



November 20, 2017

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 perspective 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 cause early death, usually by respiratory failure. CFTR modulators, which encompass the three drugs in this review — ivacaftor monotherapy, lumacaftor/ivacaftor combination therapy, and tezacaftor/ivacaftor 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. Recent discoveries and research have presented tremendous opportunity for new and existing modulators to benefit individuals beyond those currently indicated.

Reduction in rate of lung function decline is a key measure of clinical benefit.

The goal of cystic fibrosis treatment today is to minimize disease progression and prevent advanced lung disease. Pulmonary function is an important clinical indicator of health in individuals with CF as measured by forced expiratory volume in one second (FEV₁). FEV₁ is the strongest predictor of mortality in cystic fibrosis. Modulators, unlike any other therapy available for people with CF, can serve to slow or prevent the decline in lung function that characterizes this disease. Modulators hold tremendous promise for long-term benefit among those with eligible mutations, especially individuals that begin taking such a therapy before serious lung damage has occurred, including young children. For those with moderate or severe disease, these therapies can help maintain or improve lung function, thereby improving length and quality of life. Improving lung function, reducing the rate of decline, and maintaining lung function are all clinically meaningful in cystic fibrosis. Studies on ivacaftor and lumacaftor/ivacaftor have been completed and additional studies are underway to capture their long-term benefits, including the impact of decreasing rate of lung function decline. The draft scope acknowledges rate of decline as an outcome of interest, but it should also incorporate rate of decline as a key measure of clinical benefit.

The populations included in the scope of this review for each modulator must be clarified.

Ivacaftor Monotherapy: In the draft report, ICER states the population of interest for ivacaftor monotherapy includes patients who are “homozygotes (carry two alleles) for one of the gating mutations (such as *G551D*), but may carry at most one *F508del* mutation.” This is inaccurate. According to the US Food and Drug Administration (FDA), ivacaftor is “indicated for the treatment of CF in patients age 2 years and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.”ⁱ As of the date of this letter, these approved mutations include nine gating mutations, twenty-three missense residual function mutations, five splice mutations, and one conducting mutation. The draft scope also inaccurately asserts that individuals need to be homozygous for gating mutations to experience benefit from ivacaftor monotherapy; again, the presence of a single gating mutation is sufficient for an individual to be eligible for the drug and to experience clinical benefit.

We recommend that ICER limit the scope of the ivacaftor review to include gating mutations, defining the included population as individuals with cystic fibrosis who have at least one copy of an eligible gating mutation per the FDA label (i.e. individuals can be either homozygous for gating mutations OR heterozygous for gating mutations, so long as one eligible gating mutation is present). Although ivacaftor monotherapy is now available for some populations beyond those with gating mutations, the majority of published data focuses on individuals with gating mutations.

Lumacaftor/Ivacaftor Combination Therapy: Per the FDA label, lumacaftor/ivacaftor is “indicated for the treatment of cystic fibrosis in patients age 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.”ⁱⁱ The draft scope states the population of interest for lumacaftor/ivacaftor includes individuals who “are homozygotes for the *F508del* mutation (i.e. they carry two alleles of this mutation), and may carry other mutations as well.” It is extremely rare for an individual with *F508del* mutations on each of two copies of the *CFTR* gene to have any additional mutations. Further, no additional mutations are indicated for the use of lumacaftor/ivacaftor. This should be revised.

Tezacaftor/Ivacaftor Combination Therapy: Tezacaftor/ivacaftor combination therapy is currently under review by the FDA for use in individuals aged 12 and older who are homozygous for the *F508del* mutation or have one *F508del* mutation and one residual function mutation responsive to tezacaftor/ivacaftor.ⁱⁱⁱ The draft scope does not differentiate the population of interest for tezacaftor/ivacaftor from that for lumacaftor/ivacaftor. This should be revised to clarify whether:

1. The population of interest for both combination therapies includes only individuals homozygous for the *F508del* mutation; OR
2. Separate the populations of interest per the FDA label or FDA application for lumacaftor/ivacaftor and tezacaftor/ivacaftor, respectively.

Regarding the populations outlined in the *Interventions and Comparators* section, ICER must clarify the comparison population for tezacaftor/ivacaftor and lumacaftor/ivacaftor. As previously mentioned, tezacaftor/ivacaftor is being considered by the FDA for use in two distinct populations, one of which is not included in the lumacaftor/ivacaftor indication (i.e. heterozygotes with one copy of the *F508del* mutation and one residual function mutation responsive to tezacaftor/ivacaftor). We recommend focusing the scope of the lumacaftor/ivacaftor and tezacaftor/ivacaftor evaluation to those with two copies of the *F508del* mutation (i.e. homozygous for the *F508del* mutation).

Also in the *Interventions and Comparators* section, please define “best supportive care.” Effective cystic fibrosis care regimens vary greatly by disease severity and are individualized based on the health status and life circumstances of each individual. We caution efforts to assume a standard care regimen, which could greatly bias the comparative analyses. It is critical ICER recognize that, especially for cystic fibrosis, a recessive genetic disease that can be caused by over 1,700 unique mutations, individual circumstances are a crucial consideration in creating a care plan for each patient and population-based assumptions are inadequate.

Real-world and long-term data demonstrating the benefits of CFTR modulators is just now starting to accumulate given the short time the drugs have been available to patients.

Ivacaftor and lumacaftor/ivacaftor have been available to patients since January 2012 and July 2015, respectively, while tezacaftor/ivacaftor is still under review by the FDA. 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. These include the ongoing *G551D* Observational Study-Expanded to Additional Genotypes and Extended for Long Term Follow Up (GOAL-e2) and a two-part multicenter Prospective Longitudinal study of CFTR-dependent disease profiling in cystic fibrosis (PROSPECT). Early results have confirmed the beneficial effects seen in clinical trials, however, full data are not yet available as these studies are ongoing.

We seek insight on ICER’s approach to the economic model as it relates to assumptions and cost inputs given current efforts to collect data are still underway. For example, the probability of a cohort existing in each health state may vary by mutation as some mutations cause more severe disease and the probability of moving between health states may vary greatly depending on mutation, age, health status at the start of modulator therapy, long-term benefit derived from therapy, and other factors. We request additional information about where ICER will acquire these data and how accurately they reflect the current CF disease landscape.

Finally, we are concerned 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 will acknowledge such limitations under the framework for ultra-rare diseases but the importance and impact of this deficit cannot be understated.^{iv} QALYs do not adequately inform coverage decisions or value assessments as they exclude patient experience.

We appreciate the opportunity to bring the CF clinical and patient community perspective forward during this review process and the opportunity 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,

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

ⁱ Prescribing Information for Kalydeco® (ivacaftor), FDA Reference ID: 4132700. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203188s026,207925s0051bl.pdf

ⁱⁱ Prescribing Information for Orkambi® (lumacaftor/ivacaftor), FDA Reference ID: 3991904. Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206038s0051bl.pdf

ⁱⁱⁱ Vertex Pharmaceuticals Inc. (2017). *Vertex announces acceptance of its applications for review of the tezacaftor/ivacaftor combination treatment in people with cystic fibrosis by the FDA and EMA* [Press Release]. Retrieved from <http://investors.vrtx.com/releasedetail.cfm?ReleaseID=1038173>

^{iv} Institute for Clinical and Economic Review (ICER). (2017). *Modifications to the ICER value assessment framework for treatments for ultra-rare diseases*. Retrieved from: <https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf>.