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Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Draft Background and Scope
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Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Children born with CF inherit two pathogenic mutations, one from each parent. It is a relatively rare condition, occurring in approximately one in 2,500 to 3,000 live births, but it is the most common lethal genetic disease in Caucasian populations.[1-4] CF is a progressive disease that affects many organ systems, but most of its morbidity and mortality are associated with its impact on the respiratory system.

The life expectancy of patients with CF has increased substantially over the past 20 years, due in part to successes in the coordinated delivery of care and advances in CF management.[5] Until recently, treatment for CF focused on reducing symptoms and managing complications. New therapies target the abnormal proteins made by the mutated *CFTR* gene. More than 2,000 *CFTR* mutations have been identified that have different effects on the quantity and function of the CFTR protein.[6] Mutations to the *CFTR* gene can affect the amount of CFTR protein that is produced, the amount of protein integrated into the cell membrane, or the CFTR protein's ability to regulate ion and water flow.[5] This leads to thick secretions that can block passages in the lungs, pancreas, and reproductive organs, which may result in frequent lung infections and reduced lung function, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems.[7]

The focus of this review is on triple therapy that adds the novel agent elexacaftor to the combination of tezacaftor and ivacaftor (investigational, Vertex Pharmaceuticals, Inc.). Elexacaftor is another corrector therapy like lumacaftor and tezacaftor. It helps to correct folding of the CFTR protein and its trafficking to the cell surface. In addition, we will update our prior review of ivacaftor (Kalydeco®, Vertex Pharmaceuticals, Inc.) and the combinations lumacaftor/ivacaftor (Orkambi®, Vertex Pharmaceuticals, Inc.) and tezacaftor/ivacaftor (Symdeko®, Vertex Pharmaceuticals, Inc.).

The use of these agents has generated tremendous interest and hope on the part of clinicians, patients, and their families. The new triple therapy has the potential to improve the lives of patients with CF with mutations that are not effectively treated by the current generation of modulator therapies (patients who are heterozygous for the F508del mutation and a minimal

function mutation). In addition, there may be new data with longer follow-up for patients treated with currently-available therapies. All stakeholders will benefit from a comprehensive, updated review of the clinical evidence and potential economic impact of modulator treatments.

Stakeholder Input

This scoping document was developed based on input from a group of stakeholders comprised of patients and their families, clinicians, researchers, and representatives from patient organizations in preparation for this new review; additional input had been gathered during ICER's previous review of modulator therapies for CF.

Several themes arose from the discussions with patients, their caregivers, and organizations supporting patients. The first theme reflects the daily burden required to manage CF. Airway clearance activities and taking dozens of pills and inhaled therapies consumes several hours of every day for patients. This is exhausting and takes away time that would normally be spent on social activities, school, and family. It also contributes to the stigma associated with the disease. In addition, there is a substantial time burden from hospitalization for pulmonary exacerbations and the need for long-term IV antibiotic therapy.

A second theme is the psychosocial burden associated with living with a chronic, life-shortening illness. Depression and anxiety disorders contribute significantly to the overall burden of disease and are often insufficiently captured in measures of disease burden and quality of life.

A third theme is the financial burden imposed by the disease. Many of the therapies are not completely covered by insurance, requiring substantial financial contributions by patients and their families. Patients miss school and work due to routine follow-up, disease exacerbations, and eventually the disability imposed by progressive disease. In addition, caregivers often forego job opportunities, switch from full- to part-time employment, or stop working all together in order to care for their loved one who has CF. Some patients also stated that the were "deeply concerned about the staggering price of drugs."

Finally, patients highlighted the heterogeneity of the disease. Patients with different combinations of CFTR mutations have variable disease courses and even patients with the same mutation type have different lived experiences with CF. There is no "typical" patient living with CF – the patients are unique individuals.

Report Aim

This project will evaluate the health and economic outcomes of the new triple therapy CFTR modulator treatment and update our prior review of modulator therapies that are currently approved by the FDA. The ICER value framework includes both quantitative and qualitative

comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

We propose to assess some of the CFTR modulator treatments (ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor) under an adaptation of the ICER value framework for treatments of serious, ultra-rare conditions because we believe they meet the following criteria:

- The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

The candidate population for treatment with modulators may be as small as 1,200 individuals (for ivacaftor monotherapy) and is anticipated to involve 10,000 individuals or less in each genetically-specified population.

The use of triple therapy with elexacaftor may not qualify for ultra-rare designation as early reports suggest that it has the potential for use in 90% of all patients with CF, which would likely cross the 10,000 patient threshold.

Scope of Clinical Evidence Review

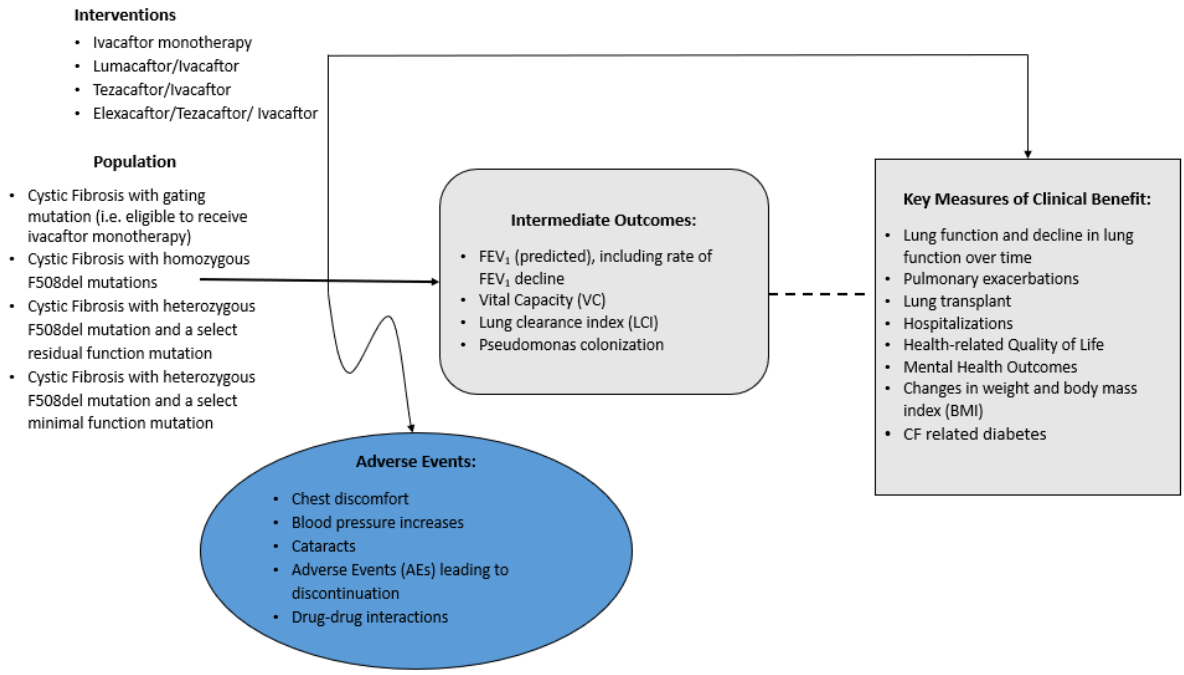
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for CF is depicted in Figure 1 on the following page.

Figure 1. Analytic Framework: Modulator Therapies for Cystic Fibrosis



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., FEV_1), and those within the squared-off boxes are key measures of benefit (e.g., hospitalization). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[8]

Populations

We will review CFTR modulator therapies in four distinct populations across all ages based on current FDA labeling and the clinical trial populations.

1. Individuals with CF who carry mutations included in the FDA-approved indications for ivacaftor.

2. Individuals with CF who are homozygous for the F508del mutation.
3. Individuals with CF who are heterozygous for the F508del mutation with a residual function mutation.
4. Individuals with CF who are heterozygous for the F508del mutation with a minimal function mutation.

Within these populations, subgroups of interest are defined according to presence of advanced nonreversible lung disease (e.g., patients with or without bronchiectasis; who have predicted FEV_1 below 40%, 40-70%, 70-90%, or above 90%) and age (groups as defined in each study). Predicted FEV_1 is a measure of lung function defined as forced expiratory volume during the first second of expiration, adjusted for age, height, sex, and race. Other subgroups of interest are people with advanced non-pulmonary disease, such as recurrent pancreatitis, liver transplantation, poor growth, and infertility.

We will include studies of individuals of any age, regardless of their past medical history, comorbidities, or the severity of their CF.

Interventions

<u>Population 1</u>

- Ivacaftor plus best supportive care

<u>Population 2: Homozygous for F508del</u>

- Lumacaftor/Ivacaftor plus best supportive care
- Tezacaftor/Ivacaftor plus best supportive care
- Elexacaftor/Tezacaftor/Ivacaftor plus best supportive care

<u>Population 3: Heterozygous F508del and a residual function mutation</u>

- Ivacaftor plus best supportive care
- Lumacaftor/Ivacaftor plus best supportive care
- Tezacaftor/Ivacaftor plus best supportive care
- Elexacaftor/Tezacaftor/Ivacaftor plus best supportive care

<u>Population 4: Heterozygous F508del and a minimal function mutation</u>

- Elexacaftor/ Tezacaftor/Ivacaftor plus best supportive care

Comparators

The comparator for each population will be best supportive care and, where applicable, the other Interventions for that population.

Outcomes

Key Outcomes

- Lung function and decline in lung function over time
- Pulmonary exacerbations
- Lung transplant
- Hospitalizations
- Health-related quality of life
- Mental health including depression and anxiety
- Weight, body mass index (BMI), and growth surrogate measures of nutrition status
- CF-related diabetes

Other Outcomes

- Time lost from school or work
- Pill burden and correlation to adherence with medication regimen
- Worry, stress, and anxiety about the disease or its financial impact
- Ability to participate in athletic activity and social functions
- Financial insecurity
- Caregiver burden
- Acute pancreatitis
- Fertility
- Liver transplant

Intermediate Outcomes

- FEV_1 (predicted), including rate of FEV_1 decline
- Vital capacity
- Lung clearance index
- Pseudomonas colonization
- Fasting glucose and related measures of glucose control

Adverse Events

- Chest discomfort
- Increased blood pressure
- Cataracts
- Adverse events (AEs) leading to treatment discontinuation
- Serious adverse events (SAEs)

Timing

Studies of all follow-up durations are eligible. Our focus will be on studies in which patients are prescribed a course of treatment.

Settings

All settings will be considered. Studies conducted in any country will be considered. However, the primary interest is in outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will modify and update existing decision-analytic models to assess the lifetime cost-effectiveness of the various CFTR modulator therapies plus best supportive care relative to best supportive care alone.[9] We will update our prior analyses conducted for the previous ICER review to incorporate new evidence as well as evaluate elexacaftor/tezacaftor/ivacaftor as a new therapy for certain populations. Hence, we will evaluate four possible therapeutic options for four CF populations as follows.

1. For patients who are candidates for ivacaftor monotherapy based on the current indications, we will compare ivacaftor plus best supportive care to best supportive care alone (updated analysis).
2. For patients who are homozygous for the F508del mutation, we will compare tezacaftor/ivacaftor plus best supportive care, lumacaftor/ivacaftor plus best supportive

care, elexacaftor/tezacaftor/ivacaftor plus best supportive care and best supportive care alone as competing alternatives (updated and new analyses).

3. For patients who are heterozygous for the F508del mutation and a residual function mutation, we will compare tezacaftor/ivacaftor plus best supportive care, ivacaftor plus best supportive care, lumacaftor/ivacaftor plus best supportive care, elexacaftor/tezacaftor/ivacaftor plus best supportive care, and best supportive care alone (updated and new analyses). The inclusion of lumacaftor/ivacaftor for this population will only be done if the evidence review establishes effectiveness with new evidence. In addition, we will use reasonable assumptions to model elexacaftor/tezacaftor/ivacaftor in this population, which differs from the study populations of the clinical trials.
4. For patients who are heterozygous for the F508del mutation and a minimal function mutation, we will compare elexacaftor/tezacaftor/ivacaftor plus best supportive care and best supportive care alone (new analysis).

Under ICER's modifications to the value assessment framework for treatments for ultra-rare diseases, we will consider dual "base cases" that will reflect the health system and societal perspectives for all therapies other than elexacaftor/tezacaftor/ivacaftor, which has an anticipated population larger than 10,000 individuals. A societal perspective will be included as a co-base case if it is anticipated that the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs are large relative to health care costs. In our last review we did not find that impact of the therapies on societal costs were large relative to the impact on health care costs; however, we will re-evaluate the balance of these costs with updated evidence. If not assessed as a dual base case, a societal perspective will be considered in a scenario analysis.

The model structures are influenced by other published models of CF treatment[10-12] and characterize patients by lung function (i.e., predicted FEV_1) and predict the decline in lung function over time for those patients receiving best supportive care. The models also include variables that have been shown to impact survival among CF patients (e.g., weight-for-age z score, pancreatic sufficiency, diabetes mellitus, number of acute pulmonary exacerbations, lung transplantation).[13] The models allow us to simulate the health states of a cohort of patients over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs include clinical probabilities, quality of life values, measures of resource utilization (such as hospitalization for pulmonary exacerbations), and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using results from relevant clinical trials, and assumptions about treatment effectiveness beyond the time horizon of trials will be varied in scenario analyses. We will incorporate the drug discontinuation rates from the trials and make reasonable assumptions about drug continuation beyond the time horizon of the trial. A 3% discount rate will be applied to both costs and outcomes.

Health outcomes will be dependent on patient health status, clinical events, and AEs. The risk of AEs may be modeled as a function of predicted FEV_1, and will include both treatment-related AEs and consequences of disease progression (e.g., new-onset diabetes). Quality of life weights will be applied to each health state, including quality of life decrements for acute exacerbations and for SAEs. The health outcome of each intervention will be evaluated in terms of numbers of acute pulmonary exacerbations and hospitalizations, incidence of lung transplantation, and life-years as well as quality-adjusted life years (QALYs) gained. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. Results will be expressed in terms of the marginal cost per QALY gained and cost per life-year gained. In addition, other cost-consequence measures will be considered, such as cost per acute pulmonary exacerbation avoided.

We will also incorporate a new effectiveness measure – the equal value life years gained (evLYG). This metric evenly measures any gains in length of life, independent of the treatment's ability to improve patient quality of life. If treatment adds a year of life to a person with compromised health (i.e., a lower quality of life) the treatment will receive the same evLYG as a different treatment that adds a year of life for healthy members of the community.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This potential budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

ICER includes information in its reports on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by the treatment regimens under review (e.g., pulmonary exacerbations, hospitalizations, etc.), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of CF beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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