



October 21, 2019

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 Background and Scope

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 Background and Scope*. We appreciate the opportunity to help incorporate the patient and clinical perspectives during this process.

Modulators mark a significant advancement in the treatment of cystic fibrosis.

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that result in the absence or malfunction of the CFTR protein. Decreased CFTR function causes progressive pulmonary and gastrointestinal disease that result in early death, usually by respiratory failure.

CFTR modulators, a class of CF drugs which encompasses the four drugs in this proposed scope — ivacaftor monotherapy, lumacaftor/ivacaftor combination therapy, tezacaftor/ivacaftor combination therapy, and elexacaftor/tezacaftor/ivacaftor triple combination therapy — are designed to correct specific defects in the CFTR protein. Modulators are the only treatments available that address the underlying cause of CF rather than alleviating the symptoms or addressing clinical manifestations of the disease. Modulator therapies are mutation-specific because different mutations lead to different defects in the protein. Research is rapidly evolving in this therapeutic area and has presented tremendous opportunity for new and existing modulators to benefit individuals beyond those currently indicated.

The scope of this review should be narrowed to elexacaftor/tezacaftor/ivacaftor.

The CF research community has continued collecting and publishing additional studies on the long-term impact of these drugs on patients eligible to take them. However, it is unlikely these additional data will significantly change ICER’s findings from last year on ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor. We recommend focusing the scope of this review on the new elexacaftor/tezacaftor/ivacaftor triple combination therapy.

Further, in the absence of data outside the clinical trial for the triple combination therapy, we advise reviewers to focus on studies of ivacaftor to best understand the long-term outcomes patients are likely to experience on elexacaftor/ivacaftor/tezacaftor. These two treatments can both be considered “highly effective modulator therapies” (HEMTs) and thus ivacaftor is the closest comparator to the triple combination modulator.

ICER should consider reviewing elexacaftor/tezacaftor/ivacaftor using the ultra-rare condition framework.

The scoping document asserts that the triple combination therapy “has the potential for use in 90% of all patients with CF.” To clarify, the introduction of the triple combination therapy to market will increase the number of people with CF benefitting from a HEMT to approximately 90%. However, not all of these individuals will be eligible for or prescribed the triple. The CF Patient Registry can be used to help estimate eligible populations.

It is also important to recognize the initial Food and Drug Administration (FDA) label for elexacaftor/tezacaftor/ivacaftor is limited to persons 12 and older.

Intervention and comparison populations that are heterozygous for the *F508del* mutation and residual function mutation must be clarified.

In both the Intervention and Comparative Analysis sections, the document notes that Population 3 (people with CF who are heterozygous *F508del* and residual function mutation) will be eligible for all four modulators. This is not correct. This population is not eligible to take lumacaftor/ivacaftor based on the FDA label. ICER should remove lumacaftor/ivacaftor from the scope of the analysis for this population.

Additionally, for Population 3, ICER states that the analysis will use “reasonable assumptions” to model the triple combination therapy. Please define what assumptions will be used in this modeling. As stated earlier, we recommend focusing on studies of ivacaftor monotherapy to reflect the long-term outcomes patients will likely realize on the triple combination modulator.

Please clarify how evidence will be used within the comparators section.

The scope of this review indicates ICER will potentially utilize studies outside of randomized control trials (RCTs). Please define how reviewers intend to address confounding by indication: specifically, for the cases where those who are prescribed a modulator are less healthy than those not prescribed the therapy.

Consider updating the Outcomes section.

We propose adding sweat chloride as an intermediate outcome as it is directly associated with many of the key outcomes identified. Further, please clarify what health-related quality of life measure will be used; we recommend using the CFQ-R respiratory domain, a validated instrument for use in cystic fibrosis.

Consider removing liver transplant from the Other Outcomes as it is a rare event: there were 22 patients with CF that received a liver transplant in 2018.¹ Within this same section, we appreciate the recognition that patient-reported outcomes and patient experience data are important components of value. However, we reiterate our comments from previous letters that ICER is conducting this review without ample long-term or patient experience data for several of these drugs. Given that data collection is still underway, ICER should recognize and note in the assessment that there will be significant limitations in this analysis.

Liver function and injury should be added to the Adverse Events list as modulators have the potential to negatively impact the liver. There is no current data on the impact of the triple combination therapy on liver function. Nevertheless, we recommend this adverse event be included in the analysis due to the potential impact on people with CF.

Finally, we recommend the following wording changes to improve the clarity of the following outcomes:

- *Pill burden and correlation to adherence with medication regimen*: we recommend changing this to “treatment burden,” perhaps in hours or minutes per day. Daily CF treatment not only includes a number of pills, including pancreatic enzyme replacement therapy with every snack and meal, but also nebulized treatments and airway clearance therapy. Of note, treatment burden can also include the time spent cleaning and maintaining devices. For example, components of nebulizers must be changed after each use.
- *Pseudomonas colonization*: we recommend changing this to “Pseudomonas infection.”

The analyses would be strengthened with the inclusion of additional scenarios.

Given the progressive nature of CF, the point at which a patient initiates modulator therapy can significantly impact clinical outcomes realized by that patient. For example, ivacaftor can be taken by children as young as 6 months old (prior to the development of lung disease and possibly prior to the development of irreversible pancreatic dysfunction) whose disease will not have progressed as much as an adult with the same mutation. We recommend including additional scenarios beyond the lifetime time horizon model that better reflect this.

We appreciate ICER’s use of measures other than the QALY to quantify benefit.

The use of quality-adjusted life-years (QALY) as the primary measure of the cost-effectiveness analysis is concerning as QALYs do not account for patient-reported outcomes. We appreciate that ICER will acknowledge such limitations under the framework for ultra-rare diseases and is incorporating the equal value life years gained (evLYG) as an additional effectiveness measure.

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 committeesⁱⁱ 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 and real-world withdrawal studies are underway or being planned to evaluate the feasibility of withdrawal or possible changes to the current CF care regimen.

Thank you again for the opportunity to bring the CF clinical and patient community perspective forward during this review process and the chance to provide comment on *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Background and Scope*. Please contact Lisa Feng, DrPH, Senior Director for Policy & Advocacy, with any questions or concerns at lfeng@cff.org.

Sincerely,

Mary B. Dwight
SVP, Policy & Advocacy

Bruce C. Marshall, MD
SVP, Clinical Affairs

ⁱ 2018 Patient Registry Annual Data Report, Cystic Fibrosis Foundation. Bethesda, MD.

ⁱⁱ Sponsored by the CF Foundation

NANCY GURNEY

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TO WHOM IT MAY CONCERN:

I am a parent of a 16 year old daughter that has Cystic Fibrosis. We have been waiting for a miracle and the triple combo is the closest thing we have to look forward to. We ae literally counting down the days until this medication will be available. Our hope is that it will make her close to normal, if not normal, while taking the triple combo, (VX-445).

If ANYTHING slows down the process or gets in the way of making this happen, we will be DEVASTATED!!!!!! Every day gets harder and harder to get my daughter to do her two 30 minute breathing treatments every day, and not to mention the mountain of pills she must take as well. There are so many health issues that are caused by the CF that complicate the condition that much more.

We pray for this new drug and that it will be available shortly after the March 19 decision deadline for the FDA. This is the first drug available for CF patients that will be a true game changer. Orkambi is better than nothing, but it does not do all the things that the triple combo can do, mainly attacking the root problem of the disease by lowering the sweat chloride level. And in only a few short weeks!! Amazing!!

Anyone or any agency that interferes with this approval process or slows it down in any way does not understand the life and death consequences that these people with CF face. Cystic Fibrosis is one of the worst progressive diseases and there is currently no cure. VX-445 is the closest thing we have and it is imperative that this is made available to the poor people that suffer with CF.

Sincerely,

Nancy Gurney



October 21, 2019

Submitted electronically to: publiccomments@icer-review.org

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Dear Dr. Pearson:

On behalf of the Institute for Patient Access (IfPA), I thank you for the opportunity to provide comments regarding ICER's Draft Background and Scope Document titled, "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value," released September 30, 2019.

IfPA urges ICER, as part of its evaluation of the new triple therapy that adds "the novel agent elexacaftor to the combination of tezacaftor and ivacaftor," to adjust its cost-effectiveness methodology to account for the following realities with respect to cystic fibrosis:

- Cystic fibrosis imposes a significant burden on patients and caregivers.
- Cystic fibrosis is a rare disease. As has been well established in the literature, the QALY's weaknesses are amplified when evaluating medicines for rare diseases.
- With respect to rare diseases, there are no definitive studies that justify either ICER's typical cost-effectiveness threshold, or its adjusted threshold, as the appropriate benchmark for judging the cost effectiveness of a medicine.
- Due to the substantial social and economic costs imposed on patients living with cystic fibrosis, ICER's evaluation should directly include the reduction in these costs as a quantified benefit.

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

Cystic Fibrosis Is a Devastating & Multifaceted Disease

Evaluating treatments for cystic fibrosis first demands a thorough appreciation for the lifetime burden of the fatal disease. Cystic fibrosis is a progressive genetic disease affecting 30,000 people in the United States. Cystic fibrosis causes persistent lung infections, wears on other organs, and is associated with a long list of co-morbidities including pancreatic insufficiency, sinus disease, pulmonary infection, asthma, diabetes, bronchiectasis and depression.ⁱ It burdens both patients and their caregivers.

Patients living with cystic fibrosis often experience increased hospitalization rates and life-threatening complications. They can expect a shortened lifespan, as the median age of death of a person diagnosed with cystic fibrosis in the U.S. is 27 years.ⁱⁱ Living with cystic fibrosis also imposes a heavy day-to-day burden on patients. Managing the disease requires a time-consuming

daily regimen that typically includes medicines, chest physiotherapy and nebulizers.

Treating cystic fibrosis is complex, because the disease is caused by thousands of different rearrangements in a person's genetic code. The current CFTR modulators, which marked a major treatment advancement, treat only a minority of patients. Lumacaftor/ivacaftor, for example, benefits only about 40 percent of patients.ⁱⁱⁱ

By adding elexacaftor to the combination of tezacaftor and ivacaftor, the forthcoming treatment is expected to bring the proportion of treatable cystic fibrosis mutations to account for approximately 90 percent of cystic fibrosis patients.^{iv} Expanding treatment from a minority of patients to the vast majority is a major advancement that will provide tremendous value to the cystic fibrosis patient community.

QALYs Are Inappropriate for Evaluating Rare Diseases

The well-known weaknesses of the QALY methodology make it inappropriate to evaluate the cost-effectiveness evaluation of rare diseases like cystic fibrosis.

Noting these weaknesses, Pearson et al. (2018) stated that measures like QALYs “may not be sensitive to the severity of rare diseases. This may be explained by the smaller populations with severe disease and by the proportionally smaller improvements in health outcomes that in turn generate smaller QALY gains than would be the case in larger, healthier populations. In addition, the assumption that a QALY is of equal value, irrespective of indication, may not adequately reflect societal preferences for the treatment of life-limiting rare diseases.”^v

Another concern is the quality of the data. As is well known, the clinical trial data for rare diseases like cystic fibrosis are limited, as are the data on the direct and indirect cost burden. Due to these data limitations, the long-term impact on patients from the new combination therapy is uncertain. By definition, since the long-term impact is uncertain, so will be the results of the cost-effectiveness evaluation. Applying the precise QALY measurement in these circumstances creates unnecessary risks for patients' access to medicines that can improve their quality of life.

The QALY methodology raises another concern for cystic fibrosis patients. People living with cystic fibrosis have severely reduced lung function that reduces their endurance, and patients have indicated that improvements in their lung function, even if they are clinically small, can have a meaningful impact on their quality of life. QALYs are designed to undervalue improvements that may be clinically small, even if they are meaningful for patients in practice. Therefore, using the QALY methodology will likely undervalue the benefit of this treatment to patients.

The draft scoping document attempts to address these by including equal value life years gained (evLYG) measure and adjusting the dollar cost thresholds (discussed below). The evLYG measure does not overcome the weaknesses of the QALY methodology with respect to rare diseases.

Consequently, we urge ICER to adopt alternative value approaches when evaluating the cost effectiveness of the triple combination therapy. In particular, ICER should rely on condition-specific assessments for cystic fibrosis to determine the value of the combination therapy.

ICER Should Consider Adjusting the Cost-Effectiveness Threshold

The cost of developing a medicine are typically higher for rare diseases, but the patient population that can benefit from the medicine are, by definition, smaller. This combination means that the

costs of medicines that treat rare diseases will be significantly higher than those of other medicines. As a result, relying on the typical cost-effectiveness thresholds of \$50,000 to \$175,000 is likely to be inappropriate for determining whether the new triple therapy medicine is cost effective.

Recognizing these concerns, ICER will, on a case-by-case basis, consider raising the cost-effectiveness threshold up to \$500,000. With respect to this therapy, we recommend that ICER, at a bare minimum, apply this higher threshold

ICER Should Include Quantified Social and Economic Benefits into the Cost-Effectiveness Model

The economic costs for managing cystic fibrosis are high. According to the American Thoracic Society, the average cost of care for cystic fibrosis was \$48,000 in 2006, a good deal of these costs due to costs associated with hospitalization. While these are the average costs, the burden for patients diagnosed with severe cystic fibrosis can be much higher.

According to a 2011 study, the annual costs for patients with mild disease severity are \$30,000, but the annual costs incurred by patients who are diagnosed with severe cystic fibrosis are much higher – \$215,000.^{vi} Younger patients diagnosed with severe cystic fibrosis incur even higher annual costs. Patients aged 10 to 14 with severe disease severity were estimated to be as high as \$343,900.^{vii}

These costs do not capture the full burden of the disease, the impact on caregivers, the lost economic opportunities, and the costs associated with patients' shorter lifespan. To the extent that more effective treatment is able to reduce these costs, these benefits must be included in the quantitative cost-effectiveness models.

Conclusion

Not only is cystic fibrosis a devastating disease, most patients living with cystic fibrosis do not have access to an effective treatment. The results from clinical studies indicate that the addition of the new triple therapy will make treatment possible for around 90 percent of patients. The patient community is eager for this advance, and it is critical that ICER acknowledge that the value a broadly effective treatment creates for patients.

Due to the importance of this therapy to the patient community, IfPA urges ICER to account for the considerations outlined above when performing its clinical evidence review; otherwise, the review may provide an inaccurate picture of the benefits derived from adding the novel agent elexacaftor to the combination of tezacaftor and ivacaftor.

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

ⁱ Hassan M, Bonafede MM, Limone B, Hodgkins P and Sawicki G (2016) “The Burden of Cystic Fibrosis: Pulmonary Exacerbations and Health Care Resource Utilization in a Commercially Insured Population in the United States” *Value in Health* 19.

ⁱⁱ Becker CC, Clements K, Delong K, Harrow B, and O’Sullivan A (2011) “Economic Burden on Cystic Fibrosis in the U.S.: Costs of Care by Disease Severity and Age” *Value in Health* 14.

ⁱⁱⁱ See Cystic Fibrosis News Today: <https://cysticfibrosisnewstoday.com/2018/09/24/vertex-and-treating-cf-costs-can-unsettle-but-vertex-remains-close-to-community-interview-series/>.

^{iv} Joseph A (2019) “‘We’re still waiting’: As cystic fibrosis drugs deliver new hope, not everyone is being swept up by scientific progress” *Stat News*, February 4.

^v Pearson I, Rothwell B, Olaye A, and Knight C (2018) “Economic Modeling Considerations for Rare Diseases” *Value in Health* 21: 515-524.

^{vi} Becker CC, Clements K, Delong K, Harrow B, and O’Sullivan A (2011) “Economic Burden on Cystic Fibrosis in the U.S.: Costs of Care by Disease Severity and Age” *Value in Health* 14.

^{vii} Ibid.

Public Comment to ICER CFTR Modulators Document

10/10/2019

I have made comments in several sections and mirrors the sections of the ICER document.

Report Aim

- When triple therapy is initially approved, it will only be available for patients over the age of 12. In addition it is not clear if the approval will for all patients who carry at least one F508del allele or only F508del/het min and F508del homozygous patients. Thus it is not clear how many patients will be eligible at initial approval and whether this will more or less than 10,000 patients in the US.

Scope of Clinical Evidence Review

- The committee should consider FEV1 decline as a key measure of clinical benefit, rather than an intermediate outcome, because this is the strongest predictor of time to death and lung transplantation, and changes in quality of life.
- There is some accumulating data on mortality benefit and should be assessed as a key measure.(1)
- When assessing adverse events, consideration should be given to assessing the reduction in adverse events (especially respiratory) in the treatment arm compared to the placebo arm as an efficacy measure.

Interventions

- In Population 2, the phase 3 study of the triple combination compared Elexacaftor/Tez/Iva to Tez/Iva/Placebo

Outcomes

- Key Outcomes
 - Estimate of effects on mortality based on attenuation of FEV1 decline should be considered and include mortality data where it exists.
 - FEV1 decline should be considered as a key outcome
- Other Outcomes
 - Reduction in nebulized therapies, time required
 - Reduction on complications such as massive hemoptysis, pneumothorax and associated costs of managing complications (i.e. bronchoscopies, chest tubes, embolizations).
 - Reduction in non-lung transplant lung surgeries
 - Reduction in gall stone, kidney stones and procedures related to manage such complications
 - Reduction in DIOS, constipation and procedures to manage such complications
 - Reduction in sinus and nasal polyp surgeries
 - Improved pregnancy rates for CF women, potentially less in vitro fertilization

Potential Other Benefits and Contextual Considerations

- Less or no disparity in outcomes between males and females
- Reduction in the impact of health outcomes related to socio-economic status (if fewer therapies are needed, access issues may have less of an impact if patients can receive CFTR modulators).
- The F508del/het min population have no approved CFTR modulators
- CFTR modulators are likely to have life-long benefit based on the underlying mechanism of action
- In F508del homozygous patients, comparison of Elexacaftor/Tez/Iva should be against Placebo/Tez/Iva as this was the comparison in the phase 3 study
- A comment should be included that beginning CFTR modulators early, prior to the development of structural lung damage, may delay or prevent downstream complications such as bronchiectasis, chronic PA, MRSA or NTM infection

Identification of Low-value services

- There are guidelines in place presently about frequency of outpatient visits, blood testing, pulmonary function, chest imaging, culturing. It is possible that in the future the intensity of monitoring could be reduced due to attenuation of disease progression.

Manu Jain MD, MS

Professor of Medicine & Pediatrics

Director of Adult CF

Feinberg School of Medicine

Northwestern University

Reference:

1. Bessonova, L., Volkova, N., Higgins, M., Bengtsson, L., Tian, S., Simard, C., Konstan, M. W., Sawicki, G. S., Sewall, A., Nyangoma, S., Elbert, A., Marshall, B. C., and Bilton, D. (2018) Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax* **73**, 731-740