By Laura Bonnell

Mother of 2 college age daughters with CF and Founder/President of The Bonnell Foundation: Living with cystic fibrosis

Almost twenty-three years ago, I was on the road to a breaking news story (I was/am news reporter for CBS radio in Detroit) when my phone rang. It was our pediatrician. “You have to pull over,” she told me when I picked up the phone.

I knew immediately what the doctor was going to tell me, Molly, had cystic fibrosis (CF).

I was familiar with CF. Long before I had children, my purpose in life was clear but not yet known to me. I took a break from my reporting career and took on a role in public relations for the Washtenaw County United Way, working on a promotional piece involving a University of Michigan researcher living with CF. That same year, 1989, Dr. Francis Collins, who was then at the university and later became the director of the National Institutes of Health, helped discover the gene that causes CF.

When Molly was born years later, I remembered enough of what I had learned to suspect Molly had CF. She was constantly hungry, had a distended stomach, a salty taste to her skin, and greasy poops. I also remembered a local PSA on TV that talked about the CF symptoms.

My husband and I cried for about 2 hours and then we thought – what do we have to do to raise a child with CF? We have to learn everything we can, and then we have to get involved.

Wanting Molly to have a sibling, we decided to have a second child. Emily also has CF.

The girls have been through health hell. Polyp surgery, some 13 pics lines, 11 cases of pneumonia, constant intestinal issues, colds, flu, breathing treatments, blood draws, pills and missing out on daily activities and school trips because of their health issues.

We have raised them to be strong, and to live life to the fullest. I have had to put aside my own fears and not hold them back. We allowed them to travel to Nicaragua on a mission trip. One went out of state for college, and got extremely ill. She was hospitalized after being misdiagnosed by a New York hospital — 3 times and almost died from a 103 fever and dehydration. I had to tell her to demand to be admitted and I got on a plane. My other daughter

is in college in Michigan but we have driven to her in the middle of the night due to a CF exacerbation to get her to a CF hospital. Still we let them, and are still letting them study abroad. We will not let CF hold them back.

The CF reality is challenging. From basic things like not being able to get life insurance because of their pre existing condition, to constant weekly insurance mess ups that we as parents have to spend hours straightening up. There is usually an error after every doctor visit or hospitalization that can potentially cost us thousands. You have to make sure there is pre authorization on medications, that the pharmacy recognizes both your insurance companies, and when they don't you have to try not to lose your mind and explain the coverage again, day after day and year after year. And the secondary insurance the girls have only covers them in Michigan, so when they live in another state that won't cover them. The girls have great friends who support them, but there are also those who think they look fine, what's the problem? There is not enough room on these pages to explain what CF is on the day to day. It is emotionally and physically exhausting for all (although what we deal with and what the girls deal with — I don't compare the two. Sadly they obviously have the biggest challenge because they live it).

In 2010 I founded the Bonnell Foundation, a non-profit organization that provides tools to help families navigate the difficulties of living with CF.

The foundation's mission is to provide families with tools for navigating life with CF, including connecting CF families, offering educational resources about CF, and sharing inspirational stories. The organization holds regular fundraisers to support its lung transplant grant and medical assistance grant programs, as well as its college scholarship program.

For me, the foundation has been my therapy, I talk to parents about raising children with CF, and I listen to their concerns and answer their questions. It just fills me up. Working to help people is so rewarding. CF family's are counting on the drugs being worked on by pharmaceutical companies. There is no time to lose. I don't know if I will see a cure for CF in my children's life time, but I am certain that CF drugs will give them a longer life. We need clinical trails, we need drugs tested and approved and reachable to the people - like my daughters who need the help.

CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

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 (FEV_1). FEV_1 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/2017/203188s026,207925s005lbl.pdf

[ii] Prescribing Information for Orkambi® (lumacaftor/ivacaftor), FDA Reference ID: 3991904. Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206038s005lbl.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.

November 15, 2017

Institute for Clinical and Economic Review
Midwest Comparative Effects Public Advisory Council
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Dear Members of the Institute for Clinical and Economic Review,

I write to you to submit my comments pertaining to the draft scoping document "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value." Sue Landgraf, executive director of Cystic Fibrosis Research, Incorporated (CFRI) had hoped to share her thoughts on this document but is currently travelling. My perspectives on this topic are both personal and professional: as the mother of a 22-year-old woman with cystic fibrosis (CF), who is homozygous for the F508del mutation and benefitting from a CFTR-modulating drug (lumacaftor/ivacaftor), and as the Associate Director of CFRI, who works directly with members of the CF community from across the United States and beyond. I cannot stress strongly enough the life-changing impact of these new CFTR-modulating therapies and the critical need to make them accessible to those who would benefit from them. To put it in the most basic terms, cystic fibrosis is still a fatal disease. Last year, half the individuals with CF who died were under 30 years old. To keep vital therapies out of the hands of those who would benefit from them would be egregious and unconscionable.

My daughter Tess was diagnosed with cystic fibrosis at five months old, when in addition to her extreme failure to thrive she developed pneumonia. I have feared for her survival since her diagnosis. She has had multiple hospitalizations for exacerbations caused by damaging lung infections, five sinus surgeries, and countless PICC-line placements for multi-week home IV antibiotics treatments. She takes nearly 50 pills per day, injects insulin to manage her CF-related diabetes, and spends a minimum of two hours per day doing respiratory therapy. She is a warrior, powering her way through the physical challenges to pursue her life goals. Through the years she has missed classes, performances and family events due to her disease. It has been extremely difficult to watch the pain and suffering she has experienced both physically and emotionally.

One year ago, Tess began taking Orkambi (lumacaftor/ivacaftor). During the past year, she has maintained her lung function, has had no exacerbations, has not been hospitalized, and has had no need for IV antibiotics. How does one put a price on the preservation of her health? While one can conduct a cost-benefit ratio analysis of the savings from avoiding hospitalizations versus the cost of the drug, this is not my concern. My concern is that my daughter has an improved quality of life. My concern is that my daughter – and others with CF - survives this cruel and debilitating disease.

Tess' health challenges and complex medical regimen are very similar to many others with CF. Today I accompanied Tess to her CF clinic appointment. While sitting in the waiting room I saw a friend, an adult with CF, whose health is rapidly declining. He shared that he is not eligible for transplant, and that he cannot return to his apartment as it is located on the second floor and he can no longer climb the stairs. He is wracked with depression and anxiety about his spiraling

health and mortality. I was pondering his tragic story as I returned to my office at CFRI, where I was informed that a member of our community passed away today at the age of 25, just two months after receiving a double lung transplant. This is what it means to have CF. It is a daily battle to slow the disease's progression. Prior to the arrival of CFTR-modulating therapies, no matter how adherent one was to the time-consuming daily CF medical regimen, the decline in lung function was inevitable. The line on the graph only trended steadily downward.

For many, transplant is the only option to prolong one's life, but this is accompanied by its own complex challenges. Sue Landgraf, CFRI's executive director, is the mother of a 33-year-old daughter with cystic fibrosis. Her daughter went into liver failure and received a liver transplant at the age of 12. At the age of 31, she developed what she thought was a cold. Two days later she was in the intensive care unit, where she experienced respiratory failure and was placed on life support for 11 days. Her life was saved by a double lung transplant. While her survival is celebrated, it came at a cost. The surgery and recovery were brutal and painful. She must now follow another complex regimen of immunosuppressant drugs that make her extraordinarily vulnerable to infection and the development of cancer. She lives with a daily fear of rejection, knowing that only half of those who receive a double lung transplant are alive after five years.

For years, the CF community has tried to maintain a difficult balance between optimism and fear, hope and grief. The arrival of the first CFTR-modulating therapies has brought realistic hope that the downward course of the disease can be halted. It is a tragedy that for many – either due to their specific CFTR mutation or lung disease that is too advanced – these therapies are not an option. It would be an equal tragedy and travesty to deny access to these medications to those individuals who would benefit from them solely due to their cost.

We know all too well that cystic fibrosis is an extremely capricious disease, and that an individual's health status can rapidly spiral out of control. That is what happened to Sue's daughter. That is what I fear for my daughter Tess. While this will never go away, her stabilized health since taking Orkambi has given me a glimmer of hope of what is yet to come.

Cystic fibrosis must be treated aggressively and early. Clinical trial results for tezacaftor/ivacaftor show tremendous promise, and there are many other therapies in the pipeline. It is imperative that cost not be a barrier to access to these life-saving therapies. They are a necessary prescribed treatment, and their cost must be covered so that they are accessible to those who are able to benefit from them.

As someone who has watched my precious daughter battle for 22 years to maintain her lung function and a decent quality of life, and as someone whose work with the CF community has brought me countless stories of hope and of heartbreak related to this brutal disease, I implore you to insure that the cost of these medications are covered for our community. It is truly a matter of life and death.

Best regards,

Siri Vaeth, MSW
CFRI Associate Director
Mother of an Adult Daughter with Cystic Fibrosis

The Search of a Breakthrough for My Son Continues

Just about 25 years ago, my son Gunnar was diagnosed with cystic fibrosis, a debilitating and unrelenting disease for which there is no cure. At the time of his diagnosis, CF was akin to a death sentence – there were no FDA-approved treatments and we could only hope that we might see a cure in time to save Gunnar's life.

I had the privilege of playing quarterback in the NFL for fourteen years. Leading the Cincinnati Bengals to a Super Bowl and being recognized as NFL MVP during the 1988 season highlighted a career that was a dream come true. However, when Gunnar was diagnosed, no successful football career, personal wealth or access to the best doctors could have prepared us for what we encountered – a lack of research and awareness of a rare disease that cut many lives far too short. For me and my wife, Cheryl, it became the cause of our lives. In 1993 the Boomer Esiason Foundation was created and continues to enhance those suffering from CF.

Fortunately, these past few decades of costly and tireless research have yielded major breakthroughs in the fight against CF. Today, there are two FDA-approved treatments available to a small group of patients that treat the underlying cause of the disease, with more on the way. Researchers are making new discoveries that stand to extend lives by years, if not decades. In the 1950s, kids with CF often didn't live long enough to attend elementary school. However, thanks to cutting-edge research and public-private collaboration, nearly half of today's CF population is over the age of 18.

While thousands of families are benefiting from these new discoveries, many continue to wait for drug options that will treat their son or daughter's specific type of CF. We are amongst those families: prescription drug treatments are still unavailable for Gunnar. There are more than 30,000 people living with CF in the U.S., and medicines that treat the underlying cause of the disease are available for only a fraction of these patients—more than two-thirds are still waiting.

What will it take to turn the corner? Beyond research and hope, we must rely on regulatory bodies such as the U.S. Food & Drug Administration to play their part and prioritize the review of treatments that have successfully completed clinical trials.

For Gunnar, we have had multiple attempts with clinical trials, but no success. The speed at which new drugs are reviewed and approved will directly impact the chances that a new treatment – whether it be in a research laboratory or one that is entering the clinical trial process – is the one to save his life.

When it comes to new drug approvals, the FDA has made considerable progress. In 2015, the agency approved 51 new medicines, the highest number since 1950. Over the past five years, Congress has helped reduce barriers by expanding what the FDA can consider for accelerated approval and permitting the use of data sets for multiple drug review processes, among other modifications.

This is laudable in every way, but our work is far from over. Again, my son is beating the odds and surviving this disease. But the fact that there is no available treatment to address the

underlying cause of his CF should be enough to demand a more aggressive review of medicines that could save lives. CF patients are in dire need of multiple treatment opportunities. The variations of how patients react to certain treatments are vast.

Today, Gunnar is a successful 26-year old young man. I'm hopeful that he'll live for many more years to come. With the right treatment, this moves from possible to reality. As an avid hockey fan, we need as many shots on goal as possible.

Boomer Esiason
Boomer Esiason Foundation
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November 20, 2017

Institute for Clinical and Economic Review
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Re: Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Scoping Document

Dear Dr. Pearson:

On behalf of the 30 million Americans with one of the nearly 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Institute for Clinical and Economic Review (ICER) for the opportunity to provide comments on the Institute's "Modular Treatments for Cystic Fibrosis: Effectiveness and Value Draft Scoping Document".

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

We are committed to fostering an ecosystem that encourages the development and accessibility of safe and effective therapies for rare disease patients. While we applaud ICER for continuing this institutional recognition and adaptation by putting forward an amended value assessment framework for rare disease healthcare interventions we continue to be concerned with ICER's division of rare diseases into ultra-rare and non-ultra-rare conditions.

Rare diseases are largely understudied, misunderstood, and often ignored due to the inherently small patient populations of each rare disease. It is for these reasons that Congress, state legislatures, and Federal and state regulatory bodies have recognized that rare diseases require a specialized, unique approach. Congress passed the Orphan Drug Act of 1983 and the Rare Diseases Act of 2002. State legislatures across the country are creating Rare Disease Advisory Councils to advise state governmental bodies on the unique needs of the rare disease patient community. The Food and Drug Administration and the National Institutes of Health have created offices dedicated to rare disease research and drug development.

While we are pleased that ICER has recognized cystic fibrosis as a rare disease, NORD continues to be very concerned with ICER's proposed division of rare diseases into ultra-rare and non-ultra-rare conditions, and the use of the proposed ultra-rare framework in this draft scoping document.

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NORD is opposed to efforts to create an ultra-rare category in various settings. And we continue to oppose the ICER proposed adaption for the assessment of treatment for ultra-rare conditions and application to new treatments for rare diseases.

We are not convinced by ICER's rationale that,

> "only when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation, and to give special consideration to value in the context of the price X volume needed to provide adequate rewards for risk and innovation".

We find this claim baseless and unfounded, and the lack of any citation or outside justification only furthers our conviction. There are many factors that contribute to the difficulty in evidence generation for orphan therapies, and we are confident they do not start and stop at the 10,000 prevalence number. For example, many diseases with prevalences above 10,000 are even more difficult to develop therapies for due to the heterogeneity of the manifestation, progression, and severity of the diseases as well as the variability of treatment effects.

We also strongly disagree with ICER's assertion that "application of adapted methods of value assessment are not needed for the majority of 'orphan' drugs as defined by the Orphan Drug Act, as sufficient patient numbers are usually available for 'routine' clinical trials, and outcome measures are likely to be relatively standardized and well-documented". We continue to disagree with this unsubstantiated claim. Congress and the FDA have long recognized the unique challenges of developing orphan therapies above population sizes of 10,000 individuals by enacting and implementing various incentives and regulatory practices that do disqualify diseases with over 10,000 individuals. For ICER to make this claim, it is directly in contrast every other institution in the United States that sets policy for the rare disease community.

We continue to encourage ICER to abandon use of an arbitrarily created subdivision of the rare disease patient community, and instead use the well-recognized and established definition for a rare disease already in existence: 200,000 or fewer individuals with the disease in the U.S.

We thank ICER for the opportunity to comment, and we look forward to working with ICER to accurately and collaboratively assess the values of orphan therapies. For questions regarding NORD or the above comments, please contact me at pmelmeyer@rarediseases.org or (202) 545-3828.

Thank you in advance for your consideration.

Sincerely,

Paul Melmeyer
Director of Federal Policy

To whom it may concern:

I am writing to share my experience of living with cystic fibrosis and how ivacaftor has immensely improved my life and given me a future that I never knew could exists. As you are aware, Ivacaftor is one of two drugs available that target the underlying cause of cystic fibrosis. These drugs are groundbreaking scientifically, but even more so clinically.

When I was diagnosed with cystic fibrosis in 1983, I was 18 months old. Upon diagnosis my parents were told that I might not live long enough to graduate from high school. At the time there were minimal treatments available for CF. Aside from the few pills I had to take, my parents had to perform manual chest percussion therapy several times a day to help me clear the mucus from my lungs. This mucus is what traps bacteria and causes recurring lung infections.

Throughout my three decades of life I have seen CF treatments evolve from vitamins and enzymes to aid with digestion and growth, to treatments that help control the respiratory disease. Today we have two treatments available that target the underlying cause of CF. This is significant for the cystic fibrosis community.

One of my gene mutations is G551D, which allowed me to participate in the Phase 2, Phase 3 and Open Label portion of the VX-770 study. Fortunately I have been able take ivacaftor since the trials ended and it gained FDA approval in 2012. The results I have experienced from taking this drug are far beyond imaginable.

My lung function (FEV1) has increased from the mid 50's to the highest level I have ever seen, the high 80's. Chronic lung infections that would land me in the hospital several times a year have been reduced to once every two or three years because the thick mucus in my lungs has been vastly reduced. My weight has stabilized, my chronic sinusitis has disappeared, and my quality of life is very rich.

Before ivacaftor I was living on Social Security and Disability and uncertain about not only my health, but also my financial stability. Because of the positive outcomes I've experienced from ivacaftor I now work full time for the Rock CF Foundation, a non profit that I founded ten years ago to heighten public awareness about cystic fibrosis and empower others with CF to lead a healthier positive life.

Over the past decade running and cycling has become a form of treatment for my CF. The coolest thing that I get to experience every day is the increased endurance from ivacaftor.

Since beginning the trials I have completed fifteen half marathons, the NYC Marathon in 2016, and five several hundred mile bike rides. I can run and ride faster and further than ever before.

In 2015 I purchased my own home, and earlier this year I set up a retirement fund. Because of ivacaftor I no longer have to worry about financial instability due to my poor health. All of the things I have listed are because of ivacaftor and the dedicated work of Vertex. Every day I wake up more thankful than the previous day because I am not only alive, but I'm thriving

Sincerely,

Emily A. Schaller

Vertex Pharmaceuticals Incorporated
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November 20, 2017

BY ELECTRONIC DELIVERY

Steven D. Pearson, M.D., M.Sc., FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Submission to ICER by Vertex Pharmaceuticals Concerning ivacaftor (KALYDECO®), lumacaftor/ivacaftor (ORKAMBI®), and tezacaftor/ivacaftor

Dr. Pearson:

This letter serves as Vertex's response to the draft scoping document of ICER's review of Cystic Fibrosis Transmembrane Conductance Regulator Modulators (CFTRm), specifically Kalydeco, Orkambi and the investigational product tezacaftor/ivacaftor, discovered and developed by Vertex Pharmaceuticals Incorporated (Vertex).

As noted in our previous letter, Vertex has delivered the first and only breakthrough medicines to treat the underlying cause of cystic fibrosis (CF) to patients living with this rare, chronic, and life-shortening disease. Since their approvals, Kalydeco and Orkambi have demonstrated not only acute health benefits, but also long-term and disease-modifying benefits for patients with CF.[1,2] Phase 3 data for tezacaftor/ivacaftor—currently under review for approval by the Food and Drug Administration (FDA)—summarized in a press release earlier this year, also showed significant clinical benefits.[3,4] Moreover, the FDA has granted orphan and breakthrough drug designations to all three of these medicines—Kalydeco, Orkambi and tezacaftor/ivacaftor—based on the small size of the treated populations and the demonstrated benefits.[5-7] Consistent with the Kalydeco and Orkambi labels, the vast majority (99 percent) of eligible patients in the U.S. currently have broad access to these therapies through public and private insurance. We are pleased that payers recognize the significant benefits these medicines bring to CF patients.

We continue to have serious concerns about ICER's methodological approach and its applicability to CF treatments, as well as the timing and goals for ICER's analysis. As a general matter, assigning a value-based price benchmark is inappropriate for rare diseases like CF given the complexity and chronicity of the disease. Typical quality of life measures fail to fully capture the perspectives of these patient populations and contradict empirically demonstrated societal preferences for prioritization of the worst off or most urgent cases. From a methodological perspective, aggregate level Markov-like simulations are ill-suited because Markov models are

less accurate for forecasting long-term outcomes in heterogeneous diseases like CF; patient-level simulation models are more appropriate for analysis of CF therapies. The purpose of the review is also unclear, as payers have expressed no ambiguity regarding whether or how to provide access to these medicines.

As we discussed with your clinical team on November 14, should ICER decide to move forward with its analysis, the ultra-rare framework would be comparatively more appropriate for a CF category review. However, *we believe ICER's ultra-rare framework has methodological flaws that make it unsuitable for a review of CFTRm.* Most significantly, ICER chose to retain the value-based price benchmark for ultra-rare conditions such as CF in the recently-published final value assessment framework for the treatment of ultra-rare diseases.[8] Given the complexity of the disease and inherent difficulty in translating the broad range of patient outcomes into quality-adjusted life years (QALYs), it is not appropriate to apply a value-based price benchmark in an ultra-rare disease assessment.

Additionally, we have identified various flaws associated with ICER's proposed scoping document, which are enumerated below:

1. **Available clinical evidence shows accumulated benefit; ICER's proposed approach erroneously discounts efficacy after two years; long-term data must be used to model treatment efficacy in CF patients.** In the published model ICER plans to use as the basis for its model,[9] the assumption that efficacy is reduced by 50 percent after two years contradicts clinical evidence, which shows distinct acute and long-term lung function benefits of treatment with both Orkambi and Kalydeco.[2,10] These published data have demonstrated substantial reductions in the rate of ppFEV1 decline among patients receiving long-term treatment with CFTRm versus matched controls and should be incorporated into the model. Long-term data—e.g., PERSIST and PROGRESS trial results[2,11]—demonstrated reductions in patient reported symptoms that were maintained over the course of the study. For Kalydeco, data from the long-term safety study show lower risks of mortality, lung transplant, pulmonary exacerbation, and hospitalization, and suggest sustained improvement or maintenance of lung function and body mass index (BMI), in addition to favorable systemic outcomes such as reductions in the prevalence of CF-related diabetes.[1,12] These important long-term real-world benefits are consistent with long-term outcomes projected in a published model for Kalydeco.[13] Similar long-term benefits have been projected for Orkambi.[14] Given that both Orkambi and tezacaftor/ivacaftor are dual therapies built on the foundation of Kalydeco, the long-term real-world benefits observed with Kalydeco are relevant for incorporation in all models.

2. **ICER has not clearly identified CF patient populations nor appropriate comparator products.**

- ***Include pediatric and adolescent patient populations***: The choice to follow a single cohort with a mean age matching that of the registrational trial (i.e., age 25 in the published model[9]) ICER plans to use as the basis for its model fails to capture the additional benefits of earlier therapy to younger patients included in the trials and the additional survival accrued in this younger population,[15,16] CFTRm are approved across a broad age range and should be modeled in the entire indicated population.[17,18]

- ***Include F508del/RF patient population:*** ICER appears to have excluded patients with residual function mutations responsive to tezacaftor/ivacaftor from the combination therapy candidate patient population. Benefits and costs for the full target patient population/indication for tezacaftor/ivacaftor should be included in the review and economic assessment of comparative value.[19,20] Exhibit A in the attached appendix outlines the appropriate patient populations and comparator products for Orkambi, Kalydeco, and tezacaftor/ivacaftor.
- ***Appropriate comparator for tezacaftor/ivacaftor in F508del/F508del is best supportive care (BSC)***: Tezacaftor/ivacaftor should not be compared to Orkambi, in part, because they have different risk-benefit profiles, including safety profiles and drug-drug interactions, such as with CYP3A4 inducers and hormonal contraceptives.[21,22]
- ***CFTR modulators target specific genetic mutations:*** Modeling sub-groups, beyond mutation type, is not appropriate given demonstration of efficacy across sub-groups as well as inherent challenges in modeling sub-populations with small numbers.

3. **ICER's assumptions for medication persistency and compliance are incorrect; ICER should use real-world data for more accurate assumptions.** The assumption of no discontinuation and perfect compliance is inconsistent with compliance observed in key CF trials and real-world patient populations. This assumption overstates the use and costs of treatment. Because the efficacy reported in the registrational trials is based on intent-to-treat (ITT) results, the corresponding trial compliance should be utilized to match drug costs with efficacy outcomes. For long-term outcomes, the assumption of 100 percent compliance even among generally well-tolerated drugs like CFTRm is unrealistic and overstates likely real-world drug use and costs. The medication possession ratio (MPR) for Kalydeco of 0.80, estimated based on real-world data,[23] reflects a more realistic estimate of CFTRm use, and importantly, this real-world MPR is associated with efficacy consistent with that observed in the long-term follow-up studies.[1,12] The sustained improvements in patient outcomes observed in the long-term data were achieved in a real-world population of CF patients who did not have perfect medication compliance.

4. **ICER's model fails to incorporate key components of value.** Failing to incorporate key components of value (i.e., direct and indirect economic impacts) to CF patients will underestimate the treatment value, cost-effectiveness and appropriate value-based price benchmark of CFTRm. For example, recently-published data have shown significant increases in absenteeism, presenteeism and work loss among caregivers of children with CF during times of pulmonary exacerbation-related hospitalization,[24] which represent only a small part of the overall burden. While ICER proposes to present the value-based pricing benchmark from both the payer and societal perspective, many of the outcomes affecting patients, families and society listed in the draft scoping document are likely to be difficult to quantify. Ignoring these very real costs of sub-optimal disease management of CF will provide an incomplete picture of the value of CFTRm.

We believe in the value of our medicines and the long-term benefits they have for people with CF and are concerned that ICER's methodology is unable to adequately capture and assess the true value of innovative medicines like Kalydeco, Orkambi and tezacaftor/ivacaftor. We do not believe that a review of CF medicines using either ICER's standard or ultra-rare value framework will benefit patients, providers, or payers. We are concerned that continued disparagement of medical

innovation disrupts the biomedical ecosystem, which is dependent on maintaining appropriate incentives for research and development to bring these life-changing medicines to people who need them.

We welcome the opportunity to discuss this information in more detail.

Sincerely,

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Exhibit A

Table: List of mutations eligible for CFTR modulators and appropriate comparators

Medication	Mutations	Age Group	Comparator
Kalydeco (Ivacaftor)	*Gating and Residual Function Mutations:* *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, D1152H, A455E, L206W, R347H, P67L, S945L, R117C, R352Q, D1270N, R74W, F1052V, D579G, R1070W, D110H, F1074L, S977F, E56K, D110E, E193K, K1060T, A1067T, G1069R, R1070Q*	≥2 years	BSC
Orkambi (Lumacaftor/Ivacaftor)	F508del homozygous	≥6 years	BSC
TEZ/IVA (Tezacaftor/Ivacaftor)	F508del homozygous	≥12 years	BSC
	Residual Function Mutations: *D1152H, A455E, L206W, P67L, S945L, R117C, R352Q, D1270N, R74W, F1052V, D579G, R1070W, D110H, F1074L, S977F, E56K, D110E, E193K, K1060T, A1067T*		BSC + Kalydeco (Ivacaftor)

BSC- Best Supportive Care