ASPC
The American Society for Preventive Cardiology

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
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Dear Dr. Pearson,

As President of the American Society for Preventive Cardiology, I am writing to you to express our strong support of bempedoic acid and the combination of bempedoic acid/ezetimibe which are undergoing ICER evaluation for patients with heterozygous familial hypercholesterolemia and established atherosclerotic cardiovascular disease.

It is unfortunately quite clear that for the last decade, the incidence of cardiovascular mortality has been on the rise again for both men and women. Recent analyses continue to show high discontinuation rates for statins and for clinical intertia among health care providers for titrating statins to appropriate doses. LDL-C goal attainment rates, especially for our highest risk patients, continue to hover at approximately 30-40%. It is highly established that LDL-C lowering reduces risk for cardiovascular events in both the primary and secondary prevention settings.

Heterozygous familial hypercholesterolemia is among the most widely prevalent metabolic disorders in the world and dramatically ncreases risk for ASCVD. ASCVD is highly prevalent in the United States and is associated with significant morbidity and mortality.

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, efficacius 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 suboptimally managed. In the end, patients will lose. The quality of care will suffer.

Thank you for your attention to this vitally important matter. With kind rgards, I am

Yours sincerely,

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SUMMARY OVERVIEW

Amgen appreciates the opportunity to comment on ICER's *Draft Evidence Report for the Condition Update to its 2020 High Cholesterol (HC) Assessment.* Cardiovascular disease (CVD) is one of the country's most significant health challenges. Approximately 655,000 Americans die from heart disease each year—that's one in every four deaths.[1] Consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establish that low-density lipoprotein cholesterol (LDL-C) causes atherosclerotic CVD.[2] Since atherosclerosis is the main cause of CVD, treatments that reduce LDL-C are important for both primary and secondary prevention in patients. Fortunately, multiple long-term studies have demonstrated that a reduction of LDL-C, whether achieved with statin (± ezetimibe) or with PCSK9 inhibitors, results in a reduction of Major Adverse Cardiovascular Events (MACE).[3,4,5]

Amgen is committed to serving patients living with high cholesterol and continues to advance the knowledge of this condition and improve patient affordability We have sponsored robust clinical trials with long-term follow-up across a variety of subpopulations and have demonstrated that Repatha® (evolocumab) effectively lowers LDL cholesterol and reduces MACE in high-risk patients while displaying a safety profile similar to the placebo arms of the trials.[6,7,8,9] With well over 3,500 publications related to PCSK9 inhibitors over the past decade,[10] we recognize that it is difficult to navigate this therapeutic area; but several excellent reviews provide an impartial summary of these findings.[11,12] Additionally, Amgen made Repatha available exclusively at the 60% lower list price of $5,850 per year to reduce out-of-pocket costs, particularly for Medicare patients, to help every patient prescribed Repatha fill their prescription at an affordable, low fixed dollar co-pay.[13]

In the spirit of scientific collaboration, Amgen would like to highlight that the cost-effectiveness analysis that ICER conducted was overall scientifically valid. Compared to previous ICER lipid lowering evaluations, there were several updates to ICER's model structure, which increased validity. For example, the updated version of the decision model allowed that people could not only have a single cardiovascular event per cycle, but they could also have an acute coronary syndrome (ACS) event and a stroke in the same year. Also, the approach for modelling efficacy was appropriate: ICER applied the relationship of an 'LDL-C reduction to hard outcomes'. The evidence used to define this relationship was derived from the CTTC (2010) data, which represent the most accurate source available.[14] Importantly, for the base case analysis, the modelled relationship did not differ across treatments. ICER's evaluation is in agreement with the current understanding of the relationship between LDL-C reduction and hard outcomes, whether achieved by statins or by PCSK9 inhibitors or inclisiran. In terms of baseline event rates, ICER did not solely refer to trial data, but also considered real-world incidence rates. In particular, ICER applied event rates from the national inpatient sample and calibrated these rates to contemporary clinical trials and prior economic models. This approach is an improvement to directly applying trial event rates, which would have a high potential to underestimate the risk for the target population. Finally, the choice of selected comparators was appropriate.

Our recommendations and comments on the report are summarized here and expanded below:

1. **Revise the current model to fully account for long-term implications of recurrent events.**
2. **Reframe the language in the report to more accurately reflect ICER's objective of providing a <u>fair and balanced assessment</u>.**

DETAILED RECOMMENDATIONS

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.

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:

Table 1: Recommendations in reframing the language and enhancing the accuracy of this report

#	Quote	Location	Comments
1	"*One important controversy is whether the mechanism of action of inclisiran suggests* ***that the degree of LDL-C lowering it provides will translate into reduction in MACE rates that are more comparable to those seen with statins or with PCSK9*** *inhibitors, the latter of which* ***showed lower than expected*** *reduction in MACE rates in their clinical outcomes trials relative to their degree of LDL-C lowering, in part due to short follow-up duration. Although inclisiran works along the same pathway as PCSK9-inhibitors, it has a novel mechanism of action that interferes with PCSK9 production, rather than inhibiting PCSK9 action*".	pg. 40, Line 1-6	• This does not necessarily reflect currently established evidence: the only relationship that has been established is that LDL-C reduction is a surrogate marker to reduction of MACE regardless of drug class. • That the mechanism of action in inclisiran could lead to better outcomes is purely speculative • A paper by Ference *et. al.*[15] shows concordance of the relationship of LDL-C reduction to MACE between statins and PCSK9 inhibitors. • That the two PCSK9 inhibitors evolocumab and alirocumab would have shown "lower than expected" reduction in MACE in clinical outcomes trials is not supported by evidence, and raises the question of subjectivity. • No evidence that an interference with PCSK9 production versus an inhibition would result in a different relationship between LDL-C reduction and MACE or lower MACE rate. • This could lead to misinterpretation that the inclisiran efficacy is, or is expected to be, superior compared with the efficacy of evolocumab or alirocumab. Furthermore, there is no evidence to date to suggest a superior mechanism of action.

Table 1: Recommendations in re-framing the language of this report - *Continued*

#	Quote	Location	Comments
3	"*ongoing trials will clarify whether LDL-C lowering with either agent results in a concordant reduction in MACE.*"	pg. 82, Line 8-9	• Clarification may be needed: there is substantial evidence that differences in MACE components (*e.g.*, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina) observed across trials could be the result of variations in trial design particularly with respect to length of follow-up.[16] • Ference *et. al*. (2018) noted that the MACE event rate reduction is well-aligned with that observed for statins *if* the length of follow-up is considered. Studies with longer observation periods demonstrate higher degrees of protection against CV events in relation to LDL-C lowering regardless of the drug studied.[17] • No evidence is available that suggests that inclisiran would be different from PCSK9 inhibitors relative to the degree of LDL-C lowering.
4	"*One important difference between inclisiran and PCSK9-inhibitors is the dosing regimen. Inclisiran has a twice-yearly dosing schedule compared with the twice-monthly or monthly dosing schedule of PCSK9-inhibitors. Data are not available, however, on the degree to which fewer injections, perhaps delivered in the clinical setting, would translate into better real-world adherence and outcomes.*" "*the cost effectiveness of inclisiran would far exceed conventional thresholds […] if its effect on cardiovascular outcomes is similar to evolocumab and alirocumab*".	pg. 40, Lines 15-19 pg. 82, Line 35-37	• A qualitative comparison is limited and is not sufficiently captured in the discussion. • Adherence and outcomes have not been established and should not be speculated on. Adherence data from a controlled clinical trial is not representative for the real world. • ICER's chosen words may be misleading. The sensitivity analysis conducted, to our understanding, is not about assuming the same efficacy for inclisiran as for evolocumab and alirocumab: the applied percentage reduction in LDL-C is still based on the inclisiran trials and not on evolocumab and alirocumab trials. The sensitivity analysis of the relationship of LDL-C reduction to MACE is based on the pivotal trials of evolocumab and alirocumab. • Previous cost-effectiveness analyses differ substantially by model structure and efficacy assumptions both for drug pricing and for event rates.
5	*"systematic cost-effectiveness analyses, coupled with market pressure from unapproved or abandoned prescriptions, were instrumental in achieving an eventual 60% reduction in the WAC of evolocumab and alirocumab (with even deeper discounts in net price)".*	pg. 83, Lines 2-5	• Amgen reduced the list price of Repatha® October 2018 to enable improved access for all our patients, especially Medicare Part D patients. This decision was not due to the cost-effectiveness assessment as reported by ICER in the draft report. In 2018, Amgen made Repatha® available at a 60% reduced list price to help lower patients' out-of-pocket costs. We estimate that more than half of all potential Repatha® patients are Medicare beneficiaries. For Medicare patients in particular, the lower list price should have immediately reduced patient out-of-pocket costs from approximately $280 - $370 per month on a specialty cost sharing tier to $25 - $50 per month on a preferred brand cost sharing tier. However, after our list price reduction for Repatha®, it took the Part D plans more than a year to pass these savings on to Medicare patients so that they could access Repatha®.[18] • Separately, it is inappropriate to lump evolocumab and alirocumab together in this statement, due to each company's different respective reasoning for lowering their price.

CONCLUSION

Cardiovascular disease is one of the country's biggest health challenges with significant negative consequences for patients, their families, and caregivers. Amgen appreciates that ICER is invested in addressing the needs of patients living with cardiovascular disease, specifically high cholesterol, with its comparative review of inclisiran and bempedoic acid. Although, we highlight areas not supported by evidence in the framing of this report, such as the impact of reduced dosing frequency to outcomes and Repatha's® pricing decisions, we commend ICER for the improvements they have made to the model, incorporating real-world event rates, and leveraging the well-established relationship between LDL-C reduction and reduction in CV events, based on the CTTC data. We reaffirm Amgen's commitment to improving patient affordability which has significantly reduced barriers and lowered patient's out-of-pocket costs. Finally, we advise ICER to include recurrent events in the cost-effectiveness modeling and adjust the recommended language for fair balance and accuracy. Amgen appreciates the opportunity to share our insights and hope that it will enhance ICER's analysis to achieve a more complete and balanced view on the available evidence.

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[5] *Op. Cit.* Ference *et al.* Link
[6] Sabatine MS, Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, et al. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease. Circulation. Aug 2018; 138: 756-766. Link
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Association of Black Cardiologists, Inc.
Saving the Hearts and Minds of a Diverse America

December 11, 2020

Submitted electronically to: publiccomments@icer-review.org

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Dear Dr. Pearson:

On behalf of the Association of Black Cardiologists (ABC), we appreciate the opportunity to comment on Institute for Clinical and Economic Review's (ICER) evaluation of inclisiran and bempedoic scid for patients with heterozygous Familial Hypercholesterolemia (HeFH) and for secondary prevention of atherosclerotic cardiovascular disease (ASCVD).

Founded in 1974, the ABC is a nonprofit organization with a national and international membership of 2,023 cardiovascular specialists, cardiologists in training and other health professionals, as well as community health advocates and corporate and institutional members. The ABC is dedicated to eliminating disparities related to cardiovascular disease for all people of color and adheres to the vision that all people regardless of race, ethnicity or gender should benefit equally from reduction in the frequency, duration and impact of diseases of the heart and blood vessels.

The focus of our comments center on three areas of draft analysis:

1. Layering of ezetimibe on top of a maximally tolerated statin as the base case for the analysis.
2. Major Adverse Cardiovascular Event (MACE) rates.
3. Reliance on clinical trial data that lacks adequate African American study participants.

We wish to preface our comments by highlighting the value of a medication does not apply across the board to *every* patient. There are an infinite number of differences between patients, and, as cardiovascular specialists, we know a one-size-fits-all approach does not exist for patients who require cholesterol-lowering therapy to reduce their risk of having a cardiovascular event. When pharmacologic therapies are reviewed by ICER for their long-term cost effectiveness and budgetary impact in relation to the price of the medication, the outcome of that review can significantly affect the ability of a physician to practice patient-centered care as we

experienced with PCSK9 inhibitors, with the initial rejection rate for approval to use PCSK9 inhibitor drugs being higher in African American patients than their white counterparts.[1]

Cardiovascular disease remains the leading cause of death for all Americans, and African Americans still feel the brunt of mortality, morbidity and reduced quality of life due to heart disease and stroke. The price of life-saving pharmaceuticals is a major contributor of health care costs; yet, cost-effectiveness is a complex matter that should be studied with the goal of achieving health equity. Cholesterol-lowering drugs are important effective and preventive treatment interventions. It is imperative that treatments for heart disease prevention are accessible and affordable to populations that are economically disadvantaged and traditionally disenfranchised from health care, as well as to racial and ethnic minorities whose risks of and complications from heart disease and stroke are persistently greater than that of white men and women.

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.

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 ezetemibe. Yet, for its base case, ICER assumes 100 percent of patients will be treated with ezetemibe 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.[3] 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

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[2] Nanna M; Navar A, Zakroysky P, Xiang Q, et al. Association of Patient Perceptions of Cardiovascular Risk and Beliefs on Statin Drugs With Racial Differences in Statin Use. JAMA Cardiol. 2018;3(8):739-748. doi:10.1001/jamacardio.2018.1511
[3] Ibid.

factors.[4] 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.[5]

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.[6] 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.[7]

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.[8] 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

[4] Nanna M; Navar A, Zakroysky P, Xiang Q, et al. Association of Patient Perceptions of Cardiovascular Risk and Beliefs on Statin Drugs With Racial Differences in Statin Use. JAMA Cardiol. 2018;3(8):739-748. doi:10.1001/jamacardio.2018.1511
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cholesterol levels for some hyperlipidemic patients, potentially leading to additional cardiovascular events and even deaths.

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[9] 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 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.[10]

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.

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.

OTHER ISSUES

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.

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[9] Dasha Cherepanov, Tanya G.K. Bentley, Wendy Hsiao, Pin Xiang, Frank O'Neill, Yi Qian, Nicole Yurgin & David Beenhouwer (2018) Real-world cardiovascular disease burden in patients with atherosclerotic cardiovascular disease: a comprehensive systematic literature review, Current Medical Research and Opinion, 34:3, 459-473, DOI: 10.1080/03007995.2017.1401529 available at: https://doi.org/10.1080/03007995.2017.1401529

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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.

CONCLUSION

In conclusion, ICER has done tremendous work with a large body of evidence to support the demonstrated benefit of using bempedoic acid on top of optimal medical therapy for secondary prevention and HeFH. Such reports fuel policy and recommendations toward its use, distribution and coverage. However, the body of data that support their evidence has a base case that reflects only a clinical trial environment, misses proportional representation of highest risk ethnic groups, assumes a faulty standard of care, and overall misjudges the benefit to real world medicine. Further consideration must occur to avoid insurance coverage policies and access barriers that can dangerously compound an already disparate health care system.

The ABC appreciates this comment opportunity. Questions or requests for additional information should be directed to Camille Bonta at (202) 320-3658 or cbonta@summithealthconsulting.com.

Sincerely,

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December 11, 2020

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RE: Draft Evidence Report and Voting Questions for ICER Evaluation of High Cholesterol

Dear Dr. Pearson,

Esperion appreciates the opportunity to submit comments regarding the Institute for Clinical and Economic Review (ICER) draft evidence report and voting questions for ICER's evaluation of "Inclisiran and Bempedoic Acid for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value."[1,2]

Esperion's comments are focused on five topics:

1. **Economic model assumption that 100% of patients in the comparator arm receive maximally tolerated statins (MTS) plus ezetimibe (EZE)**

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.[3]

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.[4] 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.[5] 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.

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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%.[6] ICER's own Draft Evidence Report[1] (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).[7,8]

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 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***".[9] 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.

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2. Prevalence of statin intolerance (SI)

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[10] and represent a population with high unmet need for non-statin treatment options.

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.[11,12]

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.[13] In a meta-analysis of 26 randomized trials, approximately 13% of patients reported muscle adverse events, the most common being myalgia.[14]

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.

3. Baseline utility estimates

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.

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[14] 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[15] reported median 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.[16,17,18] 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. Table 1 provides suggested values for ICER's consideration.

Table 1: Recommended Baseline Utility Values

	Treated population without observed events	MI	Stroke	Angina	Coronary Revascularization
ICER's Current Inputs[1]	-	0.96	0.88	0.91	-
Betts, et al[14]	-	0.79	0.64	0.72	0.81
Sullivan, et al.[15]	0.854	0.70	0.65	-	0.70
Recommended Inputs[14,15]	**0.854**	**0.79**	**0.65**	**0.72**	**0.81**

Esperion also recommends that ICER address this issue in the Contextual Considerations and facilitate further discussion at the policy roundtable. In Table 6.1[1], 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.

4. 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.[19]

5. 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

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Revised Scope and Background Document which includes 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.***

In conclusion, Esperion recommends that ICER strongly consider the key issues outlined above. Specifically, we urge ICER to:

1. Revise the patient mix in the comparator arm of the economic model to more accurately represent EZE use in the real world and large-scale clinical trials and conduct sensitivity analyses to test the potential range of prevalence estimates.
2. Conduct sensitivity analyses to test a range in prevalence for SI which is more in line with real word prevalence.
3. Use more accurate baseline utility estimates to better represent quality of life for high-risk patients that experience cardiovascular events.
4. Revise ICER's characterization of gout as a serious, treatment emergent adverse event in the economic evaluation.
5. Replace Nexletol with Nexlizet in the voting questions for Clinical Evidence and Potential Other Benefits and Contextual Considerations.
6. Revise the voting question for Long Term Value for Money to compare Nexlizet to "usual care" rather than "usual care with ezetimibe" to ensure a balanced approach in assessing value for money with each treatment considered in the evaluation.

Esperion appreciates the opportunity to share our comments with ICER. We look forward to ICER's response to our comments. Please feel free to contact me should you wish to discuss in further detail.

Sincerely,

Michael Louie, MD MPH MSc
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December 11, 2020

Maggie O'Grady
Program Manager
Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
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Submitted Electronically: mogrady@icer-review.org; publiccomments@icer-review.org

Dear Ms. O'Grady,

The FH Foundation appreciates the opportunity to submit public comments for ICER's draft evidence report *Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value.*

We find ICER's description of familial hypercholesterolemia (FH) to reflect the current understanding of FH. In particular, we appreciate ICER's recognition of the high risk for MACE in the FH population and the early onset of cardiovascular disease for many with FH. We agree that there is an "important public health need for additional treatment options to improve outcomes for patients who remain at higher risk for cardiovascular events."

We would like to highlight the areas in which we find ICER has recognized key considerations.

- The subpopulation analyses for HeFH, statin intolerance and recent ACS are very helpful.
- We agree that more diversity in study populations is needed.
- We appreciate the "areas for further investigation."

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.
- The vast majority of individuals with FH are not diagnosed (85-90%) and diagnosis often comes decades late for those who 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[1,2].
- 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.
- 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.

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[1] deGoma EM, Ahmad ZS, O'Brien EC, et al. Treatment Gaps in Adults With Heterozygous Familial Hypercholesterolemia in the United States: Data From the CASCADE-FH Registry. *Circ Cardiovasc Genet*. 2016;9(3):240-249. doi:10.1161/CIRCGENETICS.116.001381

[2] Duell PB, Gidding SS, Andersen RL, et al. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry. *Atherosclerosis*. 2019;289:85-93. doi:10.1016/j.atherosclerosis.2019.08.007

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 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.
- Adding more detail regarding the mechanisms of action for bempedoic acid, inclisiran, as well as evolocumab and alirocumab and more background on evolocumab and alirocomab. Where the voting questions ask about Other Benefits and Contextual Considerations, the reader will need more background.
- 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.
- 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.

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.

We appreciate ICER's efforts to include patient perspectives, medical expertise, and public feedback in this process and we look forward to the CEPAC meeting and the final report.

Thank you.
Sincerely,

Katherine Wilemon
CEO and Founder

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

I am writing to provide an additional clinical perspective that may better inform your review and address some issues raised in the recently released Draft Evidence Report.

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 ezetemibe.[1] Yet for its base case, ICER assumes *100%* of patients will be treated with ezetemibe on top of a maximally tolerated statin - an extaordinary 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 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.

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.

[1] ICER High Cholesterol Review Draft Evidence Report, p. 46.

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,[2] 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.

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.[3]

It is well-established that clinical trials as a whole are lacking in diversity - race as well as age and socio-economic status.[4] 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 in ICER's modeling and that hopefully will be addressed or weighted in some way in the Final Report.

Sincerely,

Dharmesh Patel, MD

[2] Dasha Cherepanov, Tanya G.K. Bentley, Wendy Hsiao, Pin Xiang, Frank O'Neill, Yi Qian, Nicole Yurgin & David Beenhouwer (2018) Real-world cardiovascular disease burden in patients with atherosclerotic cardiovascular disease: a comprehensive systematic literature review, Current Medical Research and Opinion, 34:3, 459-473, DOI: 10.1080/03007995.2017.1401529 available at: https://doi.org/10.1080/03007995.2017.1401529

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[4] Geneviève, L.D., Martani, A., Shaw, D. *et al.* Structural racism in precision medicine: leaving no one behind. *BMC Med Ethics* 21**,** 17 (2020). https://doi.org/10.1186/s12910-020-0457-8

TO: Institute for Clinical and Economic Review

FROM: Glenda Sexauer, WomenHeart Champion

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.

December 10, 2020

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Draft evidence report for high cholesterol therapies

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft evidence report titled: "Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value," dated November 12, 2020.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient-centered care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of policy-minded health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Draft Evidence Report Comments

The prevalence of high low-density lipoprotein cholesterol (LDL-C), which is a major risk factor for atherosclerotic cardiovascular disease (ASCVD), remains alarmingly high in the United States. According to the Centers for Disease Control and Prevention, "93 million U.S. adults age 20 or older have total cholesterol levels higher than 200 mg/dL. Nearly 29 million adult Americans have total cholesterol levels higher than 240 mg/dL."[1]

Untreated ASCVD imposes substantial financial costs on the health care sector and broader economy. These costs include direct costs of higher health care expenditures and the indirect

[1] "High Cholesterol Facts" *Centers for Disease Control and Prevention*; https://www.cdc.gov/cholesterol/facts.htm#:~:text=95%20million%20U.S.%20adults%20age,higher%20than%20240%20mg%2FdL.&text=7%25%20of%20U.S.%20children%20and,19%20have%20high%20total%20cholesterol.

costs that include lost productivity and decreased quality of life. Cardiac events are also responsible for serious illnesses, permanent disability and nearly 1 million deaths annually.

Effectively managing high LDL-C mitigates many of these health implications; therefore, treatments that sufficiently lower patients' LDL-C offer great value. Statins are widely available in low-cost generic formulations and help many patients lower their LDL-C, but they do not adequately reduce LDL-C for all patients. The novel treatments inclisiran and bempedoic acid are designed to help these patients, and the emerging medical literature substantiates that these medicines are meeting this goal.[2] Thus, these treatments can provide a high-value treatment to the targeted patient population.

The draft evidence report recognizes that these medicines benefit patients who cannot use statins. As noted, clinicians view bempedoic acid and the bempedoic acid/ezetimibe combination therapy as "most helpful in patients with statin intolerance" (page 11).

Despite recognizing the therapies' value for patients who are not well treated by statins, however, the draft evidence report employs several assumptions and methodologies that bias the analysis toward undervaluing these treatments. They are as follows.

The Draft Evidence Report Relies on Cost Thresholds That are Inconsistent with the Systemic Cost of ASCVD

The annual threshold prices estimated in the report range between $920 and $5,480, depending on the dollar-per-QALY benchmark and drug. These values are low relative to the direct medical costs associated with heart disease.

Consider that the total annual costs of heart disease in 2030 will reach $1.1 trillion, adjusted for inflation.[3] Of these costs, $818 billion are direct medical costs. Patients with unmanaged risk factors, including the roughly 26.7 million Americans whose cholesterol levels are not well maintained by statins, will bear a disproportionate share of these costs.[4] For example, one-third of the total direct medical costs would average $10,334 per patient annually. Looking at the full scope of direct medical costs, that figure would average $30,626 per patient annually.

These high annual costs suggest that the cost thresholds used in the model are too low, too stringent. The excessively stringent thresholds could translate into inappropriate access barriers

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[2] Jia, Xiaoming et al. (2019) "Post Statin Lipid Therapeutics: A Review" *Methodist DeBakey cardiovascular journal* vol. 15,1: 32-38. doi:10.14797/mdcj-15-1-32; Laufs U. et. al. "Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance" Journal of the American Heart Association, March 29, 2019, https://doi.org/10.1161/JAHA.118.011662.

[3] Heidenreich PA, et al. (2011) "Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association" *Circulation*, Vol. 123, No. 8, https://www.ahajournals.org/doi/full/10.1161/cir.0b013e31820a55f5.

[4] Akyea RK, et al. (2019) "Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease" *Heart*; 105:975–981. doi:10.1136/heartjnl-2018-314253. (emphasis added); Laufs U, et al. "Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance" Journal of the American Heart Association, March 29, 2019, https://doi.org/10.1161/JAHA.118.011662.

that block patients from efficacious treatments that could improve patient outcomes and decrease overall health care costs.

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.[5] 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.

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.[6]

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 premature

[5] The NHANES is a cross-sectional survey that is conducted every two years by the National Center for Health Statistics. ICER often uses this survey to provide nationally representative estimates of risk factors and disease prevalence.
[6] Heidenreich PA, et al. (2011) "Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association" *Circulation*, Vol. 123, No. 8, https://www.ahajournals.org/doi/full/10.1161/cir.0b013e31820a55f5.

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.

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.

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.

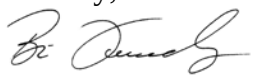
Basing the model on the relationship observed with statins introduces uncertainty into the results and undermines their reliability. And while the inclisiran relationship is used in a sensitivity analysis, this subsequent analysis does not correct the errors inherent in the base model.

Conclusion

Effective treatments that reduce the risk factors associated with ASCVD offers tremendous value to the patient community. IfPA urges ICER to account for the considerations outlined above before finalizing its evidence review.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,



Brian Kennedy
Executive Director

NATIONAL FORUM
FOR HEART DISEASE & STROKE PREVENTION
1150 Connecticut Ave. NW, Ste. 300, Washington, DC 20036

December 11, 2020

Maggie O'Grady
Program Manager
Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
Boston, MA 02109

Submitted Electronically: mogrady@icer-review.org; publiccomments@icer-review.org

Dear Ms. O'Grady,

Thank you for the opportunity to provide feedback to ICER on its draft evidence report for assessing the comparative clinical effectiveness and value of inclisiran (Novartis) and bempedoic acid (Nexletol™, Esperion Therapeutics, Inc.) for treatment of high cholesterol in the setting of heterozygous familial hypercholesterolemia (HeFH) and for secondary prevention of atherosclerotic cardiovascular disease (ASCVD). We appreciate your willingness to review comments and recommendations from the National Forum's Value & Access Steering Committee and partners working on these issues.

The Value & Access (V&A) Steering Committee and partners operate under the consensus goal to enhance health and well-being by supporting people's access to evidence-based care that is appropriate for them by:

- Identifying evidence-based strategies for determining appropriateness of care
- Supporting the implementation of evidence-based care that aligns incentives for patients, providers, payers, other stakeholders

The (V&A) Steering Committee and partners jointly offer the following feedback for ICER's consideration in the development of the draft evidence report.

Positives

The Steering Committee and partners appreciate ICER's inclusion in the draft evidence report of our recommendations on the draft scoping document :

- That ICER's value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms (e.g., health disparities and access to care issues) are evaluated. We encourage ICER to continue increasing patient advocacy groups' involvement in the process through direct outreach to groups with expertise in areas of focus, opportunities for meetings with ICER and its experts, and enhanced explanation of ICER's processes.

- The clear identification of the populations of interest for this review including all patients with HeFH and patients with established ASCVD (secondary prevention).
- The inclusion of people with statin intolerance.
- The separate evaluation of data for the subpopulations.
- The review of both bempedoic acid alone and in combination with ezetimibe.
- The inclusion of health-related quality of life among Patient-Important Outcomes.
- The inclusion of important information about the designation of adults with HeFH having a high-risk equivalent of developing ASCVD even though they have not yet had an event, and that FH remains an underdiagnosed and undertreated subpopulation.

Additionally, the V&A Steering Committee and partners appreciate the following:

- Acknowledgements throughout the report of disparities in LDL-treatment goals for people with HeFH, the overall burden of ASCVD, and under-representation by race/ethnicity and sex in clinical trials. We encourage ICER to identify strategies to address the disproportionate burden on members of populations underrepresented in clinical trials.
- The inclusion of the patient perspective, including patient statements.
- The outline describing the type of input received from patients, caregivers, and advocacy organizations that informed ICER's research approach.
- Acknowledgements addressing the lack of data regarding:
    - relatively fewer injections (for inclisiran) and administration in the clinical setting, and whether that will translate into better real-world adherence and outcomes, and
    - the effect of recurrent events on quality of life

  The Steering Committee and partners appreciate that ICER is open to stakeholders providing evidence to support alternative assumptions.
- Clear notation to caution readers against assuming values provided in the threshold analysis results section will approximate the health benefit price benchmarks (HBPBs) that will be presented in the next version of the report because results may change substantially due to input.
- Clear notation regarding uncertainty and controversies to help better understand the model and assumptions.

<u>Opportunities</u>

- Patient Perspectives
    - There are additional opportunities for even more inclusivity of input from patients, caregivers, and advocacy organizations (noted above).
    - ICER's data inputs are focused on randomized controlled trials (RCT), which do not proportionately reflect real world demographics.[1] Studies have shown that the patient populations that are underrepresented in RCTs are often those with the highest risk and lower access to treatments[2,3,4] and additional data show that when step therapy is signaled, these populations are disproportionately left out.[5] We encourage ICER to find a way address this in its modeling.

- 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.).[6,7,8] Between 2007 & 2017 (except for a small increase in 2014), the number of ezetimibe prescriptions has consistently declined.[9]
        - 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.
    - 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,[10] "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.
    - 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.

- 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*.) (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.

- Baseline Population Characteristics
    - 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.[11] 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.

- 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.[12] We suggest that ICER review this real-world data.

- Statin Intolerance
    - Statin use among patients with ASCVD remains suboptimal because of various patient- and clinician-related factors.[13]
    - 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.

- 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.

- 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
        - Adults with ASCVD and HeFH
        - Adults with ASCVD and statin intolerance
        - Adults with ASCVD and recent ACS

The V&A Steering Committee and partners would like to see how the recommendations we have provided impact the cost-effectiveness score. We know that there are additional data that come into consideration. It is important that model assumptions about the uptake of these medications

be informed by real world-evidence of uptake of other therapies. We support the right treatment to the right patient at the right time.

The V&A Steering Committee and partners recommend that ICER comment on/evaluate payer restrictions, namely the specialty restriction and step therapy considerations for bempedoic acid. Those restrictions would severely limit access to a medication that is easy to monitor, has few adverse effects, and does not require specialty training to decide whether to use it or not. In its report, ICER mentions that one payer has such specialty restrictions and also comments on the current step therapy restrictions for multiple plans.

Again, thank you for your consideration. We look forward to reviewing and providing additional comments once the evidence report is released.

Sincerely,

Members of the Value & Access Steering Committee and Partners representing the following organizations:

National Forum for Heart Disease & Stroke Prevention (convener)
American Association of Heart Failure Nurses
American Heart Association
American Pharmacists Association Foundation
American Society for Preventive Cardiology
Association of Black Cardiologists
Association of State and Territorial Health Officials
BallengeRx Consulting
The FH Foundation
Global Healthy Living Foundation
Independent Health
Institute for Patient Access
Mended Hearts
National Alliance of Healthcare Purchaser Coalitions
National Lipid Association
Partnership to Advance Cardiovascular Health
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
University of Michigan Center for Value-Based Insurance Design

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Executive Summary

Novartis Pharmaceuticals Corporation (Novartis) appreciates the opportunity to provide feedback on the Institute of Clinical and Economic Review's (ICER) draft evidence report for the assessment of treatments for high cholesterol. Novartis believes addressing the concerns below would more accurately capture the true value of inclisiran. In summary, Novartis respectfully asks for clarification of some elements of the analysis and offers the following suggestions to incorporate more relevant, appropriate, and up-to-date data in the current analysis:

- Based on the pivotal clinical trial populations for ORION-10 and ORION-11, the expected label for inclisiran, and current real-world treatment patterns, the base-case population in the cost-effectiveness analysis should focus on patients with established atherosclerotic cardiovascular disease (ASCVD) who need additional lipid-lowering therapy despite being on maximally tolerated statins. 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.
- In the cost-effectiveness model for ASCVD patients, the relative reduction in low-density lipoprotein (LDL-C) levels 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.
- More details are needed on how adherence to inclisiran, statins, and ezetimibe from clinical trials is implemented in the model. 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.
- Cardiovascular (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 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, since 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.
- 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.
- Clarification is needed on several aspects of the model structure and model inputs:
    - The inputs for baseline risks and transition probabilities.
    - The methodology used to derive non-CV mortality rates and the numbers estimated for these rates.
    - Whether the model accounts for ASCVD patients with diabetes, since patients with diabetes and ASCVD are at an increased risk of CV events.
    - What is included in "background healthcare costs for management of non-CV health conditions"?
    - What is included in the model structure for "history of other ASCVD"?
    - Are the risks of subsequent CV events dependent on the time from the previous CV event?
    - What is the rationale for following the model cohort only until the age of 95 years?
    - A description of the methodology used to derive utilities and applied to the cost-effectiveness model.
    - We could not identify the costs described in the report (e.g., Table 5.8) in the references provided. The costs of revascularization and statins are not listed in the draft evidence report.

The remainder of this letter provides a more detailed discussion of these points.

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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.

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 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.

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 approximately 15% decrease in the incremental cost-effectiveness ratio.

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

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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.

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).

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 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).

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.

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

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studies. Additionally, the 2019 publication specifically analyzed the benefit of lipid lowering therapy in various age groups. 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.

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.

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).

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 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.

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.

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.

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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.

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. Novartis recommends the approach previously shared with ICER.

What is the rationale for following the model cohort only until the age of 95 years? The report should clarify the rationale for finishing the analysis when the patients reach 95 years of age. Economic models analyzing chronic conditions typically extend the age to 100 or 120 years, or where 99.9% of people have died (Drummond 2005; Siebert 2012). If the time horizon is limited to a maximum age of 95, the model may not capture all the relevant costs and health consequences and may underestimate the quality-adjusted life-years (QALYs) gained from using inclisiran.

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.

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.

Sincerely,
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Executive Director, Cardio, Renal and Metabolism, Health Economics and Outcomes Research
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PARTNERSHIP TO ADVANCE
Cardiovascular Health

Submitted electronically to: publiccomments@icer-review.org

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Dear Dr. Pearson,

I am writing to provide an additional stakeholder perspective that may better inform your review and address some issues raised in the recently released Draft Evidence Report.

The Partnership to Advance Cardiovascular Health (PACH) is a 501(c)(4) nonprofit advocacy coalition of stakeholder groups that represent patients, patient advocates, healthcare providers and medical researchers. On behalf of its members, PACH works to promote the sanctity of the clinician-patient relationship. PACH also seeks to advocate for patient access to approved therapies and to promote accelerated innovation in cardiovascular health care for the millions of Americans who are at high risk for heart disease.

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 ezetemibe.[1] Yet for its base case, ICER assumes *100%* of patients will be treated with ezetemibe on top of a maximally tolerated statin - an extaordinary 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

[1] ICER High Cholesterol Review Draft Evidence Report, p. 46.

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.

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.[2] 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*.[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.[5]

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.[6]

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

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[2] Navar AM, Taylor B, Mulder H, et al. Association of Prior Authorization and Out-of-pocket Costs With Patient Access to PCSK9 Inhibitor Therapy. JAMA Cardiology. 2017;2(11):1217-1225. Doi:10.1001/jamacardio.2017.3451

[3] Myers KD, Farboodi N, Mwamburi M, Howard W, Staszak D, Gidding S, Baum SJ, Wilemon K, Rader DJ. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. Circ Cardiovasc Qual Outcomes. 2019; 12:e005404. doi: 10.1161/CIRCOUTCOMES.118.005404

[4] Dasha Cherepanov, Tanya G.K. Bentley, Wendy Hsiao, Pin Xiang, Frank O'Neill, Yi Qian, Nicole Yurgin & David Beenhouwer (2018) Real-world cardiovascular disease burden in patients with atherosclerotic cardiovascular disease: a comprehensive systematic literature review, Current Medical Research and Opinion, 34:3, 459-473, DOI: 10.1080/03007995.2017.1401529 available at: https://doi.org/10.1080/03007995.2017.1401529

[5] Allen JM, Arnold SV, Lohr NL, et al. Abstract 12904: Assessing Low-Density Lipoprotein Cholesterol Risk in Secondary Prevention Patients Within The PINNACLE National Outpatient Registry. Circulation. 2019;140(Suppl_1):A12904-A12904

[6] http://www.advancecardiohealth.org/pcsk9-rejection-data

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.

Sincerely,

Ryan Gough

Executive Director, Partnership to Advance Cardiovascular Health

[7] Geneviève, L.D., Martani, A., Shaw, D. *et al.* Structural racism in precision medicine: leaving no one behind. *BMC Med Ethics* 21**,** 17 (2020). https://doi.org/10.1186/s12910-020-0457-8

PIPC Partnership to Improve Patient Care

December 9, 2020

Dr. Steven D. Pearson
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Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for High Cholesterol. Cardiovascular disease (CVD) is one of the leading causes of death in the United States. Between 2013 and 2016, 12.5 million Americans experienced CVD, and between 2014 and 2015 direct and indirect costs CVD and stroke were $351.3 billion.[1] One of the major risk factors for CVD is high cholesterol. Given this large and growing human and economic cost, it is essential to ensure access to effective treatments for high cholesterol, particularly for patients who cannot tolerate statins. Therefore, PIPC encourages ICER to consider the following comments.

The model is not reflective of the indicated population

The risk of major adverse cardiovascular events (MACE) is much higher in African Americans,[2] and African Americans make up a disproportionate share of those who have atherosclerotic cardiovascular disease (ASCVD).[3] 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

[1] American Heart Association, 2019, www.heart.org/-/media/files/about-us/statistics/2020-heart-disease-and-stroke-ucm_505473.pdf?la=en.
[2] Rosamond WD, Chambless LE, Heiss G, Mosley TH, Coresh J, Whitsel E, Wagenknecht L, Ni H, Folsom AR. Twenty-two–year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987–2008.Circulation. 2012; 125:1848–1857
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communities, rather than over-relying on an "average" American.[4] 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 (I^2=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 I^2 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.

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-lowering medication. Someone with high cholesterol is typically defined as having an LDL-C level above 120 mg/dL.

ICER also underestimates the percentage of the population that cannot tolerate statins. ICER assumes statin intolerance has a prevalence of 10% but real-world estimates estimate prevalence at up to 20%.[5]

[4] Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. The American journal of managed care. 2009;25(11):540-2.
[5] Handelsman Y, Jellinger PS. Guerin CK, et al. Consensus statement by The American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm 2020 executive summary. Endocrine Practice 2020;26(10):1-29.

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.

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.[6,7,8] 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,[9] 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.

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)[10] 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.

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[6] Moran AE, Forouzanfar MH, Roth GA, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129(14):1493-1501.
[7] Moran AE, Forouzanfar MH, Roth GA, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129(14):1483-1492.
[8] Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2197-2223.
[9] Sassi F. Calculating QALYs, comparing QALY and DALY calculations. Health policy and planning. 2006 Sep 1;21(5):402-8.
[10] Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health. 2010 Aug;13(5):509-18.

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).

Conclusion

ICER continues the concerning trend of looking to an "average" patient, instead of determining value to the relevant patient populations in question. We encourage ICER to revise its model to be reflective of the actual patient population and to segment voting questions to determine value to subgroups.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

PATIENTS RISING NOW

December 11, 2020

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RE: Draft Evidence Report "Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious and chronic conditions and diseases for them to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. Our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's November 12th Draft Evidence Report, "Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD." Our comments about the draft report are organized below into sections about People-Centered Perspectives; Modeling and Projections; Uncertainties and Assumptions; and Additional Points.

People-Centered Perspectives

Clearly, high cholesterol is a serious medical condition that can lead to many extremely consequential health problems that impair quality of life and may lead to early death. That is why treatment of high cholesterol and ASCVD is very important, and shared clinical decision-making between a patient and their care team is critical. We also note that awareness of high cholesterol is a public health matter, which is why people are encouraged to "know their heart numbers" including cholesterol along with blood pressure and body mass index.

As you know, as awareness has increased that blood cholesterol levels as a risk factor for cardiovascular disease (CVD), more treatment options have been developed – from sequestrants to statins to PCSK9 inhibitors and others. And of course, diet and exercise are also clearly important for helping control risks of CVD.

We include of this background information because there are many facets and perspectives about cholesterol and ASCVD and its treatments that are important to people, but which are either scarcely mentioned or entirely missing from ICER's extremely myopic draft report. Below are some points that we strongly believe ICER should expand upon in the next version of the report, and absolutely must include as part of the discussion at ICER's committee meeting:

- The draft report notes that women with familial hypercholesterolemia are less likely to reach LCL-C treatment goals.[i] This is completely consistent with the well-known sex differences in the symptoms and presentation of heart disease, its diagnosis, and for some treatments.[ii] 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. 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[iii] 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.
- 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"[iv] 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.
- 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).[v] 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."[vi]
- 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-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."[vii] 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.

- 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.[viii]
- ICER's prioritization of economic factors and insurance company policies is also evident in how the draft report is structured, with Coverage Policies[ix] – which are based on economic considerations – being presented ahead of Clinical Guidelines[x] – which are based upon scientific and medical evidence. We suggest reversing the order of those sections to reflect a more appropriate prioritization.

Modeling and Projections

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.

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 why ICER should not model – and project – as accurate a picture of the future as possible.

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[xi] and 2019,[xii] 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.

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)."[xiii] 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.

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,"[xiv] 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 clinical trials would be replicated and sustained in clinical practice."[xv]

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."[xvi] 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.

Additional Points

- The data report for Ballantyne 2020 in the text is incorrect when it states that "63% had HeFH"[xvii] and in Table 4.1 where it lists "ASCVD: 62.5%"[xviii] The correct citation of the data from the publication is "62.5% of patients had ASCVD and/or HeFH."[xix]
- 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."[xx] 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[xxi] – 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.
- 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.
- 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."

- 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.

Conclusions

Patients Rising Now agrees with the draft report's summation: "The arrival of two new lipid-lowering therapies expands the therapeutic options available to patients with established ASCVD. This is a welcome development, given that this high-risk group of patients continues to experience recurrent CV events despite optimal therapy with statins and ezetimibe."[xxii] However, beyond that, we find the draft report lacking in many substantive and technical ways, including lack of attention to quality of life, and reliance upon so many assumptions and uncertainties that the numerical reported results are highly suspect and questionable. Overall, the draft report is very un-person-centered, and appears aimed at justifying insurance companies' erecting access restricting and affordability barriers – similar to what has occurred with other treatments for high cholesterol and cardiovascular diseases in recent years.

Therefore, we are concerned that based on the very limited data and perspectives in the draft report, access to current and future treatments for cardiovascular diseases may be limited by insurance plans through formulary, cost-sharing, or prior authorization schemes based on ICER's activities, which may at the same time expand administrative burdens for clinicians and patients.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] Draft report, p. 1

[ii] https://www.womenshealth.gov/heart-attack, https://www.nhlbi.nih.gov/science/womens-health; https://www.womenheart.org/; https://www.cdc.gov/heartdisease/women.htm; and "Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR®) PINNACLE registry,": Thompson LE, Maddox TM, Lei L, et al., *J Am Heart Assoc.* 2017;6(7).

[iii] Reference #46 in the draft report: Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *European Journal of Preventive Cardiology.* 2020;27(6):593-603.

[iv] Draft report, p. 2

[v] Draft report, p. ii

[vi] Draft report, p. 81

[vii] Draft report, p. 10

[viii] "Evolocumab for Treatment of High Cholesterol: Effectiveness and Value" ICER New Evidence Update, September 11, 2017

[ix] Draft report, p. 12

[x] Draft report, p. 16

[xi] "Evolocumab for Treatment of High Cholesterol: Effectiveness and Value" ICER New Evidence Update, September 11, 2017

[xii] Alirocumab for Treatment of High Cholesterol: Effectiveness and Value" ICER New Evidence Update, February 15, 2019

[xiii] Draft report, p. 90

[xiv] Draft report, pp 39-40
[xv] Draft report, p. 46
[xvi] Draft report, p. 53
[xvii] Draft report, p. 22
[xviii] Draft report, p. 25
[xix] Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. European Journal of Preventive Cardiology. 2020;27(6):596
[xx] Draft report, p. 88
[xxi] https://dart.deloitte.com/USDART/home/publications/deloitte/financial-reporting-alerts/2020/financial-reporting-considerations-economic-downturn-covid
[xxii] Draft report, p. 81

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President
Institute for Clinical and Economic Review
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BOSTON MA 02109

My dear Dr Pearson

11 December 2020

REF: BEMPEDOIC ACID AND INCLISIRAN FOR PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA AND FOR SECONDARY PREVENTION OF ASCVD: EFFECTIVENESS AND VALUE

I write seeking clarification from the modeling group on their use of HRQoL utility inputs to their model (pp. 53-54).

As you will remember, I have on past occasions asked for clarification from yourself and ICER staff on the application of multiattribute utility scores to create QALYs. Your responses have been less than persuasive, as detailed in the following peer reviewed commentary that appeared yesterday:

Langley PC. To Dream the Impossible Dream: The Commitment by the Institute for Clinical and Economic Review to Rewrite the Axioms of Fundamental Measurement for Hemophilia A and Bladder Cancer Value Claims. *InovPharm*.2020;11(4): No. 22
https://pubs.lib.umn.edu/index.php/innovations/article/view/3585/2642

My position and that of a number of colleagues in measurement theory is that multiattribute preference instruments such as the EQ-5D-3L yield only ordinal scores. As these cannot support arithmetic operations, the QALY is an impossible construct. It is not defensible by the axioms of fundamental measurement. Your models, therefore, lack credibility as they are founded on the notion of incremental cost-per-QALY analysis. This is, I might add, in addition to the fact that your models fail the standards of normal science, not only in terms of fundamental measurement but in terms of the absence of credible and empirically evaluable claims. To which, might be added, the reliance on multiattribute HRQoL measures that lack dimensional homogeneity (i.e., lacking construct validity). These issues are addressed in the reference above.

These considerations lead me to a few questions regarding the health related quality of life inputs (utilities?) detailed in Table 5.4. My concern is that the references supplied refer to disability adjusted life years (DALYs) and the creation of disability weights (Global Burden of Disease Study). Of course, utilities to create the impossible QALY or I-QALY, are on an entirely difference conceptual basis than DALY required disability weights. You appear to be using different sources for utility weights (and your disutility weights for transient utility tolls fail the axioms of fundamental measurement: they are ordinal measures). Certainly the DALY and QALY refer to composite descriptions of health states but they are conceptually distinct with 'utilities' in range 1 = perfect health (whatever that means) and 0 = death (with states worse than death – negative utilities) while DALYS are forced to a range 1 = death and 0 = perfect health. Can DALYs capture states worse than death (i.e. greater than 1)?

My questions are:

(a) 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.
(b) 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?
(c) 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?
(d) 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?
(e) 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?
(f) Had you considered, if this is a disease specific measure, of developing a needs fulfillment instrument utilizing Rash Measurement Theory [see Bond T and Fox C. Applying the Rasch Model 3rd Ed 2015] to assess response to therapy for competing interventions?

I look forward to you responses (and please don't just refer me to papers; I am sure other readers would appreciate a response).

Yours sincerely

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PCNA
PREVENTIVE CARDIOVASCULAR NURSES ASSOCIATION

December 11, 2020

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Public Comment – Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value Draft Evidence Report, November 12, 2020

Dear Dr. Pearson,

The Preventive Cardiovascular Nurses Association (PCNA) is the premier nursing organization that promotes nurses as leaders in cardiovascular disease prevention and management. Through education and advocacy, PCNA works to create current and improved patient care systems, increase access and compliance to treatments, enhance health and quality of life for those at risk of heart attack and stroke, and reduce death and disability from cardiovascular disease. PCNA welcomes the opportunity to comment on ICER's *Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value* Draft Evidence Report, November 12, 2020.

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.[1] Herterozygous familial hypercholesterolemia effects 1 in 250 people.[2] It is estimated 92.8 million adults have elevated serum total cholesterol levels.[3] 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.[4] Restricting access to effective non-statin treatments limits patients' ability to improve quality of life and reduce ASCVD risk.

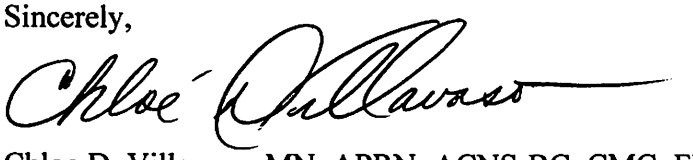
Disparities in the rates of cardiovascular disease and death among minorities continue to plague our country. The decrease in heart disease seen in Whites has not been demonstrated in Blacks, Hispanics, and Asians.[5] Taking these facts into account, PCNA feels strongly that access to safe and effective 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.[6,7] This supports the argument that limiting access to effective treatments would not promote equity in the treatment of cardiovascular disease.

Lastly, individuals of low socioeconomic status are disproportionately affected by cardiovascular disease and elevated cholesterol.[8,9] To ameliorate this disparity, the available cholesterol-lowering medications should be accessible to all patients who can benefit from their effects.

PCNA appreciates ICER's thorough review of bempedoic acid and inclisiran. We thank you for the opportunity to provide commentary on this very important matter.

Sincerely,



Chloe D. Villavaso, MN, APRN, ACNS-BC, CMC, FPCNA
On behalf of the Preventive Cardiovascular Nurses Association
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References:

1. American Heart Association. Cardiovascular diseases affect nearly half of American adults, statistics show. Available from: https://www.heart.org/en/news/2019/01/31/cardiovascular-diseases-affect-nearly-half-of-american-adults-statistics-show, Accessed on 27 November, 2020.

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December 11, 2020

Dear Steven:

I hope all is well with you and your family during this most challenging time. I am writing today to share a few comments regarding your recently released Draft Evidence Report. I know you will be hearing from many clinicians and societies as we are all very concerned that another PCSK9 inhibitor debacle might be in our future. Your voice is very powerful, and I am hopeful that your final document will reflect and fairly apply to real world patients. After all, they are the ones who will be at the receiving end of either easy and appropriate access to these medications or the opposite.

I am most concerned about some of your assumptions as they will clearly influence your findings. In your model, 100% of patients are on both a high intensity statin and ezetimibe. Most real-world studies show quite a different picture. A 2019 American Heart Association poster by Nehar Desai, MD showed that only 44% of patients one year out from an MI were taking high intensity statins[1]. 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[2]! 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[3]. Getting payers to approve and then pay for such medications is a real issue that must be considered when you build your model. Further, regarding the assumption that real world very high-risk patients have an average LDL-C 88.8 mg/dL we only need look again at FOURIER to see this cannot be so. The superbly treated patients in this study had a baseline median LDL-C of 92 mg/dL. Finally, there is ample evidence that your assumptions that

MACE is only 5.06/100 patient years and statin intolerance prevalence is only 10%, are also gross underestimates among real world patients.

The crux of this matter is that your findings will ultimately greatly influence the care of real patients. Personally I have treated high risk patients who experienced strokes and MIs after being wrongfully denied PCSK9 inhibitors. Additionally, we have published that adverse outcomes do indeed occur more frequently among high risk patients who are denied PCSK9i[4]. In 2015 and beyond, payers ran with your PCSK9i findings and left no holds barred in constructing obstacles for patient access to these vital drugs. I am afraid we will have similar matters to confront if your current assumptions are used when you model cost effectiveness of these novel lipid lowering therapies. I beseech you to reconsider your estimates and make them more consistent with real world data. Thank you in advance for your consideration.

Wishing you well,

Seth J. Baum, MD, FACC, FAHA, FNLA, FASPC

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