



April 12, 2018

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 (CF) 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 transformational and represent tremendous potential to alter the course of cystic fibrosis. We are pleased to see the report incorporates several important points of feedback we provided throughout the development of the report. We look forward to further improvements following this public comment period, particularly better characterizing the potential benefit of long-term modulator use, the impact of this chronic life-threatening disease on daily life, and the limitations of the model in capturing the complexity and heterogeneity of CF.

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

As noted in the draft report, modulator therapies “substantially improve patient outcomes” when added to best supportive care. The development of cystic fibrosis transmembrane conductance regulator (CFTR) modulators marked an important milestone in CF care. These treatments are the first to target the underlying defect in the CFTR protein caused by specific mutations of the *CFTR* gene. Short of a cure for CF, modulators have the potential to dramatically alter the course of this disease, particularly for those who start treatment at a young age. For such patients we anticipate a life span that approximates that of the general population with most, if not all, of the costs associated with current “standard of care” treatments potentially eliminated. An early start on modulators could have long-term benefits in sustaining health: 1) by 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 pancreatic exocrine function. While research on the impact of starting modulators early in life is underway, we urge ICER to fully acknowledge the potential benefit of early use of these therapies in examining their value over a lifetime in the report’s introduction, other benefits and contextual considerations section, and model assumptions.

Differences between lumacaftor/ivacaftor and tezacaftor/ivacaftor

The draft evidence report notes that for individuals with two copies of the *F508del* mutation there is “no material difference in key clinical outcomes” for tezacaftor/ivacaftor versus lumacaftor/ivacaftor. However, real world experience with lumacaftor/ivacaftor and clinical trial results for tezacaftor/ivacaftor suggest important differences that can affect health outcomes. Of

note, tezacaftor/ivacaftor is associated with fewer adverse events and drug-drug interactions compared to lumacaftor/ivacaftor. Tezacaftor/ivacaftor is a treatment option for those who could not take lumacaftor/ivacaftor due to chest tightness or drug contraindications such as oral contraceptives. The improvement in tolerability and reduction of drug-drug interactions represent a significant opportunity for individuals to benefit from modulators.

Coverage policy landscape of CFTR modulators

We appreciate ICER's attention to coverage policies for CFTR modulators as the value of these drugs is only realized if patients can access them. The draft evidence report notes that modulator coverage typically involves prior authorizations that require documentation of specified starting age and *CFTR* mutations which reflect the label approved by the Food and Drug Administration (FDA). However, while the three plans ICER reviewed may provide coverage aligned with the FDA's label there are a number of plans that have implemented more restrictive coverage criteria. In some cases, these criteria are clinically inappropriate, administratively burdensome, and create barriers to access. Some examples include:

- Use of clinical trial participation criteria to justify coverage exclusions: public and private payers cite lack of evidence that drugs work for populations excluded from trials despite the FDA's determination that the drug is safe and effective for anyone with an approved mutation;
- Increased frequency of reauthorization: payers asking repeatedly for patient's mutation, which does not change over time; and
- Requirements to be on other symptom-directed therapies as a condition of coverage without regard to the patient's unique treatment regimen or medical needs.

It is also important to note that, as we look ahead, payers should take extreme caution when considering policies that prefer use of one modulator over another. Cystic fibrosis care is complex as providers consider a multitude of factors when prescribing treatment, therefore, clinician discretion and expertise should be upheld.

Model limitations

We are pleased to see the initial economic model has been revised to include both ppFEV₁ and past pulmonary exacerbations as predictors of future pulmonary exacerbations. We recognize that not all available evidence is suited for this model. However, several of the remaining assumptions and data inputs, or lack thereof, impose significant limitations to the model. 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. Finally, echoing our statement above, the model does not yet 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 structural damage to the lungs and preserving pancreatic exocrine function.

Accredited cystic fibrosis care centers

The cystic fibrosis Care Center Network is made of over 120 accredited care centers specializing in the treatment of CF. Nearly 85% of people with CF in the United States receive care at an

accredited center. Care centers deliver multidisciplinary, evidence-based care, conduct clinical research, and maintain continuous quality improvement programs. This high-quality, specialized approach to care has improved survival for people with CF.¹ CF centers focus on addressing lung function, nutritional status, airway microbiology, and other comorbidities that affect survival. While coordinated multidisciplinary care has greatly improved mortality, clinical care alone has not been able to significantly affect morbidities such as reducing pulmonary exacerbations. Therefore, clinical care in addition to CFTR modulators provide people with CF the greatest opportunity for maintaining health. We recommend ICER include these points in the *Controversies and Uncertainties* section.

Identifying low value services

We appreciate ICER's interest in identifying low value services in CF care that arise from modulator treatment. Clinical guidelines developed by multidisciplinary and independent committees² provide population-level guidance on respiratory, nutrition and GI, modulator use, and other areas of CF care. Modulator therapies are currently intended to complement existing best practices, but CF Patient Registry data shows that some standard-of-care therapies have been discontinued. To keep up with the evolving treatment landscape, randomized withdrawal studies are being planned to help inform possible changes to the current CF care regimen.

Thank you again for the opportunity to comment on the draft report. Please note that we have included some line edit suggestions in an appendix to this letter. We look forward to the revised report and discussion at the public meeting in May.

Thank you,

Preston W. Campbell, III, MD
President and Chief Executive Officer

¹ Mogayzel, et Al. *Improving chronic care delivery and outcomes: the impact of the cystic fibrosis Care Center Network*. BMJ Qual Saf 2014 Apr; 23 Suppl 1:i3-8.

² Sponsored by the CF Foundation

Appendix

Page 1, Pathogenesis: Clarify that while approximately 300 *CFTR* mutations have been fully characterized, the majority of the 1,800 mutations identified are known to be associated with a CF phenotype. Need to correct 7th sentence: 87% of people with CF have at least one copy of the *F508del* mutation (these individuals may be heterozygous OR homozygous) and 46% of patients are homozygous for the *F508del* mutation (this is a subset of the 87%).

Page 2, Pathogenesis: Suggest revising “pulmonary toilet” to “pulmonary treatment.” *Streptococcus pneumoniae* is not an appropriate example when discussing initial infections that lead to CF pulmonary exacerbations.

Page 3, Diagnosis: Clarify that early diagnosis leads to early treatment and therefore improved health outcomes; as written, the text neglects to connect early diagnosis and early treatment.

Page 4, Management: Suggest adding “historically” to the beginning of the first paragraph. The addition of *CFTR* modulators to the CF treatment arsenal means clinicians are not solely trying to control symptoms, but rather are correcting basic protein defects causing symptoms. Suggest changing “chest physiotherapy” to “airway clearance” as this includes chest physiotherapy as well as commonly used airway clearance devices.

Page 5, CFTR modulator drugs: Sentence 4 should be edited to read “For example, patients who are homozygous for class I mutations cannot respond to modulator treatments because there is no *CFTR* protein to be modulated.”

Page 8, Clinical outcomes: Pancreatitis and infertility are clinical manifestations of CF, but not common endpoints in clinical trials.

Page 9, adverse events: Sweat chloride and fecal elastase provide evidence that modulators are addressing the basic defect of CF; for what reason were these excluded?

Page 12, Insights Gained: Suggest saying “airway clearance” rather than “airway hygiene.”

Page 15, Cystic Fibrosis Foundation guidelines: To help inform the standard of care delivered at accredited care centers, the CF Foundation brings together committees of subject matter experts to write guidelines on topics related to the care of people with cystic fibrosis. The Foundation acts as a facilitator for the development of guidelines and does not independently develop them.

Page 15, Respiratory Care Guidelines: “Tobramycin” is misspelled. Dornase alfa is recommended for patients at all stages of the disease, not only individuals with severe disease.

Page 16, Pulmonary Exacerbations: Guidelines recommend daily dosing of *intravenous* aminoglycosides during exacerbations. Further, in guidelines, “not recommended” is not equivalent to a decree that a certain treatment or treatment regimen is never indicated; it only

alludes to a lack of evidence to make a formal recommendation. Home IV treatment is often used and is an important option in certain circumstances.

Page 29, Pulmonary Exacerbations: Regarding the KONNECTION study, as we mentioned in previous comments, 8 weeks is likely too short a timeframe to capture exacerbations.

Page 39, Table 3.8: Remove negative sign in -0.0.

Page 42, Clinical benefits of tezacaftor/ivacaftor in individuals heterozygous for the *F508del* mutation: To clarify, this title refers to individuals included in the clinical trial and differs from the FDA label indication. On the FDA label, tezacaftor/ivacaftor is indicated for individuals heterozygous for an indicated residual function mutation regardless of the second mutation.

Page 49: Regarding day-to-day fluctuation in lung function, these factors should be equally distributed in a placebo-controlled trial across the arms and therefore should mitigate concerns about fluctuations. For patients that experienced lung function decline, it is difficult to be certain if an individual's decrease in lung function is causally related to the modulator or coincidental. Regarding the expansion of access to accredited CF care centers, clinical trials were conducted in many of the highest quality care centers, so it is unclear why an unanswered question about access to care centers being as impactful as modulator therapy is posed.

Page 56, Table 4.1: The assumption that best supportive care is the same in all treatment arms is questionable, especially in young patients, as this may underestimate the effect of early treatment and prevention of disease.

Page 57, Clinical Inputs: It is assumed that people with lung functions above 30% ppFEV₁ have a 0% chance of lung transplantation, which is not true. Some individuals do receive a transplant with lung function above 30% ppFEV₁.

Page 76, Other Benefits: Per our comment letter, this section should be greatly expanded and note the long-term potential of modulating therapies, especially for children who begin treatment young.