Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Final Background and Scope
November 30, 2017

Stakeholder Input:

This scoping document was developed with input from a group of stakeholders comprised of patients and their families; clinicians; researchers; representatives from the Cystic Fibrosis Foundation (CFF), a medical and patient advisory group focused on advancing care for cystic fibrosis (CF); and Vertex Pharmaceuticals, the manufacturer of the medicines that will be assessed in this review. Based on the upcoming FDA review of tezacaftor/ivacaftor, the Institute for Clinical and Economic Review (ICER) is undertaking an evaluation of the cystic fibrosis transmembrane conductance regulator (CFTR) potentiator ivacaftor (Kalydeco®) as well as the CFTR potentiator/corrector combination products lumacaftor/ivacaftor (Orkambi®) and tezacaftor/ivacaftor.

This final scoping document incorporates feedback gathered during preliminary calls with stakeholders and following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review of modulator treatments for CF and encourages comments to refine our understanding of the clinical effectiveness and value of these regimens.

Background:

CF is an autosomal recessive condition caused by mutations in the *CFTR* gene. Children born with CF inherit two pathogenic mutations, one from each parent. It is a relatively rare condition, occurring in approximately 1 in 2,500 to 3,000 livebirths, 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 10-20 years, due in part to successes in the coordinated delivery of care and advances in CF management.[5] Prior treatment for CF focused on reducing symptoms and managing complications. This review focuses on novel agents that directly modulate the pathophysiology of the disease; namely, ivacaftor, lumacaftor, and tezacaftor.

In epithelial cells, the *CFTR* gene is transcribed and translated to produce the CFTR protein, which in turn is transported to the apical membrane, the part of the membrane that faces inwards towards the lumen of an organ. There, the CFTR protein acts as a gate that regulates the flow of chloride ions, bicarbonate ions, and, indirectly, sodium ions, and other substances in and out of the cell. Mutations to the *CFTR* gene can reduce the amount of CFTR protein that is produced or transferred to the apical membrane or the CFTR protein's ability to regulate ion and water flow.[5] This reduction leads to thick secretions that can block passages in the lungs, pancreas, and reproductive organs, which may result in frequent lung

infections, reduced respiratory capacity, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems in those affected.[6]

More than 1,700 different *CFTR* mutations have been identified, with varying effects on the quantity and function of the CFTR protein.[7] A classification system for the most common mutations of the *CFTR* gene describes five classes of mutations:

> Class I (transcription-stopping or "X-group") mutations result in no CFTR protein being produced. Importantly, patients who are homozygotes for these mutations cannot respond to modulator-based treatments, because there is no CFTR protein to be modulated.
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> Class II mutations ("folding mutations") result in protein formation (folding) and trafficking defects that hinder the transport of the CFTR to the apical membrane. This group includes the most common CF-causing mutation, *F508del*. Approximately 87% of CF patients have at least one *F508del* allele (heterozygous), and 46% of patients are homozygous (have two copies) for this mutation.[7,8] *F508del* homozygotes may respond to modulator therapies, namely, combinations of lumacaftor or tezacaftor (agents that aim to "correct" folding defects and thus enable CFTR protein to traffic, or to be transported, to the cell surface) with ivacaftor (a "potentiator" of CFTR function that increases the flow of ions through the CFTR channel).
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> Class III mutations ("gating mutations") result in a non-functioning CFTR protein on the apical membrane. An example is the *G551D* mutation, which is present on one or both alleles in approximately 5% of CF cases. A patient who carries at least one copy of a gating mutation may respond to ivacaftor therapy.
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> Class IV and V mutations are associated with reduced functionality of the *CFTR* gene (often called residual function mutations).[9] Clinical trials have been performed with ivacaftor monotherapy in patients with the *R117H* mutation, and the FDA has recently approved ivacaftor use in other Class IV and V mutations based on in vitro data.

The use of CFTR modulators has generated great interest on the part of clinicians, patients, and their families. There are uncertainties around their use, however, such as the ability of surrogate endpoints of respiratory function to predict longer-term benefit and increased survival. In addition, currently marketed CFTR modulators can exceed annual costs of $250,000 per patient, and alignment of their cost to patient benefit is not well understood. All stakeholders will therefore benefit from a comprehensive review of the clinical evidence and potential economic impact of modulator treatments.

Potential major advance for a serious ultra-rare condition:

We propose to assess CFTR modulator treatments under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because we believe the assessment meets the following proposed 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 U.S. 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.

Report Aim:

This project will evaluate the health and economic outcomes of CFTR modulator treatment. 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.

Scope of the Assessment:

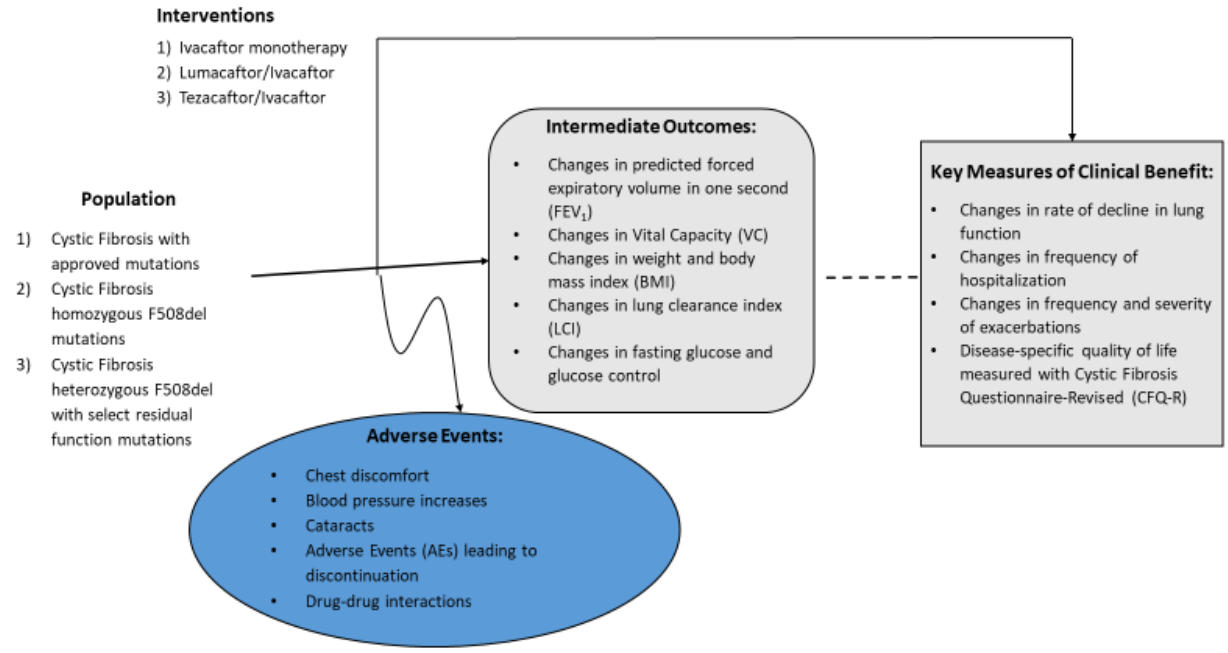
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials, comparative cohort studies, and high-quality systematic reviews. High-quality observational studies, both comparative (comparing two or more interventions) and non-comparative (evaluating only a single intervention) will be considered, particularly for long-term outcomes and uncommon adverse events. Only studies that evaluate use of the drugs of interest (or comparator treatments) in persons with CF will be included. *In vitro* studies will be excluded. 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 ICER's grey literature policy here).

All relevant evidence will be synthesized qualitatively. Data permitting, we will conduct quantitative analyses. Wherever possible, we will seek out head-to-head studies of these interventions. In the absence of head-to-head studies, we will use placebo-controlled studies and derive indirect comparisons (through network meta-analysis) when feasible and appropriate.

Analytic Framework:

The analytic framework in Figure 1 outlines the scope of this technology assessment. Other reported intermediate outcomes, key measures of clinical benefit, and adverse events not listed in the analytic framework will also be included if they meet the eligibility criteria described below.

Figure 1. Analytic Framework: Modulator Therapies for Cystic Fibrosis



Populations

We will review CFTR modulator therapies in three distinct populations across all ages. The first population includes individuals with CF and mutations consistent with the FDA-approved indications for ivacaftor. In this population, we will review evidence on ivacaftor monotherapy. It was suggested by external commenters that most of the clinical evidence for ivacaftor will be in patients with gating mutations; however, where evidence exists, we will also review studies on humans with non-gating mutations (e.g., *R117H*), so long as an outcome of interest is present.

The second population includes individuals with CF who are homozygous for the *F508del* mutation. In this population we will review evidence on both lumacaftor/ivacaftor and tezacaftor/ivacaftor combination therapy.

The third population includes individuals with CF who are heterozygous for the *F508del* mutation and a residual function mutation that is potentially responsive to tezacaftor/ivacaftor. In this population we will review evidence on tezacaftor/ivacaftor combination and ivacaftor monotherapy.

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 forced expiratory volume (FEV_1) below 40%, between 40-90% or above 90%) and age (groups as defined in each study). Predicted FEV_1 is a measure of lung function defined as the forced expiratory volume during the

first second of expiration, adjusted for age, height, sex, and race.[10,11] Other subgroups of interest are people with advanced non-pulmonary disease, such as recurrent pancreatitis, liver transplantation, poor growth, and infertility.

We will exclude patients who are homozygotes for stopping mutations (Class I or "X group") in the *CFTR* gene. These individuals are not candidates for the treatments of interest because no CFTR protein is produced and, thus, the CFTR modulators have no protein to act upon. We will impose no other restrictions regarding population eligibility.

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

Interventions and comparators

Data permitting, we intend to examine the following comparisons in the appropriate populations:

1. For individuals who are candidates for ivacaftor monotherapy, we will compare adding ivacaftor to best supportive care versus best supportive care alone.
2. For individuals who are homozygous for the *F508del* mutation, we will compare adding lumacaftor/ivacaftor or tezacaftor/ivacaftor to best supportive care versus best supportive care alone. Where the data allow, we will compare lumacaftor/ivacaftor to tezacaftor/ivacaftor.
3. For individuals who are candidates for tezacaftor/ivacaftor combination therapy because they carry one *F508del* mutation and residual function mutation that is potentially responsive to tezacaftor/ivacaftor, we will compare adding tezacaftor/ivacaftor to best supportive care versus adding ivacaftor monotherapy to best supportive care versus best supportive care alone.

We will exclude studies of lumacaftor and tezacaftor monotherapy, because, based on stakeholder feedback, neither is intended to be used as monotherapy.

Outcomes

Outcomes of interest include patient-centered outcomes, other clinical outcomes, important physiologic measurements, adverse events, and costs.

Patient-centered outcomes include many outcomes that are also classified as clinical or cost outcomes listed separately below, but also include specific outcomes that directly relate to the lived experiences of patients and their families. Examples of patient-centered outcomes of interest include:

- 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

Physiologic measurements are surrogate or intermediate measures for symptom severity, disease progression, or patient-centered outcomes. Examples of physiologic measurements of interest include:

- FEV_1 (predicted), including rate of FEV_1 decline
- Vital capacity (maximum amount of air a person can expel from the lungs after a maximum inhalation)

- Lung clearance index (LCI)
- Weight, body mass index (BMI), and growth surrogate measures of nutrition status
- Fasting glucose and related measures of glucose control or diabetes

Clinical outcomes pertain to measures of health status or events. Examples of clinical outcomes of interest include:

- Pulmonary exacerbations (acute worsening of symptoms)
- Hospitalizations
- Acute pancreatitis
- Fertility
- Disease-specific quality of life (measured with Cystic Fibrosis Questionnaire-Revised (CFQ-R)[12]
- Mental health and affect, including depression, worry, and anxiety (as measured with validated instruments)

Costs*,* for US settings, include out of pocket costs that are directly relevant to patients. Information on other costs will inform the economic modeling analysis described below.

Adverse events pertain to complications or other events caused by or attributed to the intervention, not the disease process. Examples of adverse events of interest include:

- Chest discomfort
- Increased blood pressure
- Cataracts
- Adverse events leading to treatment discontinuation
- Drug-drug interactions are also of interest

Other outcomes will be considered and reviewed depending on relevance to patients and availability of data. We anticipate that any assessments of critical outcomes such as mortality and need for lung transplantation are likely to be underpowered and therefore minimally informative. We also anticipate a paucity of data on outcomes related to resource use and ethical, legal, and social concerns.

Timing

Studies of all follow-up durations are eligible, except that single-dose studies will be excluded. 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.

Low Value Services:

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information 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 in focus (e.g., pulmonary exacerbations, hospitalizations, etc.), as these will be captured in the economic model. Rather, we are seeking services

used in the management of CF beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services throughout the review (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

Economic Models Focusing on Comparative Value:

As a complement to the evidence review, we will develop a decision-analytic model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparators. We plan to evaluate ivacaftor, as well as the combination products lumacaftor/ivacaftor and tezacaftor/ivacaftor in the appropriate population subgroups. 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. For patients who are homozygous for the *F508del* mutation, we will compare tezacaftor/ivacaftor plus best supportive care, lumacaftor/ivacaftor plus best supportive care, and best supportive care alone as competing alternatives. For patients who are heterozygous for the *F508del* mutation and a residual function mutation that is potentially responsive to tezacaftor/ivacaftor, we will compare tezacaftor/ivacaftor plus best supportive care, ivacaftor monotherapy plus best supportive care, and best supportive care alone.

Under ICER's modifications to the value assessment framework for treatments for ultra-rare diseases, we will consider dual "base cases," which will reflect the health system and societal perspectives, respectively. A societal perspective is included if appropriate data are available, and if it is anticipated that the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs are substantial, and large relative to health care costs. If not assessed as a dual base case, a societal perspective will be considered in a scenario analysis.

The model structure will be influenced by other published models of CF treatment.[13-15] The models will 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 will 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).[16] We will simulate the health states of a cohort of patients over a lifetime time horizon, modeling patients from treatment initiation until death. A 3% discount rate will be applied to both costs and outcomes.

Key model inputs will 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.

Health outcomes will be dependent on patient health status, clinical events, and adverse events (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 serious AEs. The health outcome of each intervention will be evaluated in terms of numbers of acute 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 exacerbation or transplant avoided.

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 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/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

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