



March 24, 2020

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

Re: Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Evidence Report

Dear Dr. Pearson,

On behalf of the 30,000 individuals living with cystic fibrosis in the United States, we write to provide public comment on the *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Evidence Report*. These disease-modifying therapies are transformative and represent tremendous potential to benefit people with CF by altering the course of cystic fibrosis. We appreciate that ICER incorporated several important points of feedback we provided during the review process; however we continue to have serious reservations about the model ICER used to generate this assessment. In its final report, the CF Foundation urges ICER to better characterize the potential benefit of long-term modulator use and the limitations of the economic model to capture this benefit; better reflect the impact of this chronic life-threatening disease on daily life; and highlight the limitations of the model in capturing the complexity and heterogeneity of CF.

Modulators mark a significant advancement in cystic fibrosis treatment

As noted in the draft report, modulator therapies “substantially improve patient outcomes” when added to best supportive care. These treatments are the first to target the underlying defect in the CFTR protein caused by specific mutations of the *CFTR* gene. Although each available modulator provides clinically significant benefits to people with cystic fibrosis who are eligible, two modulator drug products — ivacaftor (Kalydeco®) and elexacaftor/tezacaftor/ivacaftor (Trikafta™) — demonstrate such a high magnitude of treatment benefit that CF clinical experts consider them “highly effective modulator therapies” (HEMTs). HEMTs demonstrate dramatic benefits compared to existing therapies across key clinical outcome measures including lung function, growth, risk of pulmonary exacerbations, sweat chloride concentrations, and quality of life. Given the individualized nature of cystic fibrosis, CF clinicians, in consultation with patients, are best positioned to determine which treatment will be most effective for each individual.

Potential benefits from long-term and early initiation of CFTR modulators

Short of a cure for cystic fibrosis, modulators have the potential to dramatically alter the course of this chronic, life-shortening disease, particularly for those who start treatment at a young age. People with CF who start modulator treatment at a young age may be able to restore CFTR protein function to normal levels, thus preventing organ damage, halting the progression of the disease and avoiding future damage. An early start on modulators could have long-term benefits in sustaining health by 1) reducing the rate of lung function decline through prevention of

structural damage to the lungs; and 2) improving nutrient absorption and weight gain through preservation of exocrine pancreatic function and normalization of intestinal pH. For these people, we anticipate a life span that approximates that of the general population. Additionally, we anticipate that eventually most, if not all, of the cost associated with current “standard of care” treatments can potentially be eliminated. While studies focused on examining the impact of early initiation of modulators are underway, we urge ICER to incorporate the potential benefit of early use of these therapies in the relevant sections of the report.

Long-term and real-world data are not yet available for several of these therapies, seriously limiting the utility and reliability of the report

The first CFTR modulator, ivacaftor, became available to patients in January 2012, with the most recent approved therapy, elexacaftor/tezacaftor/ivacaftor, receiving U.S. Food and Drug Administration (FDA) approval in October 2019. ICER’s review of CFTR modulators so close to the approval date does not allow enough time to collect sufficient data to support a lifetime economic model. Without long-term data, these therapies might be significantly undervalued in ICER’s economic model. Although we appreciate ICER’s recognition of this limitation in the draft report, we are nonetheless concerned that the results of the economic modeling may be incorrectly interpreted or used by payers, the public, and other stakeholders.

It is also important to note that ICER’s decision to only include studies that have at least 100 participants disregards additional meaningful data. This participant threshold is unreasonable for a rare disease population. Given that each of the three therapies evaluated by ICER is under the rare or ultra-rare condition framework, the high participant threshold for included studies limits the data that contributed to this report.

There is a concerted effort underway in the CF research community to understand the long-term and real-world impacts of modulators on health status, quality of life, health care resource utilization, and other factors. The Cystic Fibrosis Foundation is sponsoring several studies – randomized clinical trial as well as real world research – to evaluate the safety of withdrawing symptomatic treatments, such as dornase alfa, among individuals taking elexacaftor/tezacaftor/ivacaftor. Results from these studies may impact the findings of ICER’s report. For more information on these studies, please see the CF Foundation’s [Research We Fund Highlights Report](#).

Model limitations

Several of the remaining assumptions and data inputs, or lack thereof, impose significant limitations to the model. Below, we highlight discrete aspects of this model that do not accurately reflect the value of CFTR modulators.

Quality-adjusted life years should not be the primary health outcome measurement

We would like to again express our concerns about the use of quality-adjusted life-years (QALY) as the primary measure of the cost-effectiveness analysis as QALYs do not account for patient-reported outcomes. We appreciate that ICER acknowledges such limitations and has included additional health outcome measurements such as life years (LYs) and equal value life years gained (evLYGs). However, the lack of patient relevant information in these models cannot be overstated. Furthermore, the QALY looks solely at longevity. The length of life for a person with

CF is determined primarily by the degree and decline of lung disease; therefore, by definition, this endpoint disregards all benefits outside of FEV₁. QALYs cannot adequately inform coverage decisions or value assessments as they exclude patient experience and other benefits outside of lung function, thus severely limiting this model.

Inappropriate data inputs

As we have stated previously, the costs derived from Lieu et al. and Ouyang et al. are not valid estimates for current standard of care. These papers are outdated and should not be generalized in the model. Further, while only utility scores by ppFEV₁ are available, we know that modulators have clinical and quality of life benefits beyond lung function. The utility values derived from Schechter et. al are not an adequate measure for modulator therapies as these were developed for use with inhaled antibiotics and are mediated through FEV₁.¹ This approach does not account for the clinical and quality of life data necessary for evaluating modulators, which have impact beyond the lungs, thereby imposing significant limitations to the model.

Additionally, the use of cost data from different types of payers (private vs. public) for disease management and lung transplant costs poses a noticeable limitation. Costs for private and public payers vary significantly for health care services and therapies. Using a mixture of Truven data and Medicare-specific numbers in the same model causes the resulting cost of CF to be incomparable to what is seen in the real-world and biases model outputs.

Chronic therapy outcomes should not be discounted 3% per year

We disagree with the application of a three percent annual discount rate on health outcomes. This discount rate assumes that one year of life today is valued higher than a year of life in the future. This assumption is philosophical in nature and not grounded in patient experience. While we appreciate the addition of undiscounted scenarios in the Appendix, we have concerns with the use of this discount in the base-case as that is not an appropriate perspective when evaluating chronic disease-modifying therapies.

Lack of long-term data

The timing of this review, and therefore the model, does not account for the anticipated long-term benefits of modulators. As experts in the pathophysiology of CF, we believe that early initiation and long-term use of modulators will have profound implications, altering the course of this disease by preventing downstream disease sequelae including loss of exocrine pancreatic function, structural damage to the lungs, risk of CF liver disease and failure, and CF-related diabetes, which in turn, will have a profound effect on costs to the patient and the system.

Societal outcomes must be better incorporated into the report.

We thank ICER for expanding their outreach to the CF community and their increased diligence in adding the patient perspective to the report. However, ICER has demonstrated that there is no process to incorporate critical patient-reported outcomes or the patient and caregiver experience into the economic model. This is a failing of the model, and thus will create a report that is not inclusive of the true impact of these therapies. As you have heard from people with CF, families, caregivers, and clinicians, CFTR modulators have great potential to dramatically change the trajectory of this disease and, more importantly, individual lives.

Lumacaftor/ivacaftor and tezacaftor/ivacaftor access remain important treatment options

Access to lumacaftor/ivacaftor and tezacaftor/ivacaftor remains essential, though they are not considered HEMTs. These treatments are important therapeutic options for people with CF, especially for young children not yet eligible for elexacaftor/tezacaftor/ivacaftor per the FDA label. Further, the clinical impacts of CFTR modulators vary person-to-person and having multiple treatment options available is imperative to extend disease-modifying treatment to as many people with CF as possible. Ultimately, CF clinicians, in consultation with their patients, are best positioned to determine which treatment will be most effective for each individual.

Coverage policy landscape of CFTR modulators

We appreciate ICER's attention to coverage policies for CFTR modulators as the value of these therapies is only realized if patients can access them. While many of the plans reviewed in ICER's evidence report provide coverage aligned with the FDA's label, there are multiple plans included that have implemented more restrictive coverage criteria. Many of these criteria are clinically inappropriate, administratively burdensome, and create unnecessary barriers to access. ICER's previous report on CFTR modulators stated that "public and private payers should continue to affirm their commitment to provide access to important clinical advances for CF and should remove superfluous requirements for coverage approval and continuation."ⁱⁱ This statement from ICER's earlier analysis summarizes these important facts and should be included in the current report.

Finally, we would like to stress that this report should not be the only source of data used by payers to determine coverage decisions. Although cost-effectiveness analyses can be informative, they must be used carefully and as part of a holistic evaluation of the value a treatment provides.

Thank you again for the opportunity to comment on the draft report.



Bruce C. Marshall, MD
Chief Medical Officer
Executive Vice President of Clinical Affairs



Mary B. Dwight
Chief Policy & Advocacy Officer
Senior Vice President of Policy and Advocacy

ⁱ Schechter MS, Trueman D, Farquharson R, Higuchi K, Daines CL. Inhaled aztreonam versus inhaled tobramycin in cystic fibrosis. An economic evaluation. *Annals of the American Thoracic Society*. 2015;12(7):1030-1038.

ⁱⁱ Balk E, Trikalinos T, Kuntz K, et al. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Final Evidence Report and Meeting Summary. Boston, MA: Institute for Clinical and Economic Review; June 7 2018