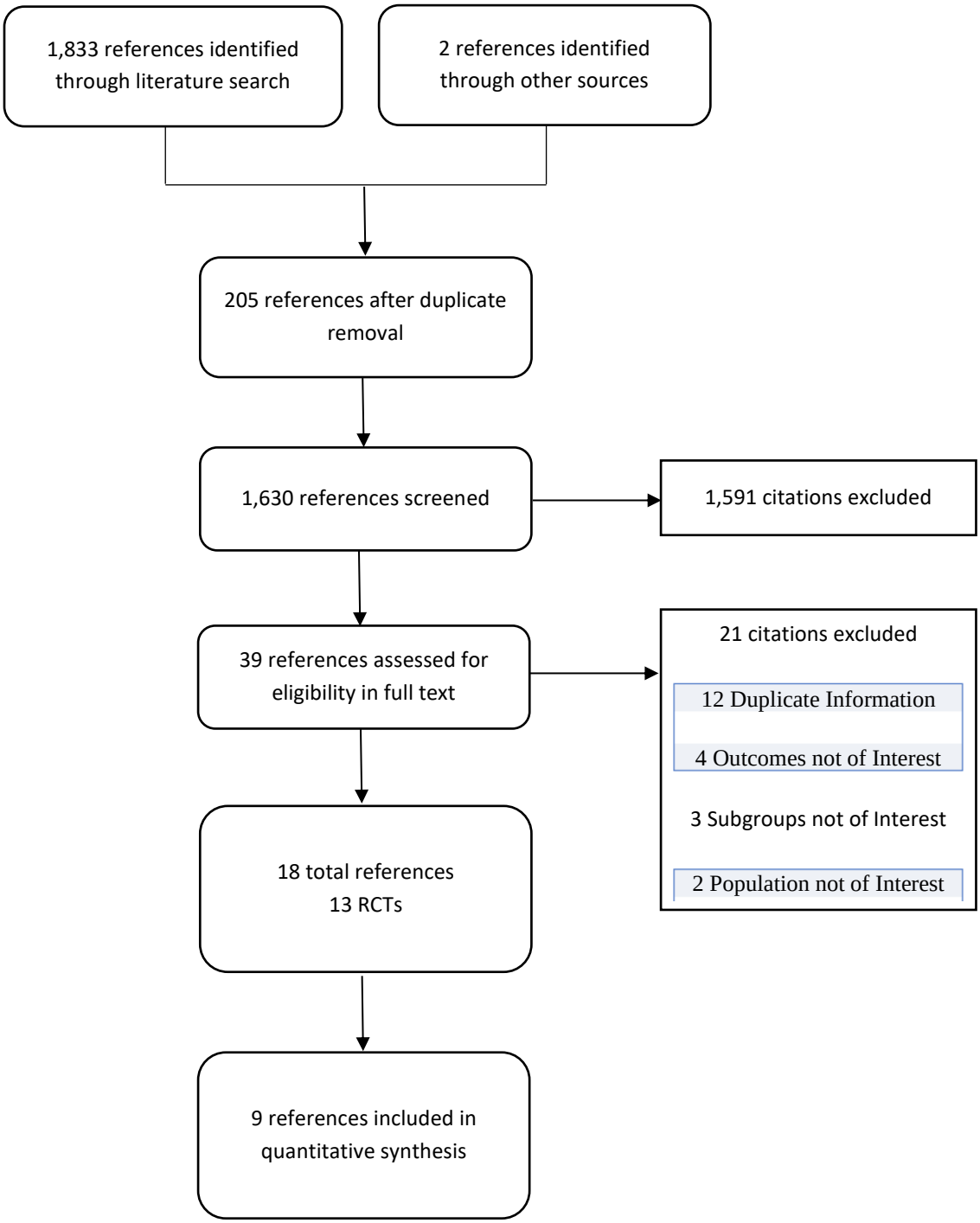
1	Hypercholesterolemia/ or Hyperlipoproteinemia Type II/ or Cardiovascular Diseases/
2	(((high or elevated) adj (cholesterol or LDL* or low-density lipoprotein)) or hypercholesterolemia or hypercholesterolemia or HeFH or heterozygous familial hypercholesterolemia or familial hypercholesterolemia or FH).ti,ab
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[108]

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[109]

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[110]

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[111]

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[112]

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	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

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			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		
An Extension Trial of Inclisiran Compared to Evolocumab in Participants With Cardiovascular Disease and High Cholesterol (ORION-3) NCT03060577 Sponsor: Novartis Pharmaceuticals	Open-Label, Active Comparator Extension Trial Estimated Enrollment: 490	1) Inclisiran 300 mg SC on day 1 and every 180 days thereafter up to 4 years 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	**Inclusions** • Completion of Study MDCO-PCS-15-01 and no contraindication to receiving inclisiran or evolocumab **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	Percent Change in LDL-C at Day 210	February 2022
A Study of Inclisiran in Participants with Homozygous Familial	Two-Part Double - Blind, Placebo Controlled/Open-	1) Inclisiran 300 mg SC on days 1 and 90	**Inclusions** • Diagnosis of HoFH by genetic confirmation or a clinical	Percent Change in LDL-C at Day 150	September 2021

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Hypercholesterolemia (HoFH) (ORION-5) NCT03851705 Sponsor: Novartis Pharmaceuticals	Label Multicenter Study Actual Enrollment: 56	2) Placebo SC on days 1 and 90 3) Inclisiran 300 mg SC on days 270, 450, and 630	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		

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• 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	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

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• 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)		
Bempedoic Acid					
Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With	Double-Blind, Placebo Controlled, Randomized Controlled Trial Actual Enrollment: 14,014	1) Bempedoic Acid 180 mg orally once daily 2) Matched Placebo	**Inclusions** • 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	Time from randomization to first occurrence of one of the following adjudicated composite endpoints: CV death, nonfatal myocardial infarction, nonfatal stroke, or coronary	August 2022

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Bempedoic Acid (ETC-1002) or Placebo NCT02993406 Sponsor: Esperion Therapeutics			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	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 [XXX]. 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). [113] 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.

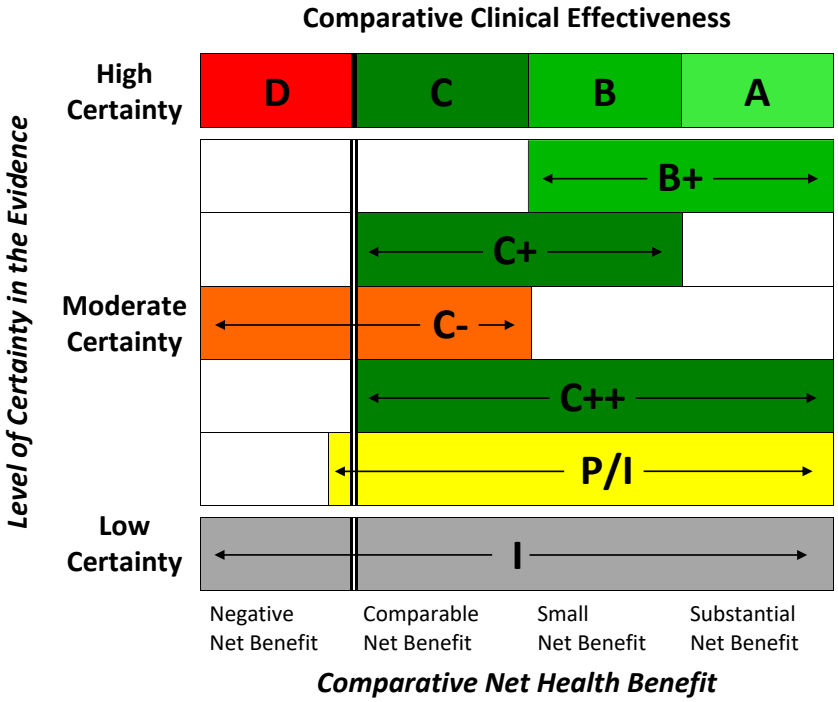
ICER Evidence Rating

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[44,114]

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[57] **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 284 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[61] **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 284 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[61] **NCT03400800**	1617	Europe & South Africa	Phase III DB, PC RCT 540 days	- Percent change in LDL-C from baseline to day 510 - Time-adjusted	1. Inclisiran 284 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	- NYHA class IV heart failure -MACE within 3 months - Uncontrolled cardiac arrhythmia

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
				percent change in LDL-C from baseline between day 90 and day 540		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	- Active liver disease - Tx within 90 days with monoclonal antibodies directed towards PCSK9
ORION 1[58] **NCT02597127**	501	US, Canada, & Europe	Phase II DB, PC RCT 210 days	-Percent change from LDL-C from baseline to day 180	<u>Single-dose regimen:</u> 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 <u>Two-dose regimen</u> 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							

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
CLEAR Wisdom[48] **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[50] **NCT0266664**	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,

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
							symptomatic cardiac arrhythmia within 3 months prior to screening - Liver disease or dysfunction
CLEAR Serenity[49] **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[45]	269	US, Canada,	Phase III, DB, PC RCT 12 weeks	- Percent change in LDL-C from	1. Bempedoic acid 180 mg (n=181)	- ≥18 years -LDL-C ≥100 mg/dL -History of statin	- Fasting blood triglycerides greater than or equal to 500

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
NCT03001076		and Europe	4-week run-in phase with ezetimibe	baseline to week 12	2. Placebo (n=88) once daily	intolerance, were on no more than low-dose statin therapy (which could include no statin)	mg/dL - BMI ≥ 50 kg/m2 - 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[46] 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	- 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

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
						tolerated statin therapy at stable dose for at least 4 weeks prior to screening	
Phase II Bempedoic Acid Trials							
Ballantyne 2016[53]	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.

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
Thompson 2016[56] **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[54]	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**

Trial Name & NCT #	N	Location	Design Duration	Primary Outcome(s)	Arms	Inclusion Criteria	Exclusion Criteria
Lalwani 2019[55]	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	Hypertension	Diabetes	Background Treatment: Overall %
			Mean (SD)	n (%)	n (%)	Mean (SD)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Inclisiran Trials[57-61]													
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)	1415 (90.6)	702 (45)	
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)	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)	58 (95)	131.3 (60.3)	43 (70)	3 (5)	NR	7 (12)	43 (70)	8 (13)	Statin: 73% High-intensity: 39% Ezetimibe: 31%

Trial	Arm	n	Age, years	Male	White	LDL-C, mg/dL	ASCVD	HeFH	ASCVD-Risk Equivalent	Current Smoker	Hypertension	Diabetes	Background Treatment: Overall %
			Mean (SD)	n (%)	n (%)	Mean (SD)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
	Placebo (Two-Dose Regimen)	62	62.8 (10.3)	33 (53)	58 (94)	125.2 (44.3)	46 (74)	3 (5)	NR	8 (13)	44 (72)	7 (11)	Ezetimibe alone (statin-intolerant): 6.4% Statin + ezetimibe: 24%
Phase III Bempedoic Acid Trials[45,48-50] [46]													
CLEAR Wisdom	Bempedoic acid	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)	236 (30.3)	
CLEAR Harmony	Bempedoic acid	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	Bempedoic acid	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	Bempedoic acid	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)	

Trial	Arm	n	Age, years	Male	White	LDL-C, mg/dL	ASCVD	HeFH	ASCVD-Risk Equivalent	Current Smoker	Hypertension	Diabetes	Background Treatment: Overall %
			Mean (SD)	n (%)	n (%)	Mean (SD)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Ballaynte 2020	Bempedoic acid + 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)	35 (40.7)	High-intensity statin: 34.6% Other-intensity statin: 30.2% No statin: 35.2%
	Bempedoic acid	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)	
	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[53-56]													
Ballantyne 2016	Bempedoic Acid 120 mg	43	59 (9)	17 (39)	37 (86)	134 (20)	NR	NR	NR	NR	NR	NR	Statin: 90% No Statin: 10%
	Bempedoic Acid 180 mg	45	57 (10)	14 (31)	37 (82)	142 (28)	NR	NR	NR	NR	NR	NR	
	Placebo	45	56 (10)	23 (51)	37 (82)	131 (22)	NR	NR	NR	NR	NR	NR	
	Overall	133	57.3 (NR)	54 (410	111 (83)	135.7 (NR)	NR	NR	NR	NR	NR	NR	
Thompson 2016	Statin Intolerant	177	62 (9)	76 (43)	158 (89)	169 (25)	NR	NR	NR	NR	NR	NR	NR
	Statin Tolerant	171	57 (9)	91 *53)	156 (91)	160 (25)	NR	NR	NR	NR	NR	NR	
	Overall	348	59.5 (NR)	17 (44)	314 (83)	164.6 (NR)	NR	NR	NR	NR	NR	NR	
	Bempedoic Acid	30	55.3 (6.9)	17 (56.7)	29 (96.7)	125.2 (27.5)	NR	NR	NR	NR	8 (26.7)	NR	NR

Trial	Arm	n	Age, years	Male	White	LDL-C, mg/dL	ASCVD	HeFH	ASCVD-Risk Equivalent	Current Smoker	Hypertension	Diabetes	Background Treatment: Overall %
			Mean (SD)	n (%)	n (%)	Mean (SD)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Gutierrez 2014	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	Atorvastatin + Bempedoic Acid	41	58 (10)	20 (48.8)	30 (73.2)	71 (19)	NR	NR	NR	NR	NR	NR	Statin: 100%
	Atorvastatin + Placebo	23	58 (8)	13 (56.6)	19 (82.6)	86 (26)	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, 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[57-61]										
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 (Two-Dose Regimen)	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 (Two-Dose Regimen)	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[45,48-50] [46]										
CLEAR Wisdom	Bempedoic acid	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	Bempedoic acid	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

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)
	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	Bempedoic acid	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	Bempedoic acid	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
Ballaynte 2020	Bempedoic acid + 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
	Bempedoic acid	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[53-56]										
Ballantyne 2016	Bempedoic Acid 120 mg	43	55 (15)	NR	216 (24)	112 (88-178)	NR	NR	1.8 (0.9-3.1)	NR
	Bempedoic Acid 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

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)
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	Bempedoic Acid	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 + Bempedoic Acid	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, 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)

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		Time-adjusted Percent Change in LDL-C, mg/dL			Time-adjusted Absolute Change in LDL-C, mg/dL		
				% Change	Between group Diff	Absolute Change	Between group Diff	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		Mean (95% CI)	Mean (95%CI), p-value		Mean (95%CI)	Mean (95%CI), p-value
Inclisiran Trials[57-61]													

Trial	Arm	n	Time-point	Percent Change in LDL-C, mg/dL		Absolute Change in LDL-C, mg/dL		Time-adjusted Percent Change in LDL-C, mg/dL			Time-adjusted Absolute Change in LDL-C, mg/dL		
				% Change	Between group Diff	Absolute Change	Between group Diff	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		Mean (95% CI)	Mean (95%CI), p-value		Mean (95%CI)	Mean (95%CI), p-value
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	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		8.2 (4.3, 12.2)		9.9 (4.1, 15.8)			6.2 (3.3, 9.2)			5.8 (NR)	
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	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		1 (NR)		-2.1 (NR)			2.5 (NR)			-0.4 (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	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		4 (NR)		1 (NR)			3.4 (NR)			0.3 (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	NR	NR	NR	NR	NR	NR
	Placebo, two dose regimen	61		1.8 (-2.6, 6.3)		-0.7 (SD: 25.6)	NR	NR	NR	NR	NR	NR	NR
	Inclisiran 300 mg, two-dose regimen	59	Day 360	-31.9 (-34.1, -29.0)	NR	NR	NR	Day 30 to 360	-46.7 (-50.3, -42.5)	NR	NR	NR	NR
	Placebo, two dose regimen	61		0.4 (-1.8, 2.8)		NR	NR		NR	NR	NR	NR	NR
Phase III Bempedoic Acid Trials[45,48-50] [46]													
CLEAR Wisdom	Bempedoic acid	498	Week 12	-15.1 (NR)	-17.4 (-21.0, -13.9), <0.001	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	253		2.4 (NR)		NR		NR	NR		NR	NR	NR
	Bempedoic acid	485	Week 24	-12.1 (NR)	-14.8 (-19.5, -10.0) <0.001	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	247		2.7 (NR)		NR		NR	NR		NR	NR	NR

Trial	Arm	n	Time-point	Percent Change in LDL-C, mg/dL		Absolute Change in LDL-C, mg/dL		Time-adjusted Percent Change in LDL-C, mg/dL			Time-adjusted Absolute Change in LDL-C, mg/dL		
				% Change	Between group Diff	Absolute Change	Between group Diff	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		Mean (95% CI)	Mean (95%CI), p-value		Mean (95%CI)	Mean (95%CI), p-value
	Bempedoic acid	467	Week 52	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	237		NR		NR		NR	NR		NR	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	NR	NR	NR	NR	NR	NR
	Placebo	725		1.6 (SE: 0.86)		0.4 (SD: 27.0)		NR	NR		NR	NR	NR
	Bempedoic acid	1397	Week 24	-14.9 (NR)	-16.1 (-18.2, -14.0), <0.001	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	707		1.2 (NR)		NR		NR	NR		NR	NR	NR
	Bempedoic acid	1364	Week 52	-12.6 (NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	685		1 (NR)		NR		NR	NR		NR	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	NR	NR	NR	NR	NR	NR
	Placebo	111		-1.3 (SE: 1.4)		-3.1 (NR)		NR	NR		NR	NR	NR
	Bempedoic acid	107	Week 24	-21.2 (SE: 1.4)	-18.9 (-23.0, -14.9), <0.001	-37 (NR)	NR	NR	NR	NR	NR	NR	NR
	Placebo	224		-2.3 (SE: 1.6)		-5.1 (NR)		NR	NR		NR	NR	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	NR	NR	NR	NR	NR	NR
	Placebo	82		5 (SE: 2.2)		4 (SE: 2.6)	NR (NR), <0.001	NR	NR		NR	NR	NR
Ballayante 2020 (Post-hoc analysis)	BA + EZE FDC	86	Week 12	-36.2 (SE: 2.6)	--	NR	NR	NR	NR	NR	NR	NR	NR
	Bempedoic acid	88		-17.2 (SE: 2.6)	-19 (-26.1, -11.9), <0.001	NR	NR	NR	NR	NR	NR	NR	NR

Trial	Arm	n	Time-point	Percent Change in LDL-C, mg/dL		Absolute Change in LDL-C, mg/dL		Time-adjusted Percent Change in LDL-C, mg/dL			Time-adjusted Absolute Change in LDL-C, mg/dL		
				% Change	Between group Diff	Absolute Change	Between group Diff	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		Mean (95% CI)	Mean (95%CI), p-value		Mean (95%CI)	Mean (95%CI), p-value
	Ezetimibe	86		-23.2 (SE: 2.2)	-13 (-19.7, -6.5), <0.001	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	41		1.8 (SE: 3.4)	-38 (-46.5, -29.6), <0.001	NR	NR	NR	NR	NR	NR	NR	NR
Ballayante 2020 (ITT analysis)	BA + EZE FDC	108	Week 12	-31.5 (SE: 2.5)	--	NR	NR	NR	NR	NR	NR	NR	NR
	Bempedoic acid	110		-17.7 (SE: 2.2)	-13.8 (-20.4, -7.1), <0.001	NR	NR	NR	NR	NR	NR	NR	NR
	Ezetimibe	109		-21 (SE: 2)	-10.5 (-16.8, -4.2), 0.001	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	55		-2.5 (SE: 3.1)	-29 (-36.8, -21.3), <0.001	NR	NR	NR	NR	NR	NR	NR	NR
Phase II Bempedoic Acid Trials[53-56]													
Ballantyne 2016	Bempedoic Acid 120 mg	41	Week 12	-17.3 (SE: 4.0)	7 (NR), <0.01	NR	NR	NR	NR	NR	NR	NR	NR
	Bempedoic Acid 180 mg	43		-24.3 (SE: 4.2)	NR (NR), <0.0001	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	43		-4.2 (SE: 4.2)	--	NR	NR	NR	NR	NR	NR	NR	NR
Thompson 2016	Bempedoic Acid 180mg	99	Week 12	-30.1 (SE: 1.3)	NR (NR), <0.0001	NR	NR	NR	NR	NR	NR	NR	NR
	Bempedoic Acid 180 mg + Ezetimibe 10 mg	22		-47.7 (SE: 2.8)	NR (NR), <0.0001	NR	NR	NR	NR	NR	NR	NR	NR
	Ezetimibe 10 mg	98		-21.2 (SE: 1.3)	--	NR	NR	NR	NR	NR	NR	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	NR	NR	NR	NR	NR	NR
	Placebo	30		-4 (SE: 2.5)		NR		NR	NR		NR	NR	NR

Trial	Arm	n	Time-point	Percent Change in LDL-C, mg/dL		Absolute Change in LDL-C, mg/dL		Time-adjusted Percent Change in LDL-C, mg/dL			Time-adjusted Absolute Change in LDL-C, mg/dL		
				% Change	Between group Diff	Absolute Change	Between group Diff	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		Mean (95% CI)	Mean (95%CI), p-value		Mean (95%CI)	Mean (95%CI), p-value
Lalwani 2019	Atorvastatin + Bempedoic Acid	41	Week 4	-13 (SE: 4.12)	-22.2 (-36.4, -8.0), 0.003	-8.25 (NR)	NR	NR	NR	NR	NR	NR	NR
	Atorvastatin + Placebo	23		9.2 (SE: 5.58)		1 (NR)		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 D5. Key Efficacy Outcomes II

Trial	Arm	n	Timepoint	Percent Change in HDL-C, mg/dL		Percent Change in Total Cholesterol, mg/d:		Percent Change in Non-HDL-C, mg/dL		Percent Change in Triglyceride, mg/dL	
				% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff
				Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Median (95% CI)	Mean (95%CI), p-value
Inclisiran Trials[57-61]											
ORION 9	Inclisiran	242	Day 510	8.6 (NR)	2.6 (NR), NR	-26.1 (NR)	-32.9 (NR), NR	-36.1 (NR)	-43.6 (NR), NR	11.1 (NR)	-11.8 (NR), NR
	Placebo	240		6 (NR)		6.8 (NR)		7.5 (NR)		-0.7 (NR)	
ORION 10	Inclisiran	781	Day 510	7.5 (NR)	5.1 (NR), NR	-33.6 (NR)	-33.1 (NR), <0.001	-47.4 (NR)	-47.4 (NR), <0.001	-14.9 (NR)	-12.6 (NR), NR
	Placebo	780		2.4 (NR)		0.4 (NR)		-0.1 (NR)		-2.3 (NR)	
ORION 11	Inclisiran	810	Day 510	10.2 (NR)	6.1 (NR), NR	-28 (NR)	-29.8 (NR), <0.001	-41.2 (NR)	-43.3 (NR), <0.001	-12 (NR)	-7 (NR), NR
	Placebo	807		4.4 (NR)		1.8 (NR)		2.2 (NR)		-5 (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	-40.6 (SD: 14.6)	NR (NR), <0.001	-14.2 (-26.4, 5.4)	NR (NR), <0.05
	Placebo, two dose regimen	61		0.5 (SD: 12.5)		0.7 (SD: 12.3)		1.3 (SD: 16.9)		-3 (-17.2, 22.6)	
Phase III Bempedoic Acid Trials[45,48-50] [46]											
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	-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		-0.2 (SE: 0.9)		1.3 (SE: 1.0)		2.3 (SE: 1.4)		6.1 (SE: 2.3)	
	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	-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		0.5 (SE: 0.9)		1.5 (SE: 1.2)		2.4 (SE: 1.6)		4.7 (SE: 2.2)	
	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	-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		-3.4 (SE: 0.8)		-1.9 (SE: 1.2)		-0.4 (SE: 1.6)		4.8 (SE: 2.5)	
CLEAR Harmony	Bempedoic acid	1424	Week 12	NR	NR	-10.3 (SE: 0.37)	-11.1 (-12.5, -9.8), <0.001	-11.9 (SE: 0.5)	-13.3 (-15.1, -11.6), <0.001	NR	NR
	Placebo	725		NR		0.8 (SE: 0.57)		1.5 (SE: 0.76)		NR	NR

Trial	Arm	n	Timepoint	Percent Change in HDL-C, mg/dL		Percent Change in Total Cholesterol, mg/d:		Percent Change in Non-HDL-C, mg/dL		Percent Change in Triglyceride, mg/dL	
				% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff
				Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Median (95% CI)	Mean (95%CI), p-value
	Bempedoic acid	1397	Week 24	NR	NR	-9.8 (NR)	NR	-11.6 (NR)	NR	NR	NR
	Placebo	707		NR		1.1 (NR)		1.5 (NR)		NR	NR
	Bempedoic acid	1364	Week 52	NR	NR	-8.9 (NR)	NR	-10 (NR)	NR	NR	NR
	Placebo	685		NR		0.3 (NR)		0.5 (NR)		NR	NR
CLEAR Serenity	Bempedoic acid	234	Week 12	NR	NR	-16.1 (SE: 1.0)	-14.8 (-17.3, -12.2), <0.001	-19 (SE: 1.3)	-17.9 (-21.1, -14.8), <0.001	NR	NR
	Placebo	111		NR		-0.6 (SE: 1.0)		-0.4 (SE: 1.0)		NR	NR
	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	-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		0.6 (SE: 1.0)		-1 (SE:1.0)		0.9 (SE: 1.3)		7.4 (SE: 3.5)	
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	-18.4 (SE: 1.7)	-23.6 (SE: 2.8), <0.001	-1.4 (NR)	NR
	Placebo	82		-1.4 (SE: 1.4)	--	2.9 (SE: 1.5)		5.2 (SE: 2.3)		7.8 (NR)	NR
Ballayante 2020 (Post-hoc analysis)	BA + EZE FDC	86	Week 12	NR	NR	-26.4 (SE: 1.9)	--	-31.9 (SE: 2.2)	--	NR	NR
	Bempedoic acid	88		NR	NR	-12.1 (SE: 1.8)	-14.2 (-20.4, -8.1), <0.001	-14.1 (SE: 2.2)	-17.8 (-25.1, -10.5), <0.001	NR	NR
	Ezetimibe	86		NR	NR	-16 (SE: 1.6)	-10.4 (-16.1, 4.6), <0.001	-19.9 (SE: 2.1)	-12.1 (-19.1, -5), <0.001	NR	NR
	Placebo	41		NR	NR	0.7 (SE: 2.5)	-27.1 (-35.1, 19.1), <0.001	1.8 (SE: 3.3)	-33.7 (-43.9, -23.4), <0.001	NR	NR
Ballayante 2020 (ITT analysis)	BA + EZE FDC	108	Week 12	NR	NR	-22.6 (SE: 1.9)	--	-27.2 (SE: 2.2)	--	NR	NR
	Bempedoic acid	110		NR	NR	-12.8 (SE: 1.7)	-9.8 (-15.7, -3.9), <0.001	-14.9 (SE: 2)	-12.3 (-19.3, -5.3), <0.001	NR	NR
	Ezetimibe	109		NR	NR	-13.5 (SE: 1.5)	-9.1 (-14.8, -3.4), <0.001	-16.3 (SE: 2)	-10.9 (-17.9, -3.9), <0.001	NR	NR
	Placebo	55		NR	NR	-2 (SE: 2.2)	-20.6 (-28, -13.2), <0.001	-1.8 (SE: 2.8)	-25.4 (-34.6, 16.1), <0.001	NR	NR

Trial	Arm	n	Timepoint	Percent Change in HDL-C, mg/dL		Percent Change in Total Cholesterol, mg/d:		Percent Change in Non-HDL-C, mg/dL		Percent Change in Triglyceride, mg/dL	
				% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff	% Change	Between group Diff
				Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Mean (95% CI)	Mean (95%CI), p-value	Median (95% CI)	Mean (95%CI), p-value
Phase II Bempedoic Acid Trials[53-56]											
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	-14.3 (SE: 3.7)	NR (NR), <0.01	-4.8 (IQR: 28)	NR (NR), NS
	Bempedoic Acid 180 mg	43		-4 (SE: 2.7)	NR (NR), NS)	-15.3 (SE: 2.9)	NR (NR), <0.01	-16.6 (SE: 3.9)	NR (NR), <0.01	-9.1 (IQR: 47)	NR (NR), NS
	Placebo	43		-2 (SE: 2.7)	--	-3.2 (SE: 2.9)	--	-1.8 (SE: 3.9)	--	-3 (IQR: 37)	NR
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	-25.4 (SE: 1.1)	NR (NR), <0.0001	-2.7 (IQR: 46.2)	NR
	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	-42.4 (SE: 2.4)	NR (NR), <0.0001	-12.2 (IQR: 36.5)	NR
	Ezetimibe 10 mg	98		5 (SE: 1.4)	--	-14.3 (SE: 0.9)	--	-18.7 (SE: 1.2)	--	-7 (IQR: 32.9)	NR
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	-32 (SE: 2.3)	-31.4 (-38.0, 24.8), <0.0001	-1 (NR)	NR (NR), 0.1219
	Placebo	30		0.5 (SE: 1.8)		-0.5 (SE: 1.9)		-0.5 (SE: 2.3)		8 (NR)	
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	-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		4.7 (SE: 3.1)		4.1 (SE: 3.1)		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 D6. Key Efficacy Outcomes III

Trial	Arm	n	Timepoint	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[57-61]													
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[45,48-50 46]													
CLEAR Wisdom	Bempedoic acid	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	
	Bempedoic acid	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	
	Bempedoic acid	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	Bempedoic acid	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	
	Bempedoic acid	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	
	Bempedoic acid	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	Bempedoic acid	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	
	Bempedoic acid	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 Tranquility	Bempedoic acid	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	
Ballayante 2020 (Post-hoc analysis)	BA + EZE FDC	86	Week 12	-35.1 (NR)	--	-24.6 (SE: 2.4)	--	NR	NR	NR	NR	NR	NR
	Bempedoic acid	88		-31.9 (NR)	NS	-11.8 (SE: 2.2)	-12.8 (-20.3, -5.3), <0.001	NR	NR	NR	NR	NR	NR
	Ezetimibe	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
Ballayante 2020 (ITT analysis)	BA + EZE FDC	108	Week 12	-34 (NR)	--	-20.1 (SE: 2.3)	--	NR	NR	NR	NR	NR	NR
	Bempedoic acid	110		-20 (NR)	NS	-11.7 (SE: 2.2)	-8.4 (-15.6, -1.1), 0.008	NR	NR	NR	NR	NR	NR
	Ezetimibe	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[53-56]													

Ballantyne 2016	Bempedoic Acid 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
	Bempedoic Acid 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
Thompson 2016	Bempedoic Acid 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
	Bempedoic Acid 180 mg + Ezetimibe 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
	Ezetimibe 10 mg	98		-10.5 (IQR: 59)	NR	-15.2 (SE: 1.2)	NR	NR	NR	NR	NR	NR	NR
Gutierrez 2014	Bempedoic Acid, 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	Atorvastatin + Bempedoic Acid	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
	Atorvastatin + Placebo	23		0.74 (SD: 50.9)		5.88 (SE: 3.9)		NR	NR	NR	NR	NR	NR

ApoB: apolipoprotein B, 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 D7. 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[57]	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[61]	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[61]	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[58]	Overall	Inclisiran	59	Day 180	-52.6	(-57.1, -48.1)	NR	NR
		Placebo	61		1.8	(-2.6, 6.3)	--	--
CLEAR Wisdom[48]	Overall (ASCVD, HeFH, or both)	Bempedoic acid	498	Week 12	-15.1	NR	-17.4	(-21.0, -13.9)
		Placebo	253		2.4	NR	--	--

Trial	Population	Arm	n	Timepoint	Percent Change in LDL-C			
					% Change		Difference	
					Mean	(95% CI)	Mean	(95% CI)
	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[50]	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)

Trial	Population	Arm	n	Timepoint	Percent Change in LDL-C			
					% Change		Difference	
					Mean	(95% CI)	Mean	(95% CI)
		Placebo	25				--	--
CLEAR Harmony & Wisdom Pooled[47]	Overall (ASCVD, HeFH, or both)	Bempedoic acid	2010	Week 12	-16	NR	-17.8	(-19.5, -16.0)
		Placebo	999		1.8	NR	--	--
	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[49]	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	--	--

Trial	Population	Arm	n	Timepoint	Percent Change in LDL-C			
					% Change		Difference	
					Mean	(95% CI)	Mean	(95% CI)
	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[45]	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[53]	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[56]	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

Trial	Population	Arm	n	Timepoint	Percent Change in LDL-C			
					% Change		Difference	
					Mean	(95% CI)	Mean	(95% CI)
		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[46]	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)

Trial	Population	Arm	n	Timepoint	Percent Change in LDL-C			
					% Change		Difference	
					Mean	(95% CI)	Mean	(95% CI)
		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 D8. Safety Outcomes I

Trial	Arm	n	Timepoint	Any AE	TEAE	Study Drug-Related AEs	D/C due to AE	Serious AE	Fatal TEAE	Uric Acid Increase	Gout	Myalgia	Injection-Site Rxn
				n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Inclisiran Trials[57-61]													
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, two-dose regimen	62	Day 210	47 (77)	NR	NR	0 (0)	7 (11)	NR	NR	NR	5 (8)	4 (7)
	Placebo, two dose regimen	62		50 (81)	NR	NR	1 (2)	6 (10	NR	NR	NR	3 (5)	0 (0)
Phase III Bempedoic Acid Trials[45,48-50 46]													
CLEAR Wisdom	Bempedoic acid	522	52 weeks	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	Bempedoic acid	1487	52 weeks	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	Bempedoic acid	234	24 weeks	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)	

Trial	Arm	n	Timepoint	Any AE	TEAE	Study Drug-Related AEs	D/C due to AE	Serious AE	Fatal TEAE	Uric Acid Increase	Gout	Myalgia	Injection-Site Rxn
				n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CLEAR Tranquility	Bempedoic acid	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	Bempedoic acid + ezetimibe	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)	
	Bempedoic acid	88		NR	58 (65.9)	12 (13.6)	9 (10.2)	7 (8)	0 (0)	1 (1.1)	0 (0)	5 (5.7)	
	Ezetimibe	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	Bempedoic Acid 120 mg	43	Week 12	15 (35)	15 (35)	4 (9)	0 (0)	0 (0)	NR	NR	NR	1 (2)	
	Bempedoic Acid 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*[53-56]**													
Thompson 2016	Bempedoic Acid 180mg	100	Week 12	55 (55)	55 (55)	18 (18)	6 (6)	1 (1)	0 (0)	NR	NR	1 (1)	NA
	Bempedoic Acid 180 mg + Ezetimibe 10 mg	24		17 (71)	17 (71)	10 (42)	1 (4)	0 (0)	0 (0)	NR	NR	1 (4)	
	Ezetimibe 10 mg	99		53 (54)	53 (54)	19 (19)	8 (8)	1 (1)	0 (0)	NR	NR	6 (6)	
Gutierrez 2014	Bempedoic Acid	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	Atorvastatin +	45	Week 4	16 (35.6)	NR	7 (15.6)	1 (2.2)	0 (0)	NR	NR	0 (0)	2 (4.4)	

Trial	Arm	n	Timepoint	Any AE	TEAE	Study Drug-Related AEs	D/C due to AE	Serious AE	Fatal TEAE	Uric Acid Increase	Gout	Myalgia	Injection-Site Rxn
				n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Bempedoic Acid												
	Atorvastatin + Placebo	23		5 (21.7)	NR	1 (4.3)	0 (0)	0 (0)	NR	NR	1 (4.3)	0 (0)	

AE: adverse event, D/C: discontinuation, mg: milligram, n: number, NA: not applicable, NR: not reported, Rxn: reaction, TEAE: treatment-emergent adverse event

Table D9. Safety Outcomes II

Trial	Arm	n	Timepoint	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[57-61]														
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[45,48-50 46]														
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)	
	BA	181		2 (1.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Trial	Arm	n	Timepoint	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)
CLEAR Tranquility	Placebo	87	Week 12	2 (2.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ballantyne 2020	BA + ezetimibe	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
	Ezetimibe	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*[53-56]**														
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 + Ezetimibe 10 mg	24		NR	0 (0)	NA	NR	NR	NR	NR	NR	NR	NR	NR
	Ezetimibe 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, n: number, NA: not applicable, NR: not reported, RR: risk ratio, 95%CI: 95% confidence interval

Table D10. 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[57-61]										
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[45,48-50 46]										
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)

Trial	Arm	n	Timepoint	Composite CV Event*		New or Worsening Cancer		ALT >3x ULN	AST >3x ULN	Creatine kinase >5x ULN
	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[53-56]										
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 D11. 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[57-61]										
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[45,48-50 46]										
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)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[115]

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.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[116]

2. 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).

3. 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.

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

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

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

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Table E2. 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		Inclisiran	
Year	Cumulative Cost	Additional Costs per Year (Non-Cumulative)	Cumulative Cost	Additional Costs per Year (Non-Cumulative)
Year 1	$2,504	$2,504	$7,997	$7,997
Year 2	$4,932	$2,428	$13,032	$5,035
Year 3	$7,304	$2,372	$17,974	$4,942
Year 4	$9,621	$2,317	$22,822	$4,848
Year 5	$11,882	$2,261	$27,575	$4,752

Table E3. 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 E4. 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 E5. 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 E6. 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).