August 22, 2018

Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston MA 02109 USA

RE: ICER Draft Scoping Document on Canakinumab for Atherosclerosis

Dear ICER Review Team:

Merck thanks ICER for the opportunity to review the draft scoping document on canakinumab for atherosclerosis. In this letter, we would like to provide our comments on the document, with a focus on its last section, Identification of Low-Value Services.

Merck appreciates ICER’s efforts to identify information on wasteful or lower-value care. Inclusion of this information in ICER reports will greatly benefit policy makers and other stakeholders who have been seeking solutions to the inefficiency issues in the health care system. Reducing or eliminating wasteful or low-value care will help alleviate the financial stress on the system and make budgetary headroom for high-value innovative drugs and other services.

In support of ICER’s efforts, below we list some wasteful care in the area of cardiovascular disease management that Merck has identified based on a rapid literature review. We also provide the rationales, including the references, for the categorization. We are hoping this information is helpful for ICER to discuss wasteful and low-value care in the canakinumab review.

<table>
<thead>
<tr>
<th>Wasteful care and references</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Inappropriate use of percutaneous coronary intervention (PCI) ¹</td>
<td>Approximately 600,000 PCIs are performed in the United States each year, at a cost that exceeds $12 billion. Although nearly all acute PCIs can be classified as appropriate, 12% of the procedures performed for non-acute indications (28.9% of the total PCI cases) are seen as inappropriate, with substantial variation in clinical practice across hospitals. Patients who undergo PCI are exposed to risks of periprocedural complications, longer-term bleeding, and stent thrombosis.</td>
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Misprescription of medication\textsuperscript{2,3}

Inappropriate medications may be prescribed to cardiovascular patients thus increase hospitalization rates and costs of care. For instance, antithrombolytic agents maybe misprescribed to elderly patients.

Unnecessary care due to over-diagnosis\textsuperscript{4}

Over-diagnosis of otherwise healthy patients has been identified in cardiovascular and other clinical areas. The follow-up interventions due to over-diagnosis expose patients to unnecessary risks and cause significant resource waste.

Use of carotid duplex ultrasound (CDUS) test for the evaluation of syncope\textsuperscript{5,6}

Despite broad consensus in the medical literature that simple, self-resolving syncope is not caused by carotid arterial occlusive disease, numerous studies have shown that CDUS testing in syncopal patients remains common practice, even in the absence of neurological signs or symptoms of concern for stroke or Transient Ischemic Attack (TIA). $33 million to $49 million are spent annually on low-value carotid ultrasound, carotid computed tomography, and carotid magnetic resonance imaging for Medicare patients with syncope in the absence of signs of stroke or TIA.

Screening for carotid artery stenosis (CAS) of low-risk or asymptomatic individuals\textsuperscript{7}

Screening for CAS in a low-risk or asymptomatic population can result in unnecessary, harmful, and costly care. Screening for CAS among adults without symptoms may result in harm, not from the screening test itself, but from the cascade of follow-up interventions. The harms include heart attacks, bleeding, strokes, and even death.

Waste also results from sub-optimal management of cardiovascular diseases. For example, poor adherence to statin therapy has been linked to significantly increased risk of cardiovascular events and an avoidable extra care cost of $44 billion in the United States.\textsuperscript{8,9} This type of waste was not included in the table above.

\begin{table}
\centering
\begin{tabular}{|l|p{0.7\textwidth}|}
\hline
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\end{tabular}
\end{table}


\textsuperscript{3} Primejdie, D. P., Bojita, M. T., & Popa, A. (2016). Potentially inappropriate medications in elderly ambulatory and institutionalized patients: an observational study. BMC Pharmacology and Toxicology, 17(1), 38.


Again, Merck appreciates the opportunity to provide feedback on the ICER draft scoping document on canakinumab. Please feel free to contact us if you have any questions about the information we provided. We look forward to reviewing the draft report this November and providing additional feedback as needed.

Sincerely,

Fang Sun, M.D., Ph.D.
Director, Medical Policy, HTA & Value Assessment
The Center for Observational and Real-World Evidence (CORE)
Merck & Company, Inc.
August 22, 2018

Mr. Matt Seidner
Program Manager
Institute for Clinical and Economic Review
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Boston, MA 02109

Dear Mr. Seidner,

Thank you for the opportunity to provide feedback to ICER on its draft scoping document for the review of canakinumab’s ASCVD indication. 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 and Access Steering Committee and partners reviewed the draft scoping document and jointly offer the following feedback for ICER’s consideration.

**Positives:**
The Steering Committee and partners appreciate that other benefits and contextual considerations (e.g., health disparities and access to care issues) will be evaluated. They are supportive of ICER’s progress in this direction; and look forward to patient advocacy groups continuing to be involved throughout the process.

**Opportunities:**
The Steering Committee and partners identified the following opportunities for the review.

- There is a need to identify which patient groups are most likely to benefit from CVD & lung cancer death risk reduction while minimizing the harms resulting from increased risk of death from infectious causes.

- The response to therapy approach advocated by Ridker, et al.¹ (e.g., if response with hsCRP <2 mg/L then continue treatment; don’t continue treatment if hsCRP > 2 mg/L after the first injection) is flawed on-treatment analysis. It fails to account for regression to the mean of hsCRP eligibility – hsCRP is an acute phase reactant. In the JUPITER trial², 25% had hsCRP <2 mg/L during follow-up. This means the low-risk patients (hsCRP <2 mg/L) who happened to have a cold (or some other acute insult) on the day of eligibility assessment (hsCRP >2 mg/L) were still low-risk after randomization, thereby inflating the apparent effect size for CVD/mortality risk reduction from canakinumab. A re-analysis, excluding those who regressed to the mean would address this issue.

(continued)
• The draft scoping document indicates that canakinumab will be compared to the standard of care, which includes high intensity statin therapy and aspirin in patients able to tolerate those therapies. And, that ICER does not expect to be able to assess the efficacy of canakinumab in patients who are receiving a PCSK9 inhibitor in addition to statin therapy. The Steering Committee and partners think that if a drug is being added to patient care, that it would be important to determine what provides the most value, canakinumab or a PCSK9i?

• Regarding low-value services used in the current management of ASCVD, the following have been identified as being those that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services:
  o screening for atrial fibrillation with electrocardiography in asymptomatic and previously undiagnosed individuals aged ≥65 years.  
  o annual electrocardiograms or cardiac screenings in low-risk asymptomatic individuals; preoperative electrocardiograms prior to low-risk surgery, and cardiac stress testing and imaging for uncomplicated headache.

Again, thank you for your consideration. We would like to have the opportunity to bring together representatives from the Steering Committee to meet with your team to further the conversation.

Sincerely,

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

*National Forum for Heart Disease & Stroke Prevention (convener)*
Alliance for Patient Access
American Association of Heart Failure Nurses
American Heart Association
American Pharmacists Association Foundation
Association of Black Cardiologists
Association of State and Territorial Health Officials
BallengeRx Consulting
Global Healthy Living Foundation
Independent Health
Mended Hearts
National Association of Chronic Disease Directors
National Lipid Association
Partnership to Advance Cardiovascular Health
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
WomenHeart
References

Executive summary
Novartis Pharmaceuticals Corporation (Novartis) appreciates the opportunity to provide feedback on ICER’s draft scoping document for the 2018 canakinumab atherosclerotic cardiovascular disease review. In summary, Novartis respectfully offers the following suggestions for consideration:

- Patients who achieve an hsCRP <2 mg/L after three months on canakinumab should be used as the base-case population in comparative value analyses.
- Clarity around how hsCRP reductions will be incorporated into comparative value model framework is needed.
- The clinical efficacy of canakinumab, relative to standard of care, should be derived from the CANTOS trial only.
- The list of clinical outcomes and events considered should be consistent with those observed in the CANTOS trial.

We further elaborate on each of these suggestions below.

Patients who achieve hsCRP <2 mg/L after three months on canakinumab should be used as the base case population in comparative value analyses.
Novartis strongly encourages ICER to consider patients who achieve an hsCRP < 2 mg/L after three months on canakinumab to be the base case population in the comparative value analyses. Targeting treatment to patients most likely to benefit from a treatment represents the core of personalized medicine. Clinicians and payers will very likely focus on this patient population to achieve the greatest benefit/risk profile and value for patients who continue treatment with canakinumab.

Novartis conducted a pre-specified secondary analysis of the CANTOS trial to better understand the link between canakinumab, hsCRP reductions, and cardiovascular outcomes. Given canakinumab’s mechanism of action and the established evidence that hsCRP is prognostic of cardiovascular risk, additional analyses were conducted to examine the relationship between hsCRP reductions and cardiovascular outcomes, taking into account other patient characteristics at baseline.

Further exploration of the data as published by Ridker et al. 2018 showed that trial participants that were randomized to any canakinumab arm and achieved on-treatment hsCRP concentrations <2 mg/L at three months had a 25% reduction in risk of major adverse cardiovascular events. [10] On the other hand, no statistically significant reduction in major adverse cardiovascular events was observed among those with on-treatment hsCRP concentrations of ≥2 mg/L at 3 months (i.e., 95% hazard ratio contained 1.0).[10] Although this particular analysis was post-hoc in nature, it was a natural outgrowth of (i) the pre-specified analyses described above and (ii) the trial inclusion criteria whereby only patients with hsCRP >2 mg/L (i.e. evidence of elevated inflammatory risk) were enrolled in the trial. Consequently, we believe that this analysis provides robust evidence that patients whose hsCRP level decreased from ≥2 mg/L to <2 mg/L at 3 months are most likely to derive the greatest benefit from continued treatment with canakinumab, and that this population should serve as the base case for ICER’s canakinumab value assessment.

Despite the need to treat any unplanned subpopulation analysis cautiously, the consistency of the improved outcomes across various endpoints and the individual components (and even other
methods of analysis [10]) strongly supports the reliability of the on-treatment hsCRP analyses i.e. among patients achieving hsCRP<2mg/L at 3 months.

Furthermore, the post-hoc analysis was from a large, well-conducted study with internal consistency of the results across endpoints. Analyses resulting from new findings in this setting can provide scientifically important and clinically relevant information.

Clarity around how hsCRP reductions will be incorporated into the comparative value model framework is needed.

Novartis recommends that the critical role of hsCRP reduction, as the key biomarker indicative of canakinumab’s efficacy, be made explicit in ICER’s modeling framework. Canakinumab is a selective, high-affinity, human monoclonal antibody which reduces inflammation in atherosclerosis through selective inhibition of the IL-1β, a prime driver of inflammation and CVD risk.[11-14] Canakinumab has been shown to significantly reduce hsCRP levels, [12] with decreases in hsCRP observed within four weeks of initial administration. [15] In addition, canakinumab is the only medication that has demonstrated reduction in inflammation among post-myocardial infarction patients with elevated levels of hsCRP.

Further, a more detailed description of the modeling framework and the inputs to be used for the comparative value analysis is needed. The draft scoping document states that a de novo state-transition Markov model will be developed for this analysis, but key inputs will be informed by the published literature as well as ICER’s prior work on simulation modeling of ASCVD. More clarification and transparency is needed on the modeling framework as well as the source of the inputs into the model, in particular how the risk of major adverse cardiovascular events is associated with higher baseline hsCRP levels and post-treatment initiation hsCRP reduction will be used within this modelling framework. Novartis is willing to share learnings and provides necessary information as needed.

The clinical efficacy of canakinumab, relative to standard of care, should be derived from the CANTOS trial only.

Novartis recommends that only the CANTOS clinical trial be used to evaluate the clinical efficacy of canakinumab, relative to standard of care.[12] Although the draft scoping document indicates that the clinical efficacy of canakinumab will be compared to standard of care (including high intensity statins and aspirin), it also states that evidence on intervention effectiveness and adverse events will be derived from studies of at least one year and at least three months duration, respectively. However, canakinumab is the only agent that has demonstrated a reduction in inflammation, as assessed by reductions in hsCRP, independent of lipid lowering, resulting in decreased cardiovascular morbidity and mortality in post-myocardial infarction patients with elevated hsCRP. Hence, there are methodological challenges in conducting a network meta-analysis since (i) the patient populations in statin and aspirin clinical trials are different from the patients included in canakinumab trials, and (ii) hsCRP levels – a key inclusion criteria for the CANTOS trial [12], as well as an intermediate outcome in ICER’s proposed analytic framework – are rarely measured in statin and aspirin clinical trials. Further, given that there are no other available anti-inflammatory agent for atherosclerosis, any other data on hsCRP levels would not be suitable for inclusion into this review. The rate of hsCRP testing in routine practice is currently very low, likely due to a lack of any available effective therapy in managing elevated hsCRP. Therefore, current real world data may not be reflective of the post-MI population of
CANTOS.[16] Similarly, treatment effectiveness and the rate of adverse events for the comparative value analyses should be derived exclusively from the CANTOS trial data.

In addition, it should be noted that the vast majority of participants in the CANTOS trial received standard of care in both the placebo arm and the three canakinumab treatment arms. At baseline, antithrombotic agents were taken by 95.0% of patients, lipid-lowering agents by 93.4%, anti-ischemia agents by 91.4%, and inhibitors of the renin angiotensin aldosterone system by 79.7%. Hence, patients were well managed in reference to cardiovascular risk factors, including treatment with anti-hyperlipidemic and antihypertensive medications.[12]

**The list of clinical outcomes and events considered should be consistent with the CANTOS trial.**

Novartis recommends that the clinical outcomes considered in the scoping document be the same as those observed in the CANTOS trial. For consistency and a comprehensive evaluation of canakinumab’s clinical profile, lung cancer, osteoarthritis, and gout should be included in ICER’s analysis. The CANTOS trial measured cancer mortality as an adverse event, for which participants who received canakinumab had a significantly lower incidence compared to the placebo group (p=0.02).[12] An additional analysis, which investigated the effect of canakinumab on cancer incidence, found that incident lung cancer was significantly less frequent in the canakinumab 150 mg group, compared to placebo (hazard ratio (HR) 0.61 [95% CI 0.39-0.97]; p=0.034).[17] Canakinumab also significantly decreased the incidence of gout and osteoarthritis, compared to placebo (p<0.001).[12]

More broadly, Novartis recommends that the reporting and labeling of events be consistent with the CANTOS trial. Specifically, Novartis recommends the inclusion of the following clinical outcomes in the comparative value analysis:

- Incidence of non-fatal MI
- Incidence of non-fatal stroke
- Cardiovascular death
- Non-cardiovascular death
- Coronary revascularizations procedures (planned and unplanned)
- Incidence of lung cancer
- Incidence of gout
- Incidence of osteoarthritis
- Incidence of serious infections

Further, some of the events listed in Table 1.2 of the draft scoping document were either not reflected in Figure 1.1 or were labelled differently. The reporting and labelling of events should be consistent throughout the scoping document for clarity.

Novartis appreciates ICER’s consideration of the enclosed comments, and is open to further discussions to support ICER’s effective assessment of canakinumab in atherosclerosis.
References