Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Response to Public Comments on Draft Evidence Report

January 22, 2021

Table of Contents

#	Comment	Response/Integration
Manufacturers		
Amgen		
1.	**Revise the current model to fully account for long-term implications of recurrent events.** ICER should revise its model to include recurrent events. Amgen acknowledges the original draft model (presented by ICER on September 22, 2020) has been updated. A clear improvement is that the model now allows for the possibility of subjects experiencing both a stroke and an acute coronary syndrome event within a one-year period. However, the current model structure does not capture the long-term impact (long-term increased event rates, utility losses and cost increase) of recurrent events. Therefore, the model structure still underestimates the value of lipid-lowering therapy. Amgen supports further revisions of the model to implement the long-term implications of recurrent events.	The model incorporates recurrent events and associated costs and quality-of-life penalties. An event with a large quality-of-life impact (e.g., a stroke in an individual with a prior history of ACS) also produces permanent quality-of-life changes. While not perfect, these attempts reflect contemporary practice in capturing the impact of acute ASCVD events.
2.	**Reframe the language in the report to more accurately reflect ICER's objective of providing a fair and balanced assessment.** In the framing of this Draft Evidence Report, we propose clarifications in language, which we believe would more accurately reflect ICER's objective of providing a fair and balanced assessment as a neutral party. For your convenience, we have summarized our proposed changes with respect to tone, balance, and accuracy in Table 1.	We appreciate the careful reading of our report, suggestions for improvement, and references for our consideration. We have updated language throughout the report to reflect the suggestions, including addressing the relationship between LDL-C and MACE rates, as well as the dosing schedule for inclisiran, and changes in pricing for PCSK9 inhibitors.
Esperion		
1.	**Esperion strongly recommends that the patient mix in the comparator arm of the economic model be revised to more accurately represent EZE use in the real world and in large scale clinical trials.** Per the approved United States Package Insert (USPI), bempedoic acid/ezetimibe fixed dose combination product (BA+EZE) is indicated as an adjunct to diet and MTS for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low-density lipoprotein cholesterol (LDL-C). There is no labelling requirement for background use of EZE prior to the use of this product.	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).

2.	When assessing non-statin treatment options for patients who are not at LDL-C goal with MTS alone, clinicians typically take into account the reduction in LDL-C needed to reach goal. For those high-risk patients on MTS requiring greater LDL-C reduction to get to goal than EZE provides, EZE is likely not the optimal non-statin therapy to add, as these patients will be delayed in reaching LDL-C goal and remain at elevated risk for CV events. The dangers of delaying access to non-statin therapies resulting in delays in LDL-C lowering were underscored in a large retrospective study of ASCVD patients, where lack of access to PCSK9 inhibitor (PCSK9i) treatment led to significantly increased risk of cardiovascular events (adjusted hazard ratio for composite cardiovascular [CV] event outcome: 1.11; 95% CI, 1.02-1.22; p=0.03) compared with those patients who received access to PCSK9i treatment. Another large retrospective analysis also found that among patients who had a claim for PCSK9i rejected, there was a higher rate of acute CV events (7.29 per 100 patient years) compared with the overall rate of 6.73 per 100 patient years. These studies highlight the importance of timely prescribing of the appropriate non-statin treatment to high risk patients not at LDL-C goal, as delays in getting to LDL-C goal put patients at increased risk for CV events.	We appreciate this comment and have included a more detailed discussion of this issue in the Patient Perspectives section.
3.	Published real-world use of EZE among patients with established ASCVD and/or HeFH with LDL-C > 70 mg/dL in the US is very low, estimated at approximately 8%. ICER's own Draft Evidence Report (page 46) further corroborates the low use of EZE based on data from the National Health and Nutrition Examination Survey (NHANES) from 2009-2016: "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." These data from a large, nationally representative and widely used data source, demonstrate actual treatment patterns and EZE usage in patients with ASCVD and are reflective of usual care in the US. Large scale clinical trials of patients with ASCVD have also demonstrated low levels of EZE use among participants. Two recent large scale clinical trials of non-statin therapies, FOURIER and ODYSSEY OUTCOMES, enrolled over 46,000 patients with ASCVD who needed additional lipid lowering despite treatment with MTS with or without other lipid lowering therapies. Baseline EZE use in both trials was reflective of real-world estimates of EZE usage: 5.2% (FOURIER) and 2.9% (ODYSSEY). Based on the rates of EZE use in the real world setting and in large scale clinical trials, it is not realistic or appropriate for ICER's cost-effectiveness model to assume that 100% of patients receive EZE in the comparator arm for the base case	See above.

	BA+EZE assessment. This assumption is not reflective of usual care in the US and contributes to a higher incremental cost-effectiveness ratio for BA+EZE resulting in an arbitrary access barrier to optimal therapy for many high-risk patients. Esperion strongly urges ICER to utilize a patient mix in the comparator arm that is more reflective of the real-world care. Specifically, the patient mix in the base case comparator arm should include 4.2% of patients receiving EZE (per ICER's NHANES analysis), with the remainder (95.8%) receiving MTS alone, with the assumption that those patients will transition to BA+EZE. From a modeling perspective, the variability in real world EZE use ranging from 0-100% can be tested in sensitivity analyses. As stated in ICER's 2020-2023 Value Assessment Framework, "ICER reports are intended to support deliberation on medical policies related to health services (e.g., tests or treatments) and delivery system interventions (e.g., preventive programs, changes to the organization of medical personnel). To inform these kinds of medical policies the ICER value framework takes a "population" level perspective as opposed to trying to serve as a shared decision-making tool to be used by individual patients and their clinicians". We urge ICER to adhere to this stated mission of informing population-level policy decisions regarding the economic value of treatments rather than inadvertently influencing treatment selection decisions at the patient level. By assuming 100% EZE use, ICER is introducing inherent clinical bias regarding treatment selection rather than focusing on policy level recommendations.	
4.	**Esperion strongly recommends that ICER consider conducting sensitivity analyses to test a range in prevalence for SI which is more in line with real word data (i.e., 10%-20%) so as to not minimize this important high-risk subgroup.** Esperion agrees with ICER that patients with statin intolerance (SI) represent a high-risk population with limited treatment options to reach LDL-C goal. SI patients are generally at higher risk of CV events compared to patients without SI due to higher baseline LDL-C levels and represent a population with high unmet need for non-statin treatment options.	We now include a sensitivity analysis that assumes a higher and lower prevalence of statin intolerance than assumed in the base case.

5.	BA is particularly suited for the treatment of patients with SI based on its mechanism of action. BA is more efficacious in patients with SI compared to those without. BA acts upstream of the enzyme inhibited by statins in the cholesterol biosynthesis pathway, and in the absence of statins results in greater reductions in LDL-C. Furthermore, BA is a prodrug that does not get activated in skeletal muscle, as opposed to statins. In the pooled BA P3 data, the incidence of skeletal muscle side effects was comparable to placebo.	This is already included in the model.
6.	ICER's Model Analysis Plan currently estimates 10% prevalence for SI, which is on the low end of reported prevalence of SI in this historically underserved, but clinically important patient subgroup. The most recent AHA/ACC Cholesterol Guidelines recognize that statin-associated muscle symptoms are the most common side effect leading to statin intolerance and that these are observed to occur in up to 20% of patients. In a meta-analysis of 26 randomized trials, approximately 13% of patients reported muscle adverse events, the most common being myalgia. Based on the clinical importance of this high-risk subgroup and published real world prevalence estimates, Esperion recommends that ICER increase the prevalence of SI in the base case patient mix and also conduct sensitivity analyses utilizing prevalence estimates that are more in line with real word data (i.e., 10%-20%) so as to not minimize this important high risk subgroup.	Statin-associated symptoms should not be equated to statin intolerance. The majority of patients who report some symptoms are able to tolerate alternative statin regimens or doses and would not be considered to have true statin intolerance. Some experts have argued that true statin intolerance may be much less frequent than our base-case estimate.
7.	**Esperion strongly recommends that ICER use baseline utility estimates that more accurately represent the quality of life of US individuals with ASCVD.** The baseline utility values used in this evaluation have been considerably overestimated relative to the quality of life of the general US population and recently published cardiovascular disease-specific baseline utility estimates.	Because the benefits of lipid lowering in a secondary prevention cohort are largely due to prolongation of survival (by averting CV death), assuming lower baseline quality of life results in a substantial increase in the incremental cost-effectiveness ratio for both of the drugs being evaluated. For instance, assuming more severe penalties for quality of life due to prior ACS or stroke, similar to those used in the ICER report for icosapent ethyl, caused the cost-effectiveness ratios for both drugs in the model to exceed $200,000 per QALY gained (data not shown). We chose the quality-of-life estimates shown here to facilitate comparisons with our prior work on lipid-lowering therapies.
8.	Cardiovascular events can be devastating and are associated with significant decrements in quality of life. The high-risk population being evaluated by ICER represents a population which typically has lower baseline utility values than the general population in the US. Jiang et al reported a mean utility value for the overall US population of 0.851, with a mean utility value of 0.835 for those in "good" health based on interviews conducted in 2017. Betts et al reported median	We have explored this in a sensitivity analysis. Note that assuming lower baseline quality of life makes lipid-lowering therapies for secondary prevention less economically attractive.

	utility values in cardiovascular disease (MI=0.79, stroke=0.64, stable angina=0.72) based on a systematic literature review conducted in 2018. These published estimates demonstrate that the baseline utility estimates utilized in this ICER evaluation (MI=0.96, stroke=0.88, angina=0.91), based on The Global Burden of Disease 2010 study, have been considerably overestimated relative to general US population norms and cardiovascular disease-specific estimates. For example, it is unlikely that a person with a history of MI has a baseline utility value (0.96) that is close to perfect health. It is imperative that ICER utilize reasonable and credible baseline utility estimates that accurately reflect the impact of cardiovascular events on quality of life. Furthermore, the utility estimates being used in this ICER evaluation deviate from those ICER has used in recent evaluations of cardiovascular disease and diabetes. We urge ICER to use a consistent approach to estimating utilities across recent evaluations for similar and/or related disease states to ensure fair and balanced evaluations of important new therapies	
9.	Esperion also recommends that ICER address this issue in the Contextual Considerations and facilitate further discussion at the policy roundtable. In Table 6.11, ICER includes a contextual consideration stating, "Assumptions made in the base-case cost-effectiveness estimates rendering results overly optimistic or pessimistic." In terms of relevant information, Esperion recommends ICER add a bullet regarding the baseline utility estimates for individuals with ASCVD. Since much higher baseline utility values are being used in this evaluation in lieu of previously established ICER estimates and published data, it is important to consider the impact of these inflated baseline utility estimates on the results of this ICER evaluation.	We appreciate this comment. We have addressed baseline utility assumptions in prior comments and also added a bullet to the Contextual Considerations table.
10.	**Gout** Esperion disagrees with ICER's characterization of gout associated with BA as a serious, treatment emergent adverse event for the economic evaluation. Among the over 3000 patients with ASCVD and/or HeFH participating in the 52-week BA phase 3 clinical trials, gout was experienced in 1.4% of patients treated with BA as compared to 0.4% for placebo. Only one gout event across the phase 3 program met the criteria for a serious adverse event. Among the patients in the BA treatment arm that experienced gout, the vast majority (89.7%) were deemed to be mild or moderate in severity.	Gout is a meaningful outcome for patients and deserves a place in the model. However, it has minimal impact on the cost-effectiveness results.
11.	**Draft Voting Questions** **a. Clinical Evidence and Potential Other Benefits and Contextual Considerations** ICER is evaluating Nexlizet in the Value for Money assessment. As such, Nexlizet should replace Nexletol in the voting questions given the scope of the evaluation described in ICER's Revised Scope and Background Document which includes	We appreciate the feedback on our voting questions. In the economic review, for bempedoic acid/ezetimibe combination, the comparator was maximally tolerated statin + ezetimibe. So, in essence, when comparing bempedoic acid/ezetimibe to statin + ezetimibe, we are assessing the

	Nexlizet. Esperion requests that ICER replace Nexletol with Nexlizet for the voting questions in these two sections. **b. Long Term Value for Money** Esperion requests that ICER clarify why the voting panel members are asked to assess value for money associated with BA+EZE compared to "usual care with ezetimibe", yet for inclisiran, the comparison is to "usual care alone". The value of BA+EZE should be assessed in alignment with Nexlizet's FDA-approved indication (as an adjunct to diet and MTS) and consistent with current standard of care in the US. Esperion requests that ICER institute a balanced approach in assessing value for money with each treatment considered in this evaluation.	value of adding bempedoic acid to the regimen, since all patients are on ezetimibe. This is the reason for voting on bempedoic acid only, not the combination pill. In addition, we believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).
Novartis		
1.	**Based on the pivotal clinical trial populations for ORION-10 and ORION-11, the expected label for inclisiran, and real-world patterns, the base-case population should include patients with established ASCVD who need additional lipid-lowering therapy despite being on maximally tolerated statins only. In case it is of interest, a separate subgroup analysis could be conducted for patients on maximally tolerated statins and ezetimibe. The assumption of inclisiran being used only after ezetimibe undervalues the assessment of inclisiran.** The base-case population should include patients with established ASCVD who need additional lipid-lowering, despite maximally tolerated statins. In the current model, the base-case population includes patients on maximally tolerated statins AND ezetimibe; however, the inclusion criteria for ORION-10 and ORION-11 were patients on maximally tolerated statins (ezetimibe was not required but allowed). Only a small percentage of patients from ORION-10 (inclisiran: 10.2%, placebo: 9.5%) and ORION-11 (inclisiran: 6.3%, placebo: 7.7%) were on ezetimibe (Ray 2020). Similarly, a very low proportion of patients receive ezetimibe in real-world practice (4.2%; Lin 2020, NHANES 2020). The analysis does not reflect real-world utilization of lipid-lowering therapies and the expected utilization of inclisiran, instead assuming an idealized scenario, substantially diminishing the value assessment to decision-makers.	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).
2.	In the model, the effect of treating all individuals with ezetimibe was estimated to reduce LDL-C levels by 23.5%, resulting in a baseline LDL-C value of 88.8 mg/dL for patients on maximally tolerated statins and ezetimibe. Rather than adjusting LDL-C using published risk reductions, ICER should try to identify real-world patients to inform baseline characteristics, as adjustments may either over- or under-estimate the real LDL-C of these populations, which is a crucial	By using the NHANES population, we generated nationally representative estimates of patients who would be eligible for additional lipid-lowering therapies despite statin treatment. We explored the effect of varying baseline LDL-C levels in sensitivity analyses.

	input of the model. Data from the ORION-10 and ORION-11 trials show that the LDL-C of those on statins and ezetimibe is higher than those on statins without ezetimibe. Therefore, adjusting the LDL-C from individuals in NHANES to reflect that their LDL-C would be lower if they were all receiving ezetimibe in addition to statins may not be appropriate and may conflict with real-world data. These differences may be explained by a number of different reasons; for example, some patients receiving ezetimibe may be statin-intolerant and therefore have worse LDL-C at baseline, or patients receiving ezetimibe in practice may be at the higher range of baseline LDL-C despite being on maximally tolerated statins. Compliance with ezetimibe in the real-world setting is also poor (only approximately 40% of Medicare patients on ezetimibe have optimal adherence over 24 months; Novartis 2020a), thus impacting the real-world treatment effect of ezetimibe. ICER should use the LDL-C of the subgroup from NHANES on statins only or ORION-10 (104.197 mg/dL) as the baseline LDL-C value for the model. In the cost-effectiveness model developed by Novartis, increasing the baseline LDL-C value from 88.8mg/dL to 104.197 mg/dL resulted in an approximately 30% decrease in the incremental cost-effectiveness ratio. The assumption of having inclisiran used only after ezetimibe undervalues the assessment of inclisiran.	
3.	**In the cost-effectiveness model for ASCVD patients, the relative reduction in LDL-C level with inclisiran should not include ORION-9 data, since this trial was conducted in patients with heterozygous familial hypercholesterolemia (HeFH). Separate analyses should be performed for ASCVD and HeFH populations, using appropriate data for the efficacy of inclisiran for ASCVD or HeFH patients, respectively.** The model from the draft evidence report for treatment efficacy of inclisiran uses a relative reduction in LDL-C level for inclisiran of 50.5% based on pooled data from ORION-9, ORION-10, and ORION-11. However, this estimate should not include ORION-9, as this trial was conducted in HeFH patients, and the base-case model is focused on patients with established ASCVD. There are important differences between ASCVD patients and HeFH, including age and LDL-C levels (on average, HeFH patients are younger and with more elevated LDL-C; Raal 2020, Ray 2020). Therefore, the base-case relative reduction in LDL-C level with inclisiran in ASCVD patients should be 56%, based on a meta-analysis of ORION-10 and ORION-11, as previously shared by Novartis (Novartis 2020b). In the cost-effectiveness model developed by Novartis, using the efficacy for inclisiran based on the general ASCVD population trials (ORION-10, and ORION-11) resulted in an	We are unclear about how to interpret these comments. The meta-analysis submitted by the manufacturer has similar results (51%) to the estimate in our model.

	approximately 15% decrease in the incremental cost-effectiveness ratio.	
4.	**More details are needed on how adherence to inclisiran, statins and ezetimibe from clinical trials is implemented. Additionally, the cost-effectiveness analysis should consider the role of discontinuation to lipid-lowering therapies and the impact of the different frequency of administrations in the likelihood of a patient remaining adherent to therapy, in line with the available published evidence. The exclusion of this component has a significant impact in the cost-effectiveness results.** The draft evidence report states that the model assumes the same adherence to the interventions as observed in the clinical trials in order to reflect the use of efficacy estimates from the trials. More information is needed on how adherence is implemented in the model, such as the rates of adherence that were used in the model, if adherence rates were applied to the intervention of interest (inclisiran) or also the comparator (statin/ezetimibe), and if the drug costs were adjusted for non-adherent patients.	Real-world evidence may demonstrate differences in long-term adherence, but the direction and magnitude of these are unknown at this time. Because of this uncertainty, the current base case does not assume differential adherence.
5.	On a related note, the biannual administration of inclisiran using a healthcare professional (HCP) could potentially have an advantage over current therapies and can circumvent typical adherence issues associated with patient self-administration (e.g., self-injection anxiety, delayed doses). One publication noted that the high medication burden (i.e., the frequency of administration) associated with statins has a negative impact on adherence and average LDL-C reduction over time, which will likely diminish the CV risk reduction benefits associated with statins, especially when compared to HCP-administered twice-yearly therapies like inclisiran (Brandts 2020). Research in other asymptomatic conditions has shown that patients have better adherence to treatment when receiving a therapy administrated by an HCP. For instance, patients with osteoporosis (an asymptomatic and chronic condition) showed improved persistence and adherence with longer-acting regimens compared to shorter ones (Freemantle 2012; Kendler 2011; Roh, 2018; Tremblay 2016). In addition, postmenopausal women with osteoporosis were more adherent, compliant, and persistent with 6-month injection therapies compared to with once-weekly oral therapies (Freemantle 2012).	We thank you for this comment and for pointing us towards data in other conditions that use similar dosing strategies. We have updated our report to reflect this.
6.	Different discontinuation rates between treatment regimens should be incorporated into the cost-effectiveness model, accounting for the expected improved adherence associated with the inclisiran administration. Novartis recommends the use of 11.5% as the discontinuation annual rate for inclisiran and 23% for statins (Burke 2016). The recommendation on the use of 11.5% as the discontinuation rate for inclisiran is	See above.

	derived by applying a rate ratio of 0.5 vs. statin discontinuation rates. This method is based on research published in osteoporosis, comparing the discontinuation rates observed by mode and frequency of administration. Additional research has shown similar discontinuation rates when adding ezetimibe to statin therapy (vs. statin monotherapy); thus, it is recommended to also to use a discontinuation rate of 23% for statins and ezetimibe (Cannon 2015; Zhan 2018).	
7.	**CV mortality rates in the model should reflect the varying risks of CV death according to prior CV event type in order to more accurately account for the history of the cohort.** The draft evidence report does not specifically report fatal event rates, and instead states that "age-specific CV mortality for patients with established ASCVD was estimated from an analysis of pooled epidemiologic cohorts, where age-specific incidence of rate of CV death was calculated as the total number of CV deaths in each age category divided by the total person-years at risk." The references cited are dated and may not accurately reflect more recent CV mortality estimates. Additionally, applying CV mortality uniformly for all ASCVD patients does not take into account the fact that there are different health states in the model reflecting the medical history of the cohort. Risk of CV deaths may be different depending on the specific health state (i.e., different CV mortality rates for patients with history of acute coronary syndrome [ACS] vs patients with history of stroke); these varying risks should be accounted for in the model. Small changes in this input can potentially have a significant impact on results.	CV mortality in the model varies by prior history of cardiovascular events and time since last cardiovascular event.
8.	**The relationship between LDL-C lowering and reduction in major adverse cardiovascular events (MACE) rates in the model should be based on the 2019 publication from the Cholesterol Treatment Trialists' Collaboration (CTTC), rather than the meta-analysis published in 2010, as using the updated analysis will ensure a more relevant and accurate assessment, as well as have a substantial impact on the cost-effectiveness of inclisiran.** Novartis would like to note that there are newer versions of the CTTC meta-analyses available after the 2010 version. The 2012 and 2019 CTTC meta-analyses each include more trials and participants compared to the previous versions (CTTC 2012; CTTC 2019). The 2019 publication also included an exploratory analysis in which four trials that exclusively enrolled patients with heart failure or were on renal dialysis were excluded, as these patients would not have benefited from lipid lowering treatment, aligning with the patient populations excluded from the ORION studies. Additionally, the 2019 publication specifically analyzed the benefit of lipid lowering therapy in various age groups.	We examined the effect sizes reported in the CTTC-2010 and CTTC-2019, and decided to continue to use CTTC-2010 for the following reasons: 1. The overall effect size is nearly identical between the two publications, and 2. Using CTTC-2010 enhances comparability with prior ICER publications on the topic. Excluding HF and RD trials did not materially alter the effect sizes. Using age-stratified inputs creates a challenge in that there were fewer older adults in these studies, introducing greater uncertainty in the effect estimates for older adults. Of note, the effect appears to be somewhat attenuated in individuals with prior ASCVD (see Figure 4, CTTC-2019) but with overlapping confidence intervals.

	Using the updated CTTC data will therefore ensure a more relevant assessment of inclisiran. Novartis would also like to note that the CTTC 2010 meta-analysis segmented the reduction in incidence of stroke per mmol/L LDL-C reduction by type of stroke (CTTC 2010). In the draft evidence report, ICER appears to be using the overall stroke rate ratio from the 2010 CTTC publication (accounting for both ischemic and hemorrhagic stroke), rather than the rate ratio specific for ischemic stroke, which is more appropriate in the context of this assessment.	With regard to stroke, statins are known to reduce the risk of ischemic stroke and increase the risk of hemorrhagic stroke. In our model, we model all stroke as an outcome, and make the simplifying assumption that the stroke HR observed in the trials can be replicated in the real world.
9.	**There should be separate assessments for ASCVD and HeFH. To account for all patient subpopulations that can benefit from inclisiran, ICER's economic evaluation should consider all patients with HeFH, including those without ASCVD, rather than limiting the model to HeFH patients who also have ASCVD.** Novartis would like clarity on ICER's rationale for not including primary prevention for HeFH patients in the model, and whether HeFH patients without ASCVD will be considered in the inclisiran's economic evaluation, if at all. Novartis recommends including both scenarios of HeFH patients with ASCVD and HeFH patients without ASCVD in the economic model, given that HeFH patients who do not have established ASCVD are still at high risk for MACE and may benefit from inclisiran, as shown in the ORION trials. ICER should therefore include HeFH patients both with and without ASCVD in the economic analysis to account for all patient subpopulations that can benefit from inclisiran.	In order to explore higher-risk subpopulations who may derive greater benefit from therapies, and to facilitate comparison with subpopulations in prior ICER reviews of PCSK9 inhibitors, this analysis explores important "high-risk" subgroups of ASCVD patients such as those with ASCVD and HeFH. We also point out that while we would expect the incremental cost-effectiveness ratios to be substantially higher when used in lower-risk populations, 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.
10.	**Clarification is needed on several aspects of the model structure and model inputs: The inputs for baseline risks and transition probabilities.** The draft evidence report did not report the increase in MACE risk per decade of advancing age despite mentioning this input in the model analysis plan. The draft report also describes outcomes in terms of rates in the first 5 years from the model, while the inputs into the model are not reported. Additionally, Table 5.3 of the draft evidence report reports only the rate of revascularization, while rates of other events in the model (e.g., ACS, stroke) are not reported. ICER assumes that "prior clinical history determines the 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." Clarity on whether the event probabilities will be segmented by time would be beneficial (i.e., whether the model actually accounts for higher risk following the first year after an event compared to subsequent years).	As the manufacturers should have noted from their review of the TreeAge model, the risk of events does increase with age and is a function of prior clinical history (e.g., patients with a history of stroke are at increased risk of recurrent stroke) and time since last event (e.g., patients who survive an ACS event are at increased risk of an ACS event in the subsequent year).
11.	**The methodology to derive non-CV mortality rates and the numbers estimated for these rates**. In the draft evidence report, ICER notes that non-CV mortality rates were calculated by first estimating the age-specific non-CV deaths as a	Please see CDC Wonder documentation for this - as the online tool allows exclusion of deaths from circulatory system causes.

	proportion of all deaths from CDC WONDER by excluding deaths related to the circulatory system and subsequently applying this proportion to the annual probability of all-cause mortality from US lifetables. More information is needed on how ICER excluded deaths related to the circulatory system (e.g., ICD codes) to derive non-CV mortality. ICER should present the actual numbers used for non-CV mortality rates.	
12.	**Whether the model accounts for ASCVD patients with diabetes, since patients with diabetes and ASCVD are at an increased risk of events.** As diabetes is an important risk factor, the model should clarify the percentage of patients from the baseline population with diabetes, as the draft evidence report does not indicate any adjustments for the risk of MACE based on the presence of diabetes. If the model does not currently include diabetes as a risk factor for MACE, the analysis should consider accounting for this comorbidity, otherwise the model may underestimate the risk of events. In ORION-10, 45% of ASCVD patients had comorbid diabetes (Ray 2020). If ICER chooses not to model the impact of diabetes as a baseline risk factor, these potential consequences should be acknowledged and discussed in the report.	Yes, but as part of overall ASCVD cohort.
13.	**What is included in "background healthcare costs for management of non-CV health conditions"?** Novartis recommends rephrasing the term "background healthcare costs for management of non-CV health conditions," since the description states that this varies by clinical history (e.g., prior ACS, prior stroke, both or neither), and would therefore also be considered a background CV cost. The report should clarify if these "background healthcare costs for management of non-CV health conditions" applies to each state (dependent on history) beyond the first year after the event.	Agreed; please see clarification of this in the report.
14.	**What is included in the model structure for "history of other ASCVD"?** The draft report indicates that one of the states of the Markov model is "history of other ASCVD, such as stable angina or prior revascularization without prior ACS or stroke." It is not clear what the "history of other ASCVD" population entails, and therefore, what the related event rates of this state are. For example, are non-elective revascularizations included in the model structure? It is important to clarify what is included in the model structure for this state of "history of other ASCVD," because a history of angina might lead to different risks of events than a history of revascularization or a history of peripheral arterial disease.	As the manufacturer observed in their review of the model, elective revascularizations are modeled as an event in the model, associated with costs and quality-of-life penalties but no permanent change in clinical trajectory. Non-elective revascularizations are captured in the costs and quality-of-life penalties associated with an ACS event. History of other ASCVD includes those with prior stable coronary disease (e.g., individuals who have had an elective PCI for stable angina but have not had an ACS event) or asymptomatic ASCVD detected by imaging. This is a small proportion of individuals in the model.
15.	**Are risks of subsequent events dependent on the time from previous event?** The draft evidence report also does not discuss whether risks are dependent on time from previous event in the model structure. This point should be clarified.	Yes, see report for additional details.

	Novartis recommends the approach previously shared with ICER.	
16.	**How utilities were derived and applied to the cost-effectiveness model?** Novartis would like clarification on whether the utility weights reported in Table 5.4 of the draft evidence report represent the actual utility values applied to the populations entering each health state, or whether these utility multipliers are applied to general population utility values. Usually, the utility associated with a particular population is calculated by first modelling the age-related utility values, then applying the utility multipliers to those baseline values. The draft report states that "a recurrent ACS or stroke 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." It is unclear whether this means that backwards transitions are allowed. Since Figure 5.1.C in the draft evidence report is replicated for each non-death arm, a patient who is in the stroke cohort may have a percutaneous coronary intervention, in which case the patient would be included in the history of ACS cohort. However, this would be a backward transition, as ACS is less severe than a stroke. Clarification is needed on whether ICER would then apply a higher utility to a patient with this transition.	See report for additional details. Backward transitions are not allowed.
17.	**We could not identify the costs described in the report (e.g., Table 5.8) on the references provided.** The costs of revascularization and statins are not listed in the draft evidence report. Novartis recommends the use of Fox 2016 (inflated to 2020 US dollars) for the cost parameters mentioned in Table 5.8. Additionally, ICER should report the costs used for revascularization, or specify whether the cost of revascularization is included in the model. Novartis also recommends that ICER report the cost of statins and whether there was a breakdown of the costs between statin intensity types.	See the revised report for further details. Cost of generic statin did not stratify by statin intensity, but this is unlikely to meaningfully alter the findings.
Patient/Patient Groups		
FH Foundation		
1.	Areas we suggest ICER might add to the report: While ICER did not include primary prevention of ASCVD in the FH population in the cost effectiveness analysis for this report, we would like to recognize the value of preventing a first cardiac event in this high risk population. Patients with FH should not have to wait to develop ASCVD before they receive adequate lipid-lowering treatment.	Thank you for your comment. This will also be discussed at the public meeting's roundtable.
2.	The vast majority of individuals with FH are not diagnosed (85-90%) and diagnosis often comes decades late for those who	Thank you for this comment. We have reflected this important information

	are diagnosed (median age 47). Delayed diagnosis contributes to delayed treatment (median age of statin initiation is 39) and the missed opportunity to prevent ASCVD	throughout the report, including in the Background and Patient Perspectives section.
3.	This report does not consider patient preference when it comes to method of drug delivery as this data is not available. It is important that, taking into consideration clinical effectiveness and cost effectiveness, patients should be offered and have access to appropriate treatments that are in line with their preference. If clinical and cost effectiveness are comparable and a treatment is clinically appropriate, the choice should be informed by patient preference.	We completely agree with this statement. It will be a component of the discussion at the public meeting's roundtable.
4.	This report does not address the Homozygous FH (HoFH) population because the clinical trial data considered for this report did not include these patients. However, it is important to recognize that the HoFH population is the most severely affected, with early onset of aggressive ASCVD, often in childhood. These patients are in urgent need of significant LDL-C lowering, with untreated LDL-C levels over 400 mg/dL and often much, much higher.	We agree that patients with HoFH are severely affected with ASCVD and have a need for effective treatment options. We have updated the report to reflect the severity of disease in this population and explicitly address the fact that this population is not included in our current report.
5.	We would like to ask ICER to consider: Including all of the subpopulations (FH, statin intolerant, recent ACS) both in the comparative clinical effectiveness evaluation and in the voting questions, as the review did for the comparative cost effectiveness. Excluding the FH+ASCVD population from the voting questions is inconsistent both with the comparative cost effectiveness analysis in this report, and with ICER's 2015 review of evolocumab and alirocumab.	Thank you for your comment. We evaluated all available data on the FH and statin intolerant subpopulations in the comparative clinical effectiveness section of the report. We found no data on any of the interventions in patients with recent ACS. We have revised our voting questions to highlight subpopulations in a way that would be most relevant to inform policy.
6.	Adding more detail regarding the mechanisms of action for bempedoic acid, inclisiran, as well as evolocumab and alirocumab and more background on evolocumab and alirocumab. Where the voting questions ask about Other Benefits and Contextual Considerations, the reader will need more background.	Thank you, we have added more detail about mechanism of action of each drug in the Background section.
7.	Recognizing that the real-world utilization of ezetimibe is very low, at 4-7%, unfortunately. Thus, the use of ezetimibe along with statins is not "usual care" even though it is guideline-recommended care. As a policy question, requiring patients to be taking ezetimibe before being considered for additional lipid-lowering therapy will be a barrier to care, particularly for those patients who may need more LDL-C lowering than is expected from ezetimibe.	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).
8.	Highlighting the potential cost savings to the healthcare system of the effective implementation of the 2018 ACC/AHA Cholesterol Guideline on the use of statins. Statins are first-line therapy for all of the patients under consideration, but they are underutilized.	This is now highlighted in the report.

9.	Finally, we hope that any assumptions ICER, or anyone referencing ICER's review, make regarding the potential uptake of these and other lipid-lowering treatments refer to real-world evidence on the size of the eligible population, the uptake of existing therapies (which is often low), and in the case of FH, the low rate of diagnosis.	Thank you for this comment. Both the economic section and the budget impact section draw on population-based sources to estimate the size of the eligible population. We have also acknowledged that real-world uptake of therapies may be low.
Institute for Patient Access		
1.	**ICER's Preferred Base Case Doesn't Reflect Clinical Practice and Will Delay Patients from Reaching their Target** The base-case analysis makes assumptions that are inconsistent with actual clinical practice. The draft evidence report assumes that all of the patients were treated with ezetimibe and a maximally tolerated statin (page 46). According to the National Health and Nutrition Examination Survey, however, only 4.2% of the relevant patient population was treated in this manner. As a consequence, the base case in the draft evidence report rests on a distorted LDL baseline of 89 mg/dl, which is significantly lower than the observed LDL values of the relevant population (110 mg/dl). The distortions created by this base case could also lead to access obstacles that delay patients from receiving efficacious treatments. As a consequence, it may take longer for many patients to reach their target LDL-C goals, with some never reaching their target. These delays increase the risks for cardiovascular events and mortality. They also will lead to avoidable increases in overall health care costs.	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).
2.	**The Base-case Analysis Should Include Indirect Costs, Not Simply a "Health Care Sector Perspective"** Consistent with past reports, the draft evidence report relies on a "health care sector perspective" for the base-case analysis. The health care sector perspective ignores the indirect costs imposed by ASCVD that harm patients, diminish their quality of life and create other health risks. Since patients' welfare improves when indirect costs are reduced or, ideally, eliminated, these costs should be included in the base-case scenario. Disregarding these costs by assumption means that the base case analysis ignores $276 billion in lost productivity and other indirect costs, causing the draft evidence report to underestimate the costs of untreated LDL-C by 33% of the actual total cost.	Please see our value assessment framework for discussion on the selection of the health care sector perspective as the base case, with a modified societal perspective also always provided.
3.	**The Indirect Cost Estimates in the Modified Societal Perspective are Undervalued** The draft evidence report accounts for indirect costs in its "modified societal perspective" by valuing the number of lost work hours based on the average earnings of all employees. These assumptions result in an estimate for indirect costs of $4,810 annually. Yet productivity losses are only one part of the indirect costs of cardiovascular disease, which also include	Because the majority of CV deaths occur among older adults, the primary source of indirect costs is the morbidity that reduces people's ability to work and engage in other productive activities. As indirect costs are highly skewed (with young adults facing the majority of indirect

	premature mortality and long-term disability. As a result, the proxy used in the draft evidence report is small relative to the current estimates for the indirect costs of heart disease. To provide a sense of how significant the underestimate is, the annual indirect costs of ASCVD are estimated to reach $276 billion by 2030. Relative to the number of patients who experienced a cardiac event last year (1.06 million), the per-patient indirect costs equals $261,611. Relative to the 26.7 million patients estimated to be statin intolerant, the indirect cost burden equals $10,334 per statin intolerant patient. The gap between these figures and the $4,810 in lost productivity costs used in the draft evidence report is substantial. By defining indirect costs solely in terms of lost productivity, the report significantly undervalues the magnitude of the indirect costs that patients are enduring. For the sake of accuracy, the final evidence report should re-evaluate its assumptions regarding the indirect costs of ASCVD and incorporate a more realistic estimate of these impacts.	costs even though they represent a small number of individuals experiencing CV events), available estimates cannot be disaggregated to estimate mean costs in the group we are studying. We do acknowledge that this may be an underestimate of the indirect costs, particularly among individuals with HeFH, who are younger when they develop ASCVD and related complications compared with the general population.
4.	**The Base Model Does Not Examine Key Subgroups** The value of inclisiran and bempedoic acid is to provide an efficacious medicine to key subgroups. These subgroups include: (a) patients who have already experienced a cardiovascular event and must reach more aggressive LDL-C targets, (b) patients that do not respond well to statins, and (c) key demographic groups, such as African Americans, who bear a disproportionate burden from cardiovascular disease. The base-case analysis does not incorporate the unique costs and benefits that the therapies offer these key subgroups. Therefore, the model contains an unacceptable amount of uncertainty regarding the estimated value that inclisiran and bempedoic acid offers the very patients these medicines are intended to help.	We are doing subgroup analyses on statin intolerant patients and the report focuses on patients with previous ASCVD events. The drug companies did not include enough Blacks in their clinical trials for us to be able to evaluate them separately. Please ask drug companies to do a better job at enrolling diverse communities; we would be very willing to look at those data if they existed.
5.	**The Long-term Cost Effectiveness Model Should be Based on the Evaluated Drugs, Not Statins** The draft evidence report "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" (page 43). This is an inappropriate assumption. The purpose of the model is to discover the cost effectiveness of the medicines under review – inclisiran and bempedoic acid – for the relevant patient group, which is patients who are statin intolerant. Consequently, the relevant relationship is the reduction in LDL-C caused by inclisiran and bempedoic acid for patients who are statin intolerant. Basing the model on the relationship observed with statins introduces uncertainty into the results and undermines their reliability. And while the inclisiran relationship is used in a sensitivity analysis, this subsequent analysis does not correct the errors inherent in the base model.	Since the drugs have not yet demonstrated the ability to reduce strokes, heart attacks, or other outcomes relevant to patients, we must assume that the LDL lowering has a beneficial effect and have selected the MOST favorable assumption -- that the LDL translates into better health in the same relationship as shown with LDL reduction by statins.

National Forum for Heart Disease and Stroke Prevention		
1.	**Comparator Populations** Despite having good outcomes, being low-cost, and being included as a step through before adding a PCSK9 inhibitor (per the 2018 ACC/AHA guidelines for the management of blood cholesterol) ezetimibe use among patients with ASCVD and HeFH is low (<7% in the U.S.). Between 2007 & 2017 (except for a small increase in 2014), the number of ezetimibe prescriptions has consistently declined. In ICER's key population characteristics estimation (pg. 60) from the National Health and Nutrition Examination Survey (NHANES), only 4.2% of people with prior ASCVD, and an LDL-C level >70 mg/dL on statin therapy were taking ezetimibe. The model assumed that all patients would take ezetimibe, which is not a real-world scenario. Furthermore, this runs counter to the FDA-approved labeling for Nexletol/Nexlizet (both of which are approved as adjuncts to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C), and do not include the step through of ezetimibe.	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).
2.	Using consistent base cases would enable users of ICER reviews to make meaningful comparisons across therapies. For example, in its 2015 review and 2019 update, "PCSK9 Inhibitors for Treatment of High Cholesterol," ICER used maximally dosed statins as the base case. Using ezetimibe as another layer of therapy in the bempedoic acid/inclisiran base case makes this assessment incongruous with the one on PCSK9i's.	Our model needs to be responsive to changes in guidelines. The ACC/AHA lipid-lowering guidelines recommend that ezetimibe be tried first before escalating to injectables (PCSK9 inhibitors).
3.	Many patients, particularly those who require more than 20% LDL-C reduction, will fail to reach LDL-C targets on ezetimibe alone. For these patients, initiating a more potent LDL-C lowering agent than ezetimibe after statin therapy has been maximized may be preferred. Moreover, inertia and the time it takes to get patients' therapy properly titrated will mean that high-risk patients will be at prolonged risk. There are large numbers of FH and/or ASCVD patients with uncontrolled LDL-C. Inclisiran and/or bempedoic acid may provide an additional line of therapy for people who are not currently adequately treated.	See above. We do not make a recommendation for step therapy in all cases but do believe that the value-based price of high-cost novel therapies should be calculated on the reasonable assumption that low-cost effective therapies have previously been tried.
4.	Base Case Results The report states that, "…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.)	ICER agrees of course that the aim of health care is to create improvements in health and survival, while also recognizing that health care interventions have resource costs that must be weighed against the opportunity cost of not using those resources for other health care interventions (or other spending).

	(pg. 60). We urge ICER to note that improvements in health and survival are the aims of health care. As presently stated, it suggests the offset of savings due to additional years of life is a negative. This is particularly important for individuals who have premature coronary artery disease and HeFH with no further events because of effective LDL-C lowering on combination therapy.	We have also revised this sentence to clarify that the offset from increased total health care spending is primarily due to increased costs of lipid-lowering therapy.
5.	Baseline Population Characteristics o The baseline LDL-C level among patients on maximally tolerated statin and ezetimibe used in the model is 88.8±1.2 mg/dL(pg. 46) is significantly lower than baseline LDL-C levels in Phase III trials. The goal for cholesterol treatment is significant, absolute lowering of LDL-C levels. Therefore, health impact and cost-effectiveness are minimized if using the lower number.	Our base case assumes LDL-C levels estimated from NHANES. In sensitivity analyses, we explore higher and lower baseline LDL-C levels.
6.	Sensitivity Analysis Results Major Adverse Cardiovascular Events (MACE) rates observed in real-world studies are substantially higher than those reported in randomized clinical trials, suggesting that the secondary MACE burden and potential benefits of effective CVD management in ASCVD patients may be underestimated if real-world data are not taken into consideration. We suggest that ICER review this real-world data.	Base-case MACE rates in the model are higher than observed in contemporary randomized trials, reflecting the high risk in real-world populations.
7.	Statin Intolerance Statin use among patients with ASCVD remains suboptimal because of various patient- and clinician-related factors. Additional treatments, such as inclisiran and bempedoic acid, could help increase access and adherence to treatments in patients who are otherwise at risk for not taking and/or adhering to medications and therefore, at higher risk for adverse events.	Thank you for your comment.
8.	Cost-effectiveness Some payers currently have bempedoic acid on Tier 2 formularies without restrictions. With an estimated cost of approximately $10/day, they deem it cost-effective. In its report, ICER has stated that bempedoic acid at current prices is unlikely to achieve the commonly cited cost-effectiveness threshold of $150K/QALY gained or the $150K/evLYG thresholds. There is concern that some payers who currently have bempedoic acid on formulary as a cost-effective option may read ICER's report and make incorrect assumptions. We advocate for finding middle ground in the language that is used, as bempedoic acid is an inexpensive therapy already covered by some payers.	Translating the evidence on clinical effectiveness and cost effectiveness into clinical and formulary considerations will be discussed during the public meeting.
9.	Voting Questions The economic analysis looks at four populations. We suggest the same approach be applied for clinical effectiveness and for the voting questions. Adults with ASCVD	Thank you for your comment. We evaluated all available data on the FH and statin intolerant subpopulations in the comparative clinical effectiveness section of the report. We found no data on any of the

	Adults with ASCVD and HeFH Adults with ASCVD and statin intolerance Adults with ASCVD and recent ACS	interventions in patients with recent ACS. We have revised our voting questions in a way that would be most relevant to inform policy.
Partnership to Advance Cardiovascular Health		
1.	**ICER's Preferred Base Case Is Out Of Step with Clinical Practice and Will Lead to a Delay in "Getting to Goal" for Patients** ICER insists on layering ezetimibe on top of a maximally tolerated statin to serve as the base case for its analysis. This is not reflective of real world evidence or clinical practice. Key population characteristics 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 - and used by ICER to provide nationally representative estimates of risk factors and disease prevalence - acknowledges that only 4.2% of these patients were treated with ezetimibe. Yet for its base case, ICER assumes 100% of patients will be treated with ezetimibe on top of a maximally tolerated statin - an extraordinary disconnect. This results in a distorted baseline LDL of 89 mg/dl in ICERs model which is much lower than Phase III trials or in the real world, which is closer to 110 mg / dl. Using this inaccurate base case – with the presumption that fail first requirements from insurers will follow - will undoubtedly lead to a delay in "getting to goal" for patients, potentially leading to additional cardiovascular events and even deaths while patients are forced to "step" through ezetimibe. It should also be noted that during the 2015 review of high cholesterol therapies (PCSK9i), ICER used maximally dosed statins only as the base case. It is troubling that ICER is now adding another layer of therapy onto the base case for this particular review particularly when that changes the outcome of its assessment here, particularly where the result can be so devastating for patients.	See above. We do not make a recommendation for step therapy in all cases but do believe that the value-based price of high-cost novel therapies should be calculated on the reasonable assumption that low-cost effective therapies have previously been tried.
2.	In fact, ICER's 2015 review had serious negative consequences for patients. Insurance companies, using ICER's adverse report, imposed life-threatening access barriers, resulting in only half of patients who were prescribed a PCSK9i receiving approval in the first year of availability. About one-third of those patients who received approval abandoned their prescription due to unaffordable copays. Patients who are prescribed additional lipid lowering therapies are either intolerant to maximally dosed statins or are high-risk patients with a family history of cardiovascular disease (CVD), already have CVD, or are diagnosed with familial hypercholesterolemia who require further LDL-lowering on top of baseline therapy. Lack of access to such prescribed medications has correlated with an increase in cardiovascular events and death, as demonstrated by data published in Circulation: Cardiovascular Quality and Outcomes.	We would be interested in receiving specific information documenting the use of ICER's report to support life-threatening access barriers. Our understanding is that our work was used to inform negotiations around fair pricing, so we would be interested in seeing evidence of use of our work to support specific barriers to access.

3.	**ICER's Use of A Low MACE Rate in Its Model Unfairly Reduces Cost-Effectiveness and Does Not Reflect Real-World Experience.** Major Adverse Cardiovascular Event (MACE) rates observed in real-world studies are substantially higher than those reported in randomized controlled trials,4 suggesting that the secondary MACE burden and potential benefits of effective CVD management in ASCVD patients may be underestimated by ICER if real-world data are not taken into consideration. In the United States, more than 95 million Americans have high cholesterol. A high proportion of those patients are severely undermanaged. The PINNACLE registry, for example, includes a cohort of 1.9 million patients with ASCVD on a statin therapy. 84.5% of those individuals did not meet LDL-C goals of less than 70 mg/dL, which is a target LDL goal for patients with ASCVD recommended in the current American Heart Association/American College of Cardiology 2019 Lipid Lowering Guidelines.	Our MACE rate is estimated from real-world data and is higher than that observed in contemporary clinical trials.
4.	**ICER's Reliance on Clinical Trials Data Over Real World Clinical Experience Will Result in Lack of Access to Treatment Options for Communities of Color** We hope ICER will consider performing an analysis of key demographic groups, such as Black Americans who bear a disproportionate burden of cardiovascular disease and are underserved in the healthcare system. As ICER is well aware, they also ultimately end up achieving less access to therapy overall from payers. It is troubling then, that ICER's core analysis relies substantially on clinical trials data without more substantive balancing with clinical practice and experience. It is well established that clinical trials as a whole are lacking in diversity - race as well as age and socio-economic status.7 ICER's persistent reliance upon this data to serve as the inputs for its core analysis contributes to a disproportionate impact on communities of color which are not well represented in clinical trials but receive less care and access to treatment overall. This is a schism that is a fundamental flaw in ICER's modeling and that hopefully will be addressed or weighted in some way in the Final Report.	Black Americans do face a health system riddled with racism and ultimately receive inferior care in many ways. We do not believe it advances the cause of reducing these inequities to abandon a "persistent reliance" on clinical trial data. We certainly believe in complementing that data whenever possible with other sources, but rarely would "experience" provide a trustworthy guide to clinical practice. We also hope you would join us in hoping that drug makers accept their responsibility to improve the diversity of clinical trial participants so that we can get the kind of data we need to distinguish differential effects of treatment in different communities. Lastly, we do not believe that the interests of underserved communities are advanced by saying that new agents that have not yet demonstrated clinical benefits should receive a higher price just because care of these patients has been substandard. All options should be available, yes, but why give special preference to new, and perhaps riskier treatments over efforts to maximize the use of treatment options that are known to be safe, effective, and less expensive?
Partnership to Improve Patient Care		
1.	**The model is not reflective of the indicated population** The risk of major adverse cardiovascular events (MACE) is much higher in African Americans, and African Americans	We are doing subgroup analyses on statin intolerant patients and the report focuses on patients with previous ASCVD events.

	make up a disproportionate share of those who have atherosclerotic cardiovascular disease (ASCVD). Despite this reality, the randomized controlled trials (RCTs) used to provide estimates of effectiveness in the ICER model were predominately populated by white individuals. For example, in CLEAR Wisdom 94% of recruited patients were white, ORION 11 was 98% white, and CLEAR Harmony was 96% white. The RCT population also does not reflect the age of actual patients. The median age of the patients in the referenced trials was 64 years, with fewer than 8% over 70 years. In reality, we know that almost half of people on lipid-lowering medication are over 70. While ICER cannot control the recruitment of people into trials, it can use the modeling process to effectively translate evidence from RCT populations into real-world populations and evaluate them in a way that provides valuable insights into the relative value of these drugs across communities, rather than over-relying on an "average" American. It should also make every effort to highlight the importance of running analyses of key subgroups of interest, such as underrepresented communities and communities that have a disproportionately high burden from the disease being addressed. Wider sets of subgroup analyses are justified as the results from RCTs show considerable heterogeneity of effect The ICER model uses a composite estimate of relative effectiveness but there was significant heterogeneity between trials (heterogeneity among these studies was high and statistically significant ($I2=69\%$, $p<0.01$). 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%). Even when broken down into two groups of (A) patients with ASCVD/HEFH and (B) patients with statin intolerance, the latter group estimate had an I2 statistic of 75%. In fact, the heterogeneity was higher than in the overall sample. This is usually an indication that subgroups should be broken into even more granular groupings to get reliable estimates of effectiveness. Therefore, we would highly encourage ICER to run additional subgroup analyses, as further investigation may show the drug to be more or less effective in different populations as defined by race, age, or baseline risk. This is highly valuable information for patients and providers in making treatment decisions.	The clinical trials did not include enough African Americans in their clinical trials for us to be able to evaluate them separately. We hope stakeholders will urge drug companies to better enroll diverse communities in trials, as we would be very interested in those data if they existed.
2.	**ICER makes some incorrect assumptions about ACSVD patients** The LDL-C levels used are lower than one would see in a real-world population. ICER's assessment uses a starting LDL-C of 88 mg/dL. This is very low for someone who requires lipid-	Our base case assumes LDL-C levels estimated from NHANES. In sensitivity analyses, we explore higher and lower baseline LDL-C levels.

	lowering medication. Someone with high cholesterol is typically defined as having an LDL-C level above 120 mg/dL.	
3.	**Voting questions should appropriately align with the assessment** The majority of the voting questions regarding ASCVD are general rather than being tailored towards the four subpopulations defined by ICER in this assessment. ICER's findings varied significantly across the four populations. In order to accurately depict value to each of these subpopulations, we would strongly recommend ICER adjust the questions and probe voting panel members on issues specific to each of the four subpopulations.	We have revised the voting questions to include the subpopulations with specific evidence and highlight what will be most relevant to inform policy decision.
4.	**ICER conflates the DALY and QALY, which are not compatible, in this model** The sources of health utilities for the model are not derived from patient reported outcomes considered to be standard. The model uses Disability-Adjusted Life Year (DALY) weights that have not been generated by patients at all. Although the QALY and the DALY look very similar, they are in fact different. One measures health states and one measures disease states. The DALY is largely seen as a measure of disease burden – most commonly used in developing countries, whereas the QALY is a measure of health gain. The two metrics are not interchangeable, and as such alternative interventions measured using a QALY will not be comparable to estimates developed using the DALY.	Although there are key differences in how the weights are derived for DALYs and QALYs, a simplifying assumption that q = 1-d (where q is the weight for QALYs and d is the weight for DALYs) is reasonable provided the DALY weights are not age-adjusted. Differences in how these weights are elicited are real, but differences among the techniques used to elicit QoL weights can also be problematic. For instance, one study showed that QoL went *__up__* after an MI, primarily because the QoL declined so much right before the MI that any interventions (e.g., PCI) made the QoL better. While possible this is unlikely, and the authors themselves cast doubt on the results.
5.	**The use of DALY weights, rather than HSUVs, significantly undervalues the burden of disease states and CV events** Putting aside the point that the source for health state utility values (HSUV) used to calculate QALYs are not in fact health state values calculated for the QALY, it is also worth noting the paucity of the actual numbers being used. The DALY weights used in the model, such as History of Angina, and History of ACS are estimated at between 0.88-0.96 (Table 5.4). These are "utility values" that are higher than most "healthy" states in most cost-per-QALY models. For context, a recent review of HSUVs (using the more traditional EuroQol 5-dimension method) shows that HSUVs for history of angina range from 0.615-0.775, HSUVs for history of stroke range from 0.626-0.668, and HSUVs for history of heart attack range from 0.721-0.742.	The data source most widely used for QoL weights in the US, the MEPS analysis by Sullivan (Med Decision Making 2006), is a good source of QoL data for chronic states but was not designed to estimate QoL penalties related to acute events. The discrepancy between the higher weights used in our paper and lower weights based on EQ-5D estimates is, in part, philosophical. Do we only account for QoL changes related to CVD (which is what we do), or do we also include QoL decrements from other comorbidities present in individuals with established ASCVD? For instance, if folks who have a stroke also have DM, CKD, and hypertensive cardiomyopathy, do we account for the QoL decrements from these comorbidities in the base case? We chose not to because this would undervalue ASCVD prevention but acknowledge the latter would also be reasonable in some settings. This discrepancy is not an error but a framework for thinking about QoL

		decrements in ASCVD. Sullivan and Ghushchyan themselves recommended using the regression coefficients rather than unadjusted median QoL estimate from their dataset. Acknowledging these data limitations, we used the GBD weights for this analysis to facilitate comparisons with the prior body of work on PCSK9i. We now also use another source of QoL estimates (MEPS) in sensitivity analyses, as well as discuss the limitations of using the MEPS data for this purpose. In the end, using more severe QoL penalties for CV states undervalues interventions used for secondary prevention in terms of dollars per QALY and causes the cost per QALY to increase considerably.
6.	**ICER includes lifetime health care costs unrelated to ASCVD** ICER's model includes all lifetime medical costs, including those unrelated to ASCVD. Modeling of medical costs unrelated to the disease in question is uncommon. Beyond the inconsistency in modeling of these costs when ICER has not typically included them in its past models (with the exception of its COVID-19 model), the logic and implementation of ICER's inclusion of these costs raises questions. The incorporation of such costs introduces a questionable incentive structure for the analysis. Even if a manufacturer were to offer a life-saving therapy for free, inclusion of these costs would raise the question of whether it is worth providing life-saving treatment to a patient given that they will go on to incur medical costs unrelated to the clinical decision in question. This would mean only treating patients who never get sick again in their lifetime would have value, a decision process that is not desired in any healthcare system. Also, while ICER includes these unrelated healthcare costs for all surviving patients, these patients' contributions to the healthcare system are excluded. For example, surviving patients may incur medical costs, but they also may pay premiums, deductibles, and co-pays to their insurance payer, which then pays for the medical costs. Similarly, surviving patients may pay or have paid taxes that fund their insurance (e.g., Medicare and Medicaid).	It is not uncommon for cost-effectiveness analyses to include lifetime health care costs, including unrelated medical costs, as has been recommended by the 2nd Panel on Cost-Effectiveness in Health and Medicine. (Note that these costs are only relevant in situations where treatment leads to differential survival, as otherwise these costs would be the same for the treatment and comparator arms.) This does not "mean only treating patients who never get sick again in their lifetime would have value" but does recognize that these are real costs that would be expected in the future.
Patients Rising Now		
1.	The draft report notes that women with familial hypercholesterolemia are less likely to reach LDL-C treatment goals. This is completely consistent with the well-known sex differences in the symptoms and presentation of heart disease, its diagnosis, and for some treatments. There is also a tendency to think of heart disease as a "man's disease," creating a systemic – if unintentional – systemic bias against female heart disease patients in the U.S. health care system.	We presented the information on the proportion of men in Ballantyne 2020 to be consistent with other trials in our report. We have updated our report to present the proportion of women enrolled in all included trials.

	Such bias is also evident in ICER's draft report where it summarizes the Ballantyne 2020 study by characterizing the participants as "50% were male." However, the actual published report clearly states that "50.5% of patients were women," and the word "male" appears nowhere in the publication. It is improper and misleading for ICER to ignore the known real-world sex differences in heart disease. We strongly suggest that ICER evaluate its own perspectives and biases, and address this issue in the next version of the report and in ICER's committee discussions.	
2.	Diet, exercise, and smoking cessation – as well as treating other conditions such as diabetes mellitus – contribute to prevention of CVD outcomes such as myocardial infarction, heart failure, peripheral vascular disease, amputations, sexual dysfunction secondary to vascular insufficiency, and stroke. The draft report lumps those factors together into the catch-all "risk factor modification" without exploring the importance of addressing any of them individually or collectively via comprehensive patient-centered medical care (outside of biopharmaceutical treatments), or the importance of doing so for improving the lives and clinical outcomes for people with high cholesterol and CVD.	We agree that lifestyle modifications such as diet, exercise, and smoking cessation and treatment of risk medical conditions that heighten one's risk of CVD are important cornerstones of treatment for patients with ASCVD and FH. Although our report is focused on evaluating pharmaceutical treatments for ASCVD and FH, we have inserted some additional language acknowledging the importance of these factors in the report.
3.	The draft report contains extremely limited information about quality of life (QoL). This may be due to the limited number of clinical trials ICER relied upon as input for this draft report, which themselves contained limited assessment of QoL. Regardless, we strongly feel that even if specific metrics of QoL were not included in those studies, ICER should note the lack of those metrics, discuss other sources of information about the QoL implications of CVD and various treatment options (including diet and exercise), and propose how to fill that data void going forward. Similarly, we noted that in the description of the Midwest CEPAC's role that QoL is not part of their mandate from ICER: "The Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the **quality and value of health care"** (emphasis added). We see it as unethical for ICER's committees to omit QoL factors and perspectives from their stated core mandate and urge ICER to update the committee's focus and responsibilities. We are particularly concerned about this lack of attention to QoL because toward the end of the discussion of the uncertainties about the model created for the draft report, it is stated that the model "does not assume any permanent quality-of-life reduction from recurrent [Major Adverse Cardiovascular Event] of the same type as prior events."	We found no data on health-related quality of life on any of the drugs of interest. We have highlighted this data gap in our revised report.
4.	The draft report states: "Access to new therapies was of particular concern to patients, given the often-cumbersome insurance prior authorization process for newer cholesterol-	We heard from multiple patient groups that patients often face a host of barriers when trying to access new therapies, and we

	lowering drugs like PCSK9-inhibitors and has resulted in delayed or denial of access to therapy for some patients." And further, "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." Rather than just repeat what patients and clinicians have said, ICER should discuss how its own reviews contribute to this challenge, as they are used by insurance companies to justify access barriers that prevent patients from receiving treatments recommended by their clinicians.	incorporated this feedback in the "Patient Perspectives" section, which is meant to describe what patients and patient groups have told us. We would be interested in receiving specific information documenting the use of ICER's report to support life-threatening access barriers. Our understanding is that our work was used to inform negotiations around fair pricing, so we would be interested in seeing evidence of use of our work to support specific barriers to access.
5.	Supporting the previous point is the evidence cited in other ICER reports about PCSK9 inhibitors about access and affordability problems for patients. Specifically, in 2017, ICER found that only 17% of prescriptions for PCSK9 inhibitor medicines were being initially approved (with another 26% approved after appeal), and 25-40% of patients did not fill their prescriptions – presumably because of insurance company cost-sharing requirements.	It is not insurance companies that determine cost-sharing; it is people's employers. Employers determine the benefit design, insurers implement it.
6.	The draft report contains an extremely complicated modeling scenario using an almost countless number of assumptions – many of which are based upon divergent sources that may or not be applicable for the populations and treatments that are the subject of the draft review.	Cost-effectiveness models have been used for decades by researchers, international health technology assessment agencies, and pharmaceutical manufacturers. The results of these models may be calibrated with other data and analyses and replicated by other researchers.
7.	Beyond that complexity and extreme uncertainty based upon various assumptions, we note that the projections fail to recognize the possibility of future developments in the treatments for high cholesterol. Specifically, the draft report assumes the FDA will approve inclisiran, but there is no mention of other potential treatments that may be undergoing advanced clinical testing and could also be approved for use in the next few years. Additional treatment availability would dramatically affect the budget impact assessment that ICER has already split between inclisiran and the bempedoic acid medicines. We are highly confident that ICER could evaluate that pipeline based upon information from ClinicalTrials.gov, public disclosures from companies, analysts' reports, and projected PDUFA dates and windows. Clearly no modeling of this type would be perfect, but we recognize that ICER's standard practice is to do reports involving limited data, including about compounds undergoing FDA review – some of which later do not get approval as expected. Given that ICER regularly bases its models and projections on yet-to-happen events, this would seem to be completely within ICER's capabilities, and we see no reason	ICER's reports typically use long-term models to inform assessments of the value of individual drugs that are potentially nearing FDA approval. We note that the availability of additional treatments in the future would not only alter the split between treatments but also potentially reduce the amount of the budget available to spend on each treatment.

	why ICER should not model – and project – as accurate a picture of the future as possible.	
8.	Similarly, for the long-term cost-effectiveness modeling, we strongly recommend that ICER include cost calculations based upon the expected competition from generic and biosimilar versions of the two compounds reviewed in the draft report. While it could be argued that it is uncertain as to when that competition will occur, rather than viewing the future world as essentially static, ICER should adopt realistic perspectives factoring in those significant cost reductions. Consistent with that real-world understanding, we note that ICER presented updated reviews for the PCSK9 inhibitor medicines in 2017 and 2019, which included reductions in costs based upon lower net and list prices. Although we are puzzled that ICER did not use net prices in both cases, even if that net price had to be estimated rather than based upon specific data sources – particularly since Medicaid, Medicare Part D and the Veterans Administration receive specific minimum discounts off of the list prices. Therefore, using list price alone is knowingly presenting a fictional scenario.	ICER's recent assessments consistently use estimated net prices. We note that current net prices are difficult to determine, as they are generally considered to be proprietary information in the US market. The projection of future list and net prices would be even more difficult, as these often increase over time, especially before loss of exclusivity. In addition, the timing of loss of exclusivity is also uncertain, as manufacturers often take actions to delay the loss of exclusivity or entry of biosimilars.
9.	Related to the utility of the budget impact projections, ICER states that those projections are to potentially "**trigger policy actions to manage access and affordability**" (emphasis added)." Again, this assertion assumes a monolithic, uniform health care payer system in the United States, rather than the reality that there are a number of different – and sometimes overlapping – payers and care providers, such as Medicare, the VA and HMOs, each of whom has different populations, legal and regulatory obligations, and abilities, and hence different abilities to enact "policy actions" that would restrict patients' access to treatments, or influence the organization's or individual patient costs.	ICER's analyses are intended to provide a signal to health care payers of the potential for large budget impact, but not to inform budget impact analyses for any particular payer. We understand that individual payers will want to use budget impact models to customize analyses for their own patient population, treatment mix, and costs.
10.	Uncertainties and Assumptions The draft report summarizes and attempts to analyze the clinical trial data for two experimental treatments. While the draft report contains a little over one page about "Uncertainties and Controversies," other parts of the draft report are littered with mentions of the various assumptions that are made in taking data from a variety of sources and using it to numerate aspects of potential real-world situations. Such cherry-picking of data from controlled trials and scientific studies leads to serious questions about the applicability of such quantitative outputs to real world situations and care decisions. The draft report touches upon this absurdity with this statement: "Our goal was to examine the cost-effectiveness of these novel lipid-lowering therapies in real world populations, assuming that the efficacy observed in	Along with qualitative discussion of major uncertainties and controversies, the report includes multiple sensitivity and scenario analyses measuring the impact of variation in inputs or the assumptions used in the cost-effectiveness analyses.

	clinical trials would be replicated and sustained in clinical practice."	
11.	One particular assumption in the draft report that we want to highlight is: "[W]e assumed that the age-specific non-CV mortality in this cohort was similar to the general US population." While the draft report cites a CDC dataset, it is a broad, and dramatic assumption considering that people with CVD may have risk factors (e.g., diet, exercise, and smoking) that would put them at increased risk for other conditions, such as cancer. ICER should explain its justification for this assumption and the CDC's WONDER database is used.	It is plausible that patients with CV disease are at increased risk of non-CV death. We made the conservative assumption that non-CV death was similar to the general population in the base case and varied it in sensitivity analyses.
12.	The data report for Ballantyne 2020 in the text is incorrect when it states that "63% had HeFH" and in Table 4.1 where it lists "ASCVD: 62.5%" The correct citation of the data from the publication is "62.5% of patients had ASCVD and/or HeFH."	Thank you. We have corrected this error in the revised report.
13.	In the discussion of the methodology for the Potential Budget Impact we note that these calculations are intended to be "aligned with the overall growth in the US economy." Given that the US and global economies have been extremely hard hit by the COVID-19 pandemic, significantly challenging companies projecting and reporting their financials as required by the Securities and Exchange Commission – ICER should explain how it has developed its insights for the "growth in the US economy," particularly if it is relying on projections that predate the COVID-19 pandemic.	As pointed out, it is challenging to project financial trends in the current environment, including growth in GDP. ICER will update its potential budget impact threshold as new projections become available in 2021.
14.	The draft report states that the Midwest CEPAC is "an independent committee of medical evidence experts from across California," however, according to ICER's website with information about Midwest CEPAC, none of the members are from California. Similarly, the list of acronyms lists "CTAF California Technology Assessment Forum," which we find referenced nowhere else in the draft report.	Thank you. We have corrected this sentence in the report.
15.	In Section 4 of the draft report ("Comparative Clinical Effectiveness"), the name implies that the two compounds that are the focus of the draft report are actually compared to one another directly. However, as the draft report notes, no such comparisons were made, and the review was conducted using a meta-analysis; thus the results are associative rather than directly comparative. Therefore, we strongly suggest that the title for this section be "Associated Relative Clinical Effectiveness" or "Indirect Clinical Effectiveness Associations.	As described in our research protocol and in our report, our goal was to compare each of the interventions in conjunction with maximally tolerated background lipid-lowering therapy to ongoing maximally tolerated lipid-lowering therapy (i.e., intervention vs. placebo arms of clinical trials). We clearly stated in our report that given the lack of data on the effects of the interventions on key clinical outcomes, we did not attempt to compare the interventions to each other.
16.	The draft report uses both "quality of life" and "quality-of-life." ICER should pick one and be consistent. The draft report uses both "healthcare" and "health care." We've previously expressed a preference for "health care," but ICER should pick one and use it consistently	We have corrected this in the report.

Clinical Experts		
Dr. Seth Baum		
1.	I am most concerned about some of your assumptions as they will clearly influence your findings. In your model, 100% of patients are on both a high intensity statin and ezetimibe. Most real-world studies show quite a different picture. A 2019 American Heart Association poster by Nehar Desai, MD showed that only 44% of patients one year out from an MI were taking high intensity statins. We must remember that this is our highest risk cohort, patients within a year of an Acute Coronary Syndrome. If these individuals are not using high intensity statins, imagine how the rest of the secondary prevention population is doing. Further, assuming that 100% of very high risk patients are taking ezetimibe appears almost to be a typographical error. In FOURIER, a 27,564 patient CVOT of very high risk patients, only 5.2% were taking ezetimibe! We know that our best-managed patients are in trials such as this. How then can we posit that 100% of real-world patients are treated so much better? Making matters worse, in the real-world payers paid only about 65% of claims for ezetimibe in patients with FH and LDL-C > 190 mg/dL on maximally tolerated statins. Getting payers to approve and then pay for such medications is a real issue that must be considered when you build your model.	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).
2.	Further, regarding the assumption that real world very high-risk patients have an average LDL-C 88.8 mg/dL we only need look again at FOURIER to see this cannot be so. The superbly treated patients in this study had a baseline median LDL-C of 92 mg/dL. Finally, there is ample evidence that your assumptions that MACE is only 5.06/100 patient years and statin intolerance prevalence is only 10%, are also gross underestimates among real world patients.	Our MACE rate is estimated from real-world data and is higher than that observed in contemporary clinical trials.
Dr. Dharmesh Patel		
1.	**ICER's Preferred Base Case Is Out Of Step with Clinical Practice and Will Lead to a Delay in "Getting to Goal" for Patients** ICER insists on layering ezetimibe on top of a maximally tolerated statin to serve as the base case for its analysis. This is not reflective of real world evidence or clinical practice. Key population characteristics 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 and used by ICER to provide nationally representative estimates of risk factors and disease prevalence, acknowledges that only 4.2% of these patients were treated with ezetimibe. Yet for its base case, ICER assumes 100% of patients will be treated with ezetimibe on top of a maximally tolerated statin - an extraordinary disconnect. This results in a distorted baseline LDL of 89 mg/dl in ICERs model which is much lower than Phase III trials or in	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).

	the real world, which is closer to 110 mg / dl. Using this distorted base case – with the presumption that fail first requirements from insurers will follow - will undoubtedly lead to a delay in "getting to goal" for patients, potentially leading to additional cardiovascular events and even deaths while patients are forced to "step" through ezetimibe. It should be noted that during their 2015 review of high cholesterol therapies (PCSK9i), ICER used maximally dosed statins only as the base case. It is troubling that ICER is now adding another layer of therapy onto the base case for this particular review particularly when that changes the outcome of its assessment here.	
2.	Most importantly, the management of high cholesterol to prevent cardiovascular disease is not a one-size-fits-all approach. Many of my patients require individualized care to get them to goal LDL levels, according to current lipid lowering guidelines set forth by the American College of Cardiology and American Heart Association. Patients who cannot tolerant statins and are considered high risk either with ASCVD, FH, or those who have already experienced a cardiovascular event require additional LDL-lowering therapies for optimal, patient-centric management.	We appreciate that treatment of ASCVD should be individualized and patient centered. We have tried to reflect this sentiment throughout our report.
3.	**ICER's Use of A Low MACE Rate in Its Model Unfairly Reduces Cost-Effectiveness and Does Not Reflect Real-World Experience.** Major Adverse Cardiovascular Event (MACE) rates observed in real-world studies are substantially higher than those reported in randomized controlled trials, suggesting that the secondary MACE burden and potential benefits of effective CVD management in ASCVD patients may be underestimated by ICER if real-world data are not taken into consideration.	Our MACE rate is estimated from real-world data and is higher than that observed in contemporary clinical trials.
4.	**ICER's Reliance on Clinical Trials Data Over Real World Clinical Experience Will Result in Lack of Access to Treatment Options for Communities of Color** We hope ICER will consider performing an analysis of key demographic groups, such as Black Americans who bear a disproportionate burden of cardiovascular disease and are underserved in the healthcare system. As ICER is well aware, they also ultimately end up achieving less access to therapy overall from payers. It is well-established that clinical trials as a whole are lacking in diversity - race as well as age and socio-economic status. ICER's persistently focused reliance upon this data set to serve as the inputs for its model contributes to a disproportionate impact on communities of color which are not well represented in clinical trials but receive less care and access to treatment overall. This is a schism that is a fundamental flaw	Black Americans do face a health system riddled with racism and ultimately receive inferior care in many ways. We do not believe it advances the cause of reducing these inequities to abandon a "persistently focused reliance" on clinical trial data. We certainly believe in complementing that data whenever possible with other sources, but rarely would "experience" provide a trustworthy guide to clinical practice. We also hope you would join us in hoping that drug makers accept their responsibility to improve the diversity of clinical trial participants so that we can get the kind of data we need to distinguish differential effects of treatment in different communities. Lastly, we do not believe that the interests of underserved communities

	in ICER's modeling and that hopefully will be addressed or weighted in some way in the Final Report.	are advanced by saying that new agents that have not yet demonstrated clinical benefits should receive a higher price just because care of these patients has been substandard. All options should be available, yes, but why give special preference to new, and perhaps riskier treatments over efforts to maximize the use of treatment options that are known to be safe, effective, and less expensive?
Clinical Societies		
American Society for Preventative Cardiology		
1.	The ASPC membership is deeply committed to the prevention of cardiovascular morbidity and mortality in both the primary and secondary prevention setting. Although a randomized, prospective clinical trial with bempedoic acid is not yet completed (though fully enrolled), we believe it should receive a favorable review. Given the difficulties posed by pharmacogenomics, many patients are intolerant to established LDL-lowering drugs such as statins, bile acid binding resins, and even ezetimibe and the PCSK9 monoclonal antibodies. Any safe addition to our tool box is a welcome development. Already many of us can say we have patients who only tolerate bempedoic acid or the combination of bempedoic acid and ezetimibe because of intolerance to other drugs. Moreover, these drugs can also be used as adjuvant therapies over and above other lipid lowering therapies such as statins and PCSK9 monoclonal antibodies as deemed appropriate by managing physicians. Being overly restrictive on appropriate use in high risk populations poses hazard as: (1) a clinical useful, efficacious drug will be unnecessarily withheld from the very patients most in need of it; (2) it will be too easy for insurance benefit providers to say "no" in a blanket way; and (3) patients will be left inadequately treated with risk sub optimally managed. In the end, patients will lose. The quality of care will suffer.	Thank you for your comment**.**
Association of Black Cardiologists		
1.	**LAYERING OF EZETIMIBE ON TOP OF A MAXIMALLY TOLERATED STATIN AS THE BASE CASE FOR THE ICER ANALYSIS** As stated in the draft report, the population of focus for the economic evaluation of bempedoic acid and inclisiran is patients with established ASCVD who need additional lipid lowering despite maximally tolerated lipid-lowering therapy (ezetimibe and maximally tolerated statins). Layering of ezetimibe on top of a maximally tolerated statin as the base case for ICER's analysis is not reflective of real-world evidence or clinical practice. As a starting point, adherence to therapy, in this case statins, is higher in patients enrolled in clinical trials and, consequently, the benefit of bempedoic acid may be underestimated compared to usual clinical practice.	We acknowledge that ezetimibe is not used in the majority of patients, but we heard from clinicians that they would likely consider ezetimibe as the first treatment that would be used. We aren't suggesting in the model that step therapy through ezetimibe would be the only appropriate clinical strategy, but do believe that the value-based price of bempedoic acid should not include the lipid-lowering benefit of ezetimibe (which is now generic).

	Key population characteristics estimated from the National Health and Nutrition Examination Survey (US adults age 35 years or older, with prior ASCVD, and an LDL-C level ≥70mg/dL on statin therapy) and used by ICER to provide nationally representative estimates of risk factors and disease prevalence, acknowledge that only 4.2 percent of these patients were treated with ezetimibe. Yet, for its base case, ICER assumes 100 percent of patients will be treated with ezetimibe on top of a maximally tolerated statin. The result is a distorted baseline LDL of 89 mg/dl in ICER's model, which may underestimate the effectiveness of bempedoic acid. While current guidelines suggest addition of ezetimibe when LDL remains above threshold levels, many patients never receive this therapy or patients need more than an additional 15 percent LDL reduction that ezetimibe typically offers. Based on our real-world experience, ezetimibe is denied by payers unless there are documented attempts at achieving maximally tolerated statin use. Yet, maximally tolerated statin use in African Americans is met with many barriers.	
2.	African American individuals are less likely to receive guideline-recommended statin therapy. The reasons for this disparity are multi-faceted but can be explained by a combination of demographics, clinical characteristics, socioeconomic status, patient beliefs, and clinician factors. Anecdotally, statin use is lower in Blacks for multiple reasons beyond socioeconomic status, including mistrust of the health care system, less ability to take time from work to attend doctor visits, undesirable motivation to add medications on top of multiple other medications used for comorbidities, and lack of perceived benefit/education. Even the specialty and location of the treating physician can have an effect on use and statin compliance, as well as use of ezetimibe. Many providers may miss the fact that only two statins, atorvastatin and rosuvastatin, are considered high potency for high-risk cardiovascular disease. Oftentimes, patients are prescribed a less effective statin therapy, which is never modified, and ezetimibe is not added out of belief that some statin is better than no statin. As a result, the urgency for more aggressive LDL reduction is attenuated. The biggest barriers of adding ezetimibe to a maximally tolerated statin dose also include: seeking a non-pharmacologic treatment around diet modification and exercise which is not as widely accepted in Black communities; acceptance that the benefit of statin therapy may be the best option a patient can achieve; misbelief that Blacks are more noncompliant; limited patient-physician interactions; and ineffective patient-provider shared decision making. It is easy to then understand why ezetimibe would be lower on the list to try in the real world algorithm.	Thank you for this comment. We have highlighted the reasons cited in our expanded discussion of racial and ethnic disparities in treatment in the Patient Perspectives section.

	Lastly, an estimate of a patient's cardiovascular disease over 10 years, or ASCVD score, can be calculated, but is not yet widely done. An ASCVD score stratifies patients into many different risk categories. High-risk patients require maximally tolerated statins and the ICER assumes ezetimibe is added on for patients not at LDL goal as usual care. In real-world practice, such assumptions are incorrect, particularly in communities of color where more rushed or low-yield doctor visits occur and, such risk estimate algorithms overestimate outcomes. Ezetimibe tends to be added later in the course of intensified treatment plans which usually, and unfortunately, occur after a patient has had an event like heart attack or stroke rather than before an event and irrespective of ASCVD score. Typically, only once an event occurs would aggressive optimal medical therapy be added and specialized care be more available, which underscores the need for earlier intervention and guaranteed equity in communities of color before resolving a benefit profile of a medication or therapy. Often, maximally tolerated statin use is not even achieved in inner city community clinics before getting to the use of ezetimibe, a finding associated with prediction modeling using Black race based on the ASCVD score. Inaccurately assuming the standard hyperlipidemia treatment protocol is adding ezetimibe on top of a maximally tolerated statin as is the basis for ICER's comparative risk analysis, payers will likely require patients to step through ezetimibe on top of a maximally tolerated statin, before bempedoic acid with or without ezetimibe or inclisiran will be approved. When real world experience tells us, as described above, that there are barriers to achieving maximally tolerated statin use and underuse of ezetimibe, especially in African American patients, the result will undoubtedly be a delay or inability to achieve target cholesterol levels for some hyperlipidemic patients, potentially leading to additional cardiovascular events and even deaths.	
3.	**MAJOR ADVERSE CARDIOVASCULAR EVENT RATES** ABC appreciates that in response to feedback received during the preliminary model presentation, ICER made changes to key inputs to the cost effectiveness model, including using Cholesterol Treatment Trialists Collaboration data for converting LDL-C reduction into MACE rates for both drugs. The result was a MACE rate in the control group of 5.06 per 100 person-years, an improvement from the MACE rate of 4.1 included in the model analysis plan. Even with this modification, MACE rates observed in real-world studies are substantially higher than those reported in randomized controlled trials and are much higher in Blacks — especially in older Black patients with high-risk ASCVD — which suggests secondary MACE burden and potential benefits of effective cardiovascular disease management in ASCVD patients may be underestimated by ICER if real-world data are not taken into consideration. Once MACE occurs, the event is monitored	MACE rates in the model represent a composite of MACE rates across the secondary prevention population, of which older adults are a subset and are not modeled separately. We agree that the cost-effectiveness of a drug would be better in higher-risk subgroups, but the purpose of this modeling is to estimate the value-based price for the entire cohort being studied.

	over time while the patient is on maximal optimal medical therapy, including higher compliance with maximally tolerated statin use. Even after MACE, we know subsequent MACE for Blacks is still roughly double that of whites. ICER should factor total major MACE into inputs and resultant analyses. In the real world, cardiovascular disease patients have multiple events, each one carrying costs and other burdens that, if not captured holistically, can undermine the accuracy of cost-effectiveness estimates.	
4.	**RELIANCE ON CLINICAL TRIALS DATA THAT LACKS ADEQUATE AFRICAN AMERICAN STUDY PARTICIPANTS** It is well-established that clinical trials as a whole are lacking in diversity — race as well as age and socio-economic status. We appreciate ICER's acknowledgement in the draft report the clinical trials of both bempedoic acid and inclisiran lacked racial and ethnic diversity. It is therefore possible ICER's analysis misrepresents the value of bempedoic acid with or without ezetimibe or inclisiran in the African American patient population. We ask ICER to consider performing an analysis of key demographic groups, such as Black and Latino Americans who bear a disproportionate burden of cardiovascular disease and who are underserved in the health care system.	We are doing subgroup analyses on statin intolerant patients and the report focuses on patients with previous ASCVD events. The clinical trials did not include enough African Americans in their clinical trials for us to be able to evaluate them separately. We hope stakeholders will urge drug companies to better enroll diverse communities in trials, as we would be very interested in those data if they existed.
5.	We appreciate ICER's economic evaluation assumes that patients intolerant of statins achieve a larger LDL-C reduction with the addition of bempedoic acid/ezetimibe than patients receiving statin therapy. We agree with ICER that whether this translates to larger clinical benefits in statin-intolerant patients merits further investigation. We continue to view QALY as an imperfect metric because it has potential for discrimination against those with baseline disabilities, co-morbidities and advanced age, all of which are common in cardiovascular disease patients.	Please see results using the evLYG approach in the report.
Preventive Cardiovascular Nurses Association		
1.	Elevated low-density lipoprotein cholesterol (LDL-C) is a primary risk factor contributing to the development of cardiovascular disease. Cardiovascular disease effects 48% of the U.S. population with heart attack as the number one cause of death. Heterozygous familial hypercholesterolemia effects 1 in 250 people. It is estimated 92.8 million adults have elevated serum total cholesterol levels. Given these statistics, patients requiring a reduction in cholesterol should not be limited to approved cholesterol-lowering medications. It is also of importance to note not all patients receiving statin therapy achieve LDL-C levels needed to optimally reduce atherosclerotic cardiovascular disease (ASCVD). Statin intolerance affects up to 50% of patients. Restricting access to effective non-statin treatments limits patient s' ability to improve quality of life and reduce ASCVD risk.	Thank you for your comments.

	Disparities in the rates of cardiovascular disease and death among minorities continue to plague our country. The decrease in heart disease seen in Whites has not been demonstrated in Blacks, Hispanics, and Asians. Taking these facts into account, PCNA feels strongly that access to safe and effective cholesterol-lowering drugs should not be restricted. Cardiovascular disease is more prevalent in Blacks compared to Whites; however, Blacks are less likely to receive evidence-based treatments such as statin therapy. This supports the argument that limiting access to effective treatments would not promote equity in the treatment of cardiovascular disease. Individuals of low socioeconomic status are disproportionately affected by cardiovascular disease and elevated cholesterol. To ameliorate this disparity, the available cholesterol lowering medications should be accessible to all patients who can benefit from their effects.	
Other		
Paul Langley		
1.	Given the references are to DALYs (disability weight) how have you moved from these weights to what appear to be utilities (creating QALYs)? Your references are not clear on this point.	Although there are key differences in how weights are derived for DALYs and QALYs, a simplifying assumption that q = 1-d (where q is the weight for QALYs and d is the weight for DALYs) is reasonable provided the DALY weights are not age-adjusted.
2.	If your HRQoL inputs are applied to time spent to create I-QALYs, can you demonstrate that your utility the HRQoL scale has ratio properties? Can you demonstrate that the HRQoL scale has interval properties (to support addition and subtraction) as well, by extension, a true zero to support multiplication and division?	Given that we have responded to these comments regarding prior ICER reports, we refer the reader to our prior responses to public comments.
3.	What are the health status (symptom) attributes captured by your HRQoL scale? Are they equivalent to the EQ-5D-3L attributes? Or are they disease specific? Or what?	The weights used here are generally higher than those based on EQ-5D estimates, in part because we only account for QoL changes related to CVD, rather than including QoL decrements from other comorbidities present in individuals with established ASCVD. Using more severe QoL penalties for CV states (as we do in a sensitivity analysis) causes the cost per QALY to increase considerably.
4.	What are the measurement properties of the disability weight scale? From the literature, it would appear that they are just ordinal measures so that the DALY is mathematically impossible? Could you clarify?	Please see response to comment above. We are not calculating DALYs in this analysis.
5.	Had you considered, if this is a disease specific measure, of developing a needs fulfillment instrument utilizing Rasch Measurement Theory [see Bond T and Fox C. Applying the	That would be beyond the scope of this assessment, but we encourage the development of additional measures.

	Rasch Model 3rd Ed 2015] to assess response to therapy for competing interventions?	
Glenda Sexauer		
1.	I am writing as a WomenHeart Champion that educates other women about the importance of cholesterol management as a way to reduce risk factors for heart disease. It is important that doctors having all options available to them to prescribe to women what is the most effective medication for managing their cholesterol. Patients need access to new cholesterol-lowering therapies. More treatment options for patients will help give patients options that work for them. Often women have statin-associated side effects and need to expand beyond statins to other types of cholesterol medication management.	Thank you for your comments.