Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Draft Background and Scope
October 31, 2017

Stakeholder Input:

This scoping document was developed with input from a group of stakeholders comprising 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 agents of focus in this review. Based on the upcoming FDA review of tezacaftor/ivacaftor, ICER is undertaking an evaluation of 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 draft scoping document incorporates feedback gathered during preliminary calls with stakeholders. A final scoping document will be posted 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, an autosomal recessive condition caused by mutations in the *CFTR* gene, is a relatively rare condition, occurring in approximately 1 in 2,500 to 3,000 livebirths, but 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. The focus of this review is on agents that modulate the pathophysiology of the disease, namely, ivacaftor, lumacaftor, and tezacaftor.

More specifically, in epithelial cells, the *CFTR* gene is transcribed and translated to produce the CFTR protein, which is in turn, transported to the apical membrane, the part of the membrane that faces inwards towards the lumen of an organ. There it acts as a gate that regulates the flow of chloride ions,

and indirectly, of sodium ions and other substances in and out of the cell. Mutations to the *CFTR* gene can affect the amount of CFTR protein that is produced and transferred to the apical membrane or the CFTR protein's ability to regulate chloride and sodium ion 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 respiratory capacity, poor weight gain, diabetes, 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, and 46% of patients have both alleles.[7,8] Patients with class II mutations (mainly, F508del homozygotes) may respond to combination modulator therapies, namely, combinations of a lumacaftor or tezacaftor (agents that aim to "correct" folding defects and thus revert their implications) with ivacaftor (a "potentiator" of CFTR function).
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> Class III mutations ("gating mutations") result in a non-functioning CTFR protein on the apical membrane. An example is the G551D mutation, that is responsible for approximately 5% of CF cases. Patients who are homozygotes for gating mutations may respond to ivacaftor monotherapy.
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> Class IV and V mutations are associated with reduced functionality of the *CFTR* gene. Modulator therapy has not been approved for almost none class IV and V mutation, but some studies have been conducted in such populations.[9]

Among patients who are candidates for ivacaftor monotherapy or combination therapy with lumacaftor or tezacaftor, the use of these agents 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 are very expensive, 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 it meets the following proposed criteria:

- *The treatment is envisaged for a patient population of fewer than 10,000 individuals*
- *There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals*
- *The treatment potentially offers a major gain in improved quality of life and/or length of life*

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. As the first treatments to target the underlying pathophysiology for CF, modulators have the potential to offer a major improvement in the care of this 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:

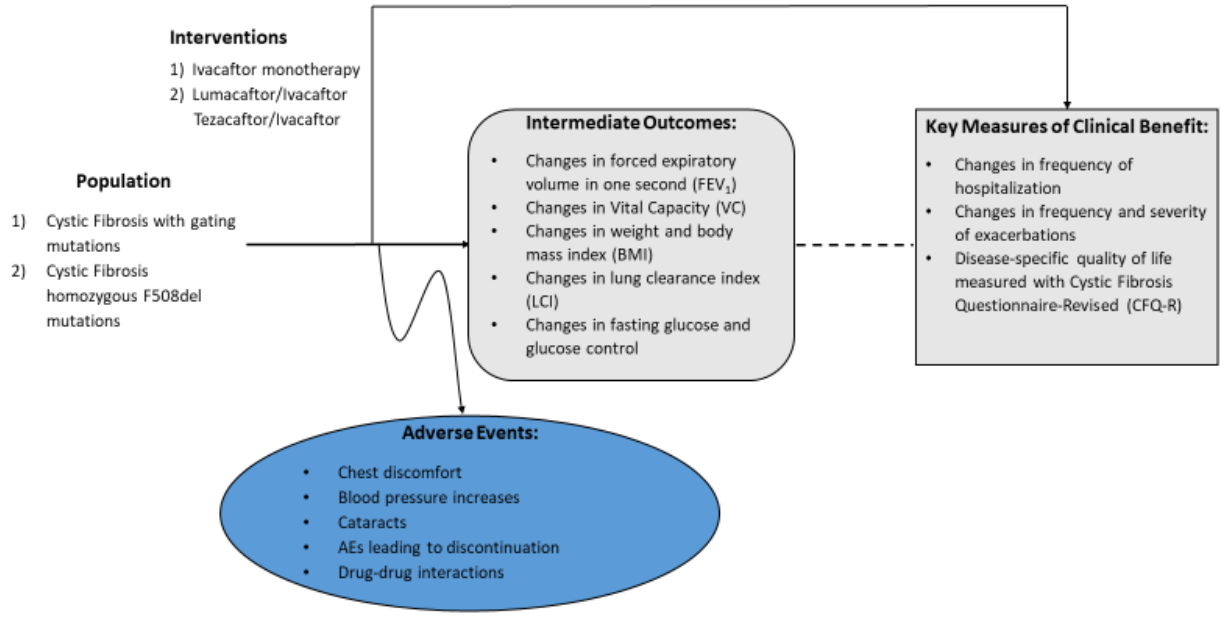
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews. High-quality cohort 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. 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 from a network meta-analysis when feasible and appropriate. High-quality non-comparative observational studies also will be included.

Analytic Framework:

The analytic framework in Figure 1 outlines the scope of this technology assessment.

Figure 1. Analytic Framework: Modulator Therapies for Cystic Fibrosis



Populations

The population of interest comprises two discrete groups. The first group includes people with CF who are candidates for ivacaftor monotherapy. These patients are homozygotes (carry two alleles) for one of the gating mutations (such as the G551D), but may carry at most one F508del mutation allele. The second group includes patients who are candidates for lumacaftor/ivacaftor or tezacaftor/ivacaftor combination therapy. These patients are homozygotes for the F508del mutation (i.e., they carry two alleles of this mutation), and may carry other mutations as well.

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 [forced expiratory volume during the first second of expiration, adjusted for age, height, gender, and race] below 40%, between 40% and 75%, and above 75% of predicted) and age (groups as defined in each study).

We will exclude patients who are homozygotes for stopping mutations (Class I or "X group") in the *CFTR* gene; as described above, they are not candidates for the treatments of interest because no CFTR protein is produced. We will review studies of patients with Class IV or V mutations, if they are otherwise eligible. We will impose no other restrictions.

Interventions and comparators

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

1. For patients who are candidates for ivacaftor monotherapy, we will compare adding versus not adding ivacaftor to best supportive care.
2. For patients who are candidates for the combination therapies, we will compare adding to standard care lumacaftor/ivacaftor versus tezacaftor/ivacaftor versus best supportive care alone (i.e., no modulator).

Outcomes

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

Patient-centric outcomes include many outcomes that we have classified as clinical (e.g., exacerbations, hospitalizations; see below) or cost outcomes, but also include other outcomes that directly relate to the lived experiences of patients and their families. Measures 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 and test results are surrogate measures for symptom severity, disease progression, or patient-centric outcomes. Measures of interest include:

- FEV_1 (predicted)
- 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 (a measurement based on imaging results)
- Weight and body mass index (BMI), a surrogate measure of nutrition status
- Fasting glucose and related measures of glucose control or diabetes

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

- Pulmonary exacerbations (acute worsening of symptoms)
- Hospitalizations
- Disease-specific quality of life (measured with Cystic Fibrosis Questionnaire-Revised (CFQ-R)[10]
- Mental health and affect, including depression, worry, and anxiety (as measured with validated instruments)

Costs, for US settings: Out of pocket costs are directly relevant to patients. Information on other costs can inform the economic modeling analysis (described below).

Adverse events including but not limited to:

- 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, thus 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.

Settings

All settings will be considered. The main interest is in outpatient settings in the United States.

Economic Models Focusing on Comparative Value:

As a complement to the evidence review, we will develop a Markov cohort 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, we will compare ivacaftor added to best supportive care to best supportive care alone. For patients who are candidates for the combination therapies, we will compare tezacaftor/ivacaftor added to best supportive care to lumacaftor/ivacaftor plus best supportive care and to best supportive care alone.

The model structure will be based in part on prior published models of CF treatment.[11] The base case analysis will take a health-care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses and other indirect costs will be considered in a separate scenario analysis. The two target populations will consist of people with CF eligible for treatment with: 1) ivacaftor monotherapy, or 2) with lumacaftor/ivacaftor or tezacaftor/ivacaftor combination therapy, as described in the *Populations* section above. The model will consist of health states that categorize patients by level of predicted FEV_1 (e.g., ≥70%, 40%-69%, <40%) and body mass index (BMI), as well as states for lung transplantation and death. A cohort of patients will transition between states during predetermined cycles (of 1 year) 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 for pulmonary exacerbations (such as hospitalization), 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.

Health outcomes will be dependent on time spent in each health state, 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). 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. Quality of life weights will be applied to each health state, including quality of life decrements for acute exacerbations and for serious adverse events. 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. In addition, productivity losses and other indirect costs (e.g., caregiver impacts) will be included in a separate scenario analysis if available data allow. Pairwise comparisons will be made between each treatment and best supportive care; data permitting, a comparison between tezacaftor/ivacaftor and lumacaftor/ivacaftor also will be considered. 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 Markov 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.

References:

1. Comeau AM, Parad RB, Dorkin HL, et al. Population-based newborn screening for genetic disorders when multiple mutation DNA testing is incorporated: a cystic fibrosis newborn screening model demonstrating increased sensitivity but more carrier detections. *Pediatrics.* 2004;113(6):1573-1581.
2. Scotet V, Duguépéroux I, Saliou P, et al. Evidence for decline in the incidence of cystic fibrosis: a 35-year observational study in Brittany, France. *Orphanet journal of rare diseases.* 2012;7:14-14.
3. Parad RB, Comeau AM. Newborn screening for cystic fibrosis. *Pediatric Annals.* 2003;32(8):528-535.
4. Grosse SD, Boyle CA, Botkin JR, et al. Newborn Screening for Cystic Fibrosis: Evaluation of Benefits and Risks and Recommendations for State Newborn Screening Programs. *CDC MMWR.* 2004(53(RR13)):1-36.
5. O'Sullivan BP, Freedman SD. Cystic fibrosis. *The Lancet.* 2009;373(9678):1891-1904.
6. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *The Cochrane database of systematic reviews.* 2015;3:CD009841.
7. Foundation CF. What is Cystic Fibrosis. 2017; https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed October 24, 2017.
8. Donaldson SH, Pilewski JM, Griese M, et al. Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. *American journal of respiratory and critical care medicine.* 2017.
9. Guigui S, Wang J, Cohen RI. The use of ivacaftor in CFTR mutations resulting in residual functioning protein. *Respiratory medicine case reports.* 2016;19:193-195.
10. University of Miami. Cystic Fibrosis Questionnaire- Revised. 2017; http://www.psy.miami.edu/cfq_QLab/index.html. Accessed October 30, 2017.
11. Dilokthornsakul P, Hansen RN, Campbell JD. Forecasting US ivacaftor outcomes and cost in cystic fibrosis patients with the G551D mutation. *The European respiratory journal.* 2016;47(6):1697-1705.