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Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators for Treatment of Cystic Fibrosis: Effectiveness and Value

Modeling Analysis Plan

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1. Approach

The primary aim of this analysis is to estimate the cost-effectiveness of cystic fibrosis transmembrane conductance regulator (CFTR) modulator treatments plus best supportive care for cystic fibrosis (CF) patients compared to best supportive care alone. 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.

The model structure for this assessment is described below. As a condition falling under ICER's ultra-rare disease framework, we will consider dual base-case analyses that will reflect the health system and the societal perspectives. A societal perspective is included as a base case if the impact of the treatment on patient and caregiver productivity, education, disability, and residential care costs are substantial, and these costs are large relative to total health care costs. Outcomes will be estimated over a lifetime time horizon using one-year time increments from treatment initiation until death. Costs and health outcomes will be discounted at 3% per year. The model will be developed in TreeAge software version 2017 (Williamstown, MA).

2. Methods

2.1 Overview and Model Structure

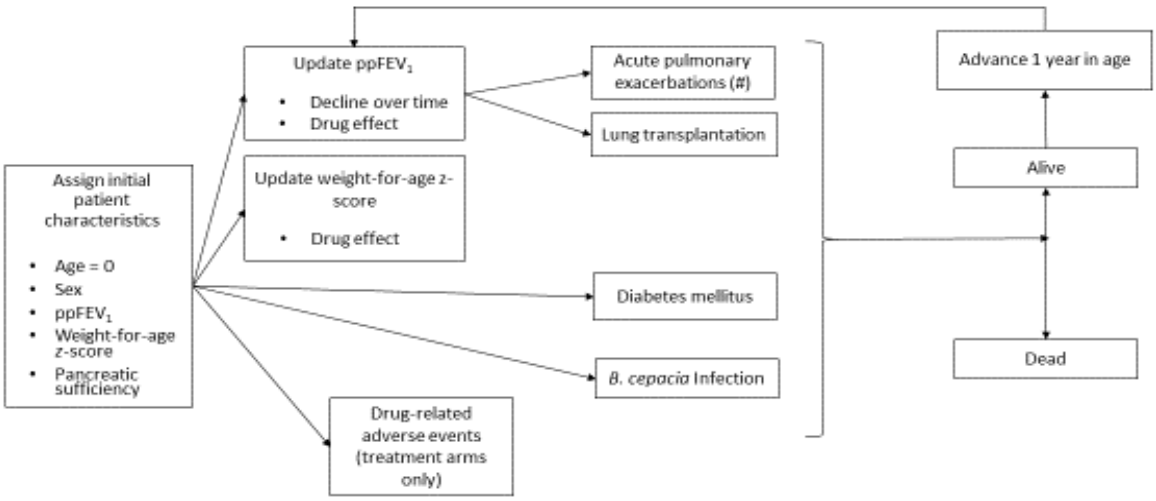
We will develop a *de novo* discrete-time microsimulation model. The primary model variable will be percent predicted forced expiratory volume in 1 second ($ppFEV_1$), modeled as a continuous variable. This model type was chosen to account for the continuous nature of $ppFEV_1$ and to capture the primary effect of the drugs (i.e., to increase $ppFEV_1$). CF patients begin the model at birth with a mean $ppFEV_1$ of 100% and experience annual age-specific declines in their lung function. Simulated individuals are assigned a heterogeneity parameter that determines whether the person progresses faster or slower in their lung function ($ppFEV_1$). Without assuming a heterogeneity parameter (the value of which can increase or decrease the rate of lung function progression for a simulated person), age and $ppFEV_1$ track together. By changing the variance of the heterogeneity parameter (drawn from a Gamma distribution with a mean of 1), we are able to fit to both the median life expectancy and the median $ppFEV_1$ by age. Simulated individuals will be

matched to observed statistics of CF patients: median age of survival, percent in lung function categories (≤40% ppFEV$_1$, severe; between 40% and 70% ppFEV$_1$, moderate; ≥70% pp FEV$_1$, mild) by age, and median ppFEV$_1$ by age.[1] In addition to ppFEV$_1$, we will also track other variables for each simulated person: sex, weight-for-age *z*-score, number of acute pulmonary exacerbations per year, pancreatic sufficiency, lung transplantation, and diagnosis of diabetes mellitus or *B. cepacia* infection. During any given year, a simulated person may experience a change in their ppFEV$_1$, may experience a pulmonary exacerbation (or more), may be diagnosed with diabetes mellitus or the two infections listed above, or undergo lung transplantation. The annual risk of death is a function of all of these variables. Figure 1 shows a diagram of the model, with the risk of pulmonary exacerbation and lung transplantation dependent on ppFEV$_1$ level. Persons are simulated for their lifetime and each year we will accumulate quality-adjusted life years (QALYs) and costs.

For the treatment arms, we will allow the ppFEV$_1$ value at age of treatment initiation and weight-for-age *z*-score to change based on trial results. We will also allow for the occurrence of treatment-related side effects, and assign costs and disutilities accordingly.

Figure 1. Model Framework

Patients move through the model from left to right for each one-year cycle. Patient risk of death is calculated based on age, sex, and clinical characteristics shown (Liou). Patients who survive a year repeat the cycle until death.



2.2 Target Populations

We will consider three distinct populations for this analysis. The first population includes individuals with CF and mutations consistent with the FDA-approved indications for ivacaftor monotherapy. This population will consist of patients with gating mutations, such as the *G551D* mutation; the age of treatment initiation will be 2 years and older, consistent with FDA labeling. The second population includes individuals with CF who are homozygous for the *F508del* mutation. This population is eligible for treatment with lumacaftor/ivacaftor or tezacaftor/ivacaftor, and the age of treatment initiation will be 6 years and older. 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. This population is eligible for treatment with tezacaftor/ivacaftor combination or ivacaftor monotherapy, and the age of treatment initiation will be 12 years and older.

The target populations will vary in terms of their prognosis.[2] On average, CF patients who are homozygous for *F508del* have a more severe prognosis than patients with one or no *F508del* mutation. McKone et al. classified patients into high-risk and low-risk groups based on the effects of the functional class of their phenotype. They found that the median age of death was much shorter for the high-risk genotypes (24.2 years vs. 37.6 years). Sawicki et al. showed that *F508del* homozygous patients had a faster rate of decline in their lung function compared with patients with a residual function mutation heterozygous for *F508del.*[3] We will adjust the lung function declines in our model to represent these different subgroups of patients.

Best supportive care [1] will consist of the following pulmonary therapies (percent utilization): dornase alfa (87.5%), inhaled tobramycin (69.4%), inhaled aztreonam (43.2%), azithromycin (65.5%), hypertonic saline (70.7%), oxygen (10.4%), non-invasive ventilation (2.8%). Other therapies include pancreatic enzyme replacement therapy (86.5%), supplemental feeding (tube or oral, 56.4%). Diabetic patients require oral hyperglycemic agents (3.9%), intermittent insulin (5.9%) and chronic insulin (76.3%) and will require diabetes-specific follow-up care (e.g., HbA1c measurements). Acute pulmonary exacerbations will involve treatment with intravenous antibiotics either in the hospital or with home treatment. We will estimate a disease management cost for all patients (including annual clinic visits) that include all costs except those of acute pulmonary exacerbations and lung transplantation, and will allow the disease management costs to vary by $ppFEV_1$. Acute pulmonary exacerbations and lung transplantation will be costed separately. The rationale for this approach is that the disease management cost will be the same for patients in both arms (modulator therapy vs. no modulator therapy). Disease management costs will vary, as patients who live longer will have higher management costs, although patients on modulator therapy will also have higher lung function, which will result in lower management costs.

2.3 Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. For each population, we will compare the eligible modulator treatment(s) plus best supportive care with other eligible modulator treatments plus best supportive care (when available) and with best supportive care alone.

2.4 Key Model Choices and Assumptions

Key model assumptions and the rationale for each are listed in Table 1.

Table 1. Key Model Assumptions

Assumption	Rationale
ppFEV1 percent predicted does not increase over time.	We make this assumption because it is true in general that lung function declines with age.
Best supportive care is assumed to be the same in all treatment arms.	Modulator therapy will have an impact on costs associated with acute pulmonary exacerbations and lung transplantation, but all other costs of care not associated with lung function will not be affected by modulator therapies.
We will assume the same treatment discontinuation as reported in the trials, and assume that there is no further discontinuation after the end of the trial time horizon.	Because we are using trial effectiveness estimates, we assume the same percentage of patients are taking the drug in the model as in the trials.

2.5 Input Parameters

CF outcomes

We will model the $ppFEV_1$ trajectories through age-specific annual declines.[4,5] The annual risk of having acute pulmonary exacerbation is a function of $ppFEV_1$ and age.[6,7] The annual risk of lung transplant is a function of age and is 0 for $ppFEV_1$ >30%. [8] The annual risk of diabetes as a function of age and sex is shown in Table 2.[9] We will adjust these overall rates to account for differential risk by CFTR mutation class (RR of I/II vs. III/IV/V = 1.7).[9] Over 95% of CF patients with severe genotypes (class I-III) have pancreatic insufficiency at diagnosis or progress to pancreatic insufficiency after diagnosis.[10] We will assume that 95% of the simulated cohort has pancreatic insufficiency and that this is stable over their lifetime. Similarly, we will assume that weight-for-age *z*-score is constant for each person throughout their life (in the absence of modulator therapy). [11] The other clinical

outcomes (rates of infections) will be derived from age-specific prevalence values from the CFF Registry, [1] and will not depend on lung function severity. Base-case values are listed in Table 2.

Table 2. Base-case values for CF outcomes

	Baseline value	Source
Annual decline in $ppFEV_1$*		Konstan, 2007[4] Konstan, 2012[5]
Age 6-8 years	-1.12	
Age 9-12 years	-2.39	
Age 13-17 years	-2.34	
Age 18-24 years	-1.92	
Age ≥25 years	-1.45	
Annual risk of acute pulmonary exacerbation by age and $ppFEV_1$		Goss, 2007[6] Whiting, 2014[7]
Age <18	8.5938*exp(-0.035*FEV)	
Age ≥18	3.7885*exp(-0.026*FEV)	
Number of pulmonary exacerbations per year (conditional on 1+)		Goss, 2007[6]
Age < 5	0.76, 0.19, 0.05	
Age 5-10	0.68, 0.20, 0.12	
Age 11-17	0.54, 0.22, 0.24	
Age 18-29	0.48, 0.23, 0.29	
Age ≥30	0.53, 0.27, 0.20	
Annual risk of lung transplantation		Thabut, 2013[12]
$ppFEV_1$ >30	0	
$ppFEV_1$ ≤30	0.647	
Annual risk of diabetes (male, female)		Adler, 2008[9]
Age 0-9	0.008, 0.016	
Age 10-19	0.039, 0.060	
Age 20-29	0.049, 0.071	
Age 30-39	0.065, 0.072	
Age 40+	0.051, 0.029	
Weight-for-age *z*-score		Lai, 1999[11]
Male	-1.3	
Female	-1.1	

* Represents overall CF population. Lung function declines are averages and may be higher or lower for individual patients (based on the heterogeneity parameter).

Each year patients will face a risk of dying. This will be a combination of their age-specific mortality rate based on the US life tables[13] and the CF-specific rate. CF-specific mortality rates are a function of sex, $ppFEV_1$, weight-for-age *z*-scores, pancreatic sufficiency, number of acute pulmonary exacerbations, and diagnosis of diabetes mellitus or *B. cepacia* infection.[14] The Liou analysis also found that *S. aureus* infection was an independent predictor of mortality; however, the impact of

infection was to decrease the mortality rate. Because we found no explanation as to why infection with *S. aureus* would be associated with better survival, and because of the recent rise in methicillin resistant *S. aureus* [1], we opted to not include this characteristic in the mortality rate function. The following equation will be used to model the annual mortality rate for age *a* (h_a) for non-transplanted patients[14]:

$$h_a = b_a e^{(K)}$$

$$K = 0.15(SEX - 0.47) - 0.042(ppFEV_1 - 67.7) - 0.028(WFA + 0.85) + 0.350(\#PE - 1.1) + 0.440(DIAB - 0.061) - 0.140(PS - 0.053) + 1.410(BAI - 0.032) - 0.280(\#PE - 1.1)(BAI - 0.032)$$

The patient-specific parameters that affect mortality among non-transplanted patients are *SEX* (0 male, 1 female), *ppFEV$_1$* (%), *WFA* (weight-for-age *z* score), *#PE* (number of acute pulmonary exacerbations in the current year), *DIAB* (0 no diagnosis of diabetes, 1 yes), *PS* (0 no pulmonary sufficiency, 1 yes), *BAI* (0 no *B. cepacia* infection, 1 yes). The age-specific baseline hazard (b_a) will be a product of the age-specific rates from the US life tables [13] and an adjustment factor that is needed to match the life expectancy targets of a CF cohort. Survival after lung transplant is a function of time since transplant and is better than prior to transplant. [12]

Table 3. Treatment effectiveness (from evidence review)

	Increase in ppFEV$_1$	Change in weight-for age *z*-score	Source
Population 1			
Ivacaftor	10.0 (4.5-15.5)	0.45	Davies, 2013[15]; Ramsey, 2011[16]
Population 2			
Lumacaftor/ivacaftor	2.8 (1.8-3.8)	NR	Wainwright,2015[17]
Tezacaftor/ivacaftor	4.0 (3.1-4.8)	-0.04 (-0.15-0.07)	Taylor-Cousar, 2017[18]
Population 3			
Tezacaftor/ivacaftor	6.8 (5.7-7.8)	NR	Rowe, 2017[19]

NR = not reported

To model the treatment effect, we will assume that there is an immediate increase in ppFEV$_1$ and improvement in weight-for-age *z*-score, as observed in the trials. We will model various assumptions about the treatment effect beyond the time horizon of the trials: (1) no ppFEV$_1$ decline as long as patient is on drug, (2) no ppFEV$_1$ decline on drug for 2 years and then 50% of the standard

care rate thereafter, (3) no ppFEV$_1$ declines on drug for 2 years and then equal to the standard care rate thereafter. We will use the second assumption in the base-case analysis.

Utilities

We will use the linear interpolation of EQ-5D utilities by ppFEV$_1$ used by Schechter et al. (Table 4).[20] The extrapolation was based on EQ-5D estimates estimated for wider ppFEV1 groups (0.864 for >70%, 0.810 for 40%-69%, and 0.641 for <40%). We will use similar assumptions as Schechter at al. [20], and apply a utility decrement of 0.174 to acute pulmonary exacerbations and a utility of 0.32 for the first year post-lung transplantation. (Subsequent years will be set equivalent to ppFEV$_1$ of 70%-79%.)

Table 4. EQ-5D utility values by ppFEV$_1$

ppFEV$_1$	Utility
>90	0.920
80-89	0.873
70-79	0.838
60-69	0.801
50-59	0.765
40-49	0.729
30-39	0.692
20-29	0.653
15-19	0.625

Adverse Events

Costs and disutilities will be applied for each serious adverse event (AE) at the rates described in Table 5. These rates will be based on data from the evidence review.

Table 5. Rates of adverse events associated with each drug

	Adverse event rate*	Cost	Disutility
Ivacaftor			
TBD	TBD	TBD	TBD
Lumacaftor/Ivacaftor			
TBD	TBD	TBD	TBD
Tezacaftor/Ivacaftor			
TBD	TBD	TBD	TBD

***Incremental to the control arm**

Cost Inputs

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.

Drug Acquisition Costs

We use estimates of net prices from the Federal Supply Schedule[21] since we did not find reliable estimates on these from SSR Health, as the base case input for drug prices (Table 6). For interventions without a list price, we will use the stated assumed price if available from the manufacturer; if an assumed price is not available, threshold prices at willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY will be calculated.

Table 6. Drug Cost Inputs

Intervention	Administration	Unit	WAC per Unit/Dose*[22]	Net price per unit†	Annual Drug Cost‡
Ivacaftor	Oral twice daily	150mg tablet	$426.72	$424.15	$309,841.58
Lumacaftor/ Ivacaftor					
Age 6-11 years	Oral, 2 tablets twice daily	100mg/125mg	$186.78	$180.76	$264,085.53
Age 12+ years	Oral, 2 tablets twice daily	200mg/125mg	$186.78	$180.76	$264,085.53
Tezacaftor/ Ivacaftor	Oral (once/twice) daily	100mg/150mg	-	-	-

*WAC as of January 12th, 2018

†FSS prices as of January 2nd, 2018

We will use an approach similar to that taken by Dilokthornsakul et al. in their cost-effectiveness analyses. [23,24] Healthcare costs are assumed to include an annual disease management cost based on severity of disease, plus an incremental cost associated with antibiotic treatment for acute pulmonary exacerbations. The cost of an acute pulmonary exacerbation is based on categories of age (reflecting higher percentage of total treatment time spent in the hospital for children) and lung function (reflecting an increasing length of treatment associated with more severe disease). Estimates are derived from the CF literature [25] and adjusted to match CFF registry data for current treatment durations associated with pulmonary exacerbations (i.e., applying the longer treatment

durations observed in current patients).[1] Cost estimates are shown in Table 7. Transplant costs include the one-time cost of receiving a lung transplant followed by an annual cost associated with the post-transplant condition. We will compare our costs with those reported by van Gool et al. [26] to inform our sensitivity analysis.

The societal perspective is important if the impact of modulator treatments on patient and caregiver productivity are substantial. A large impact of caregiver productivity from modulator treatment would require that caregiver burden be associated with lung function (e.g., characteristics for which modulator treatments change). However, Neri et al. [27] found no relationship between caregiver burden, as measured by the General Strain Index, and patient factors such as $ppFEV_1$ or occurrence of acute pulmonary exacerbation. There are mixed results in terms of the degree to which $ppFEV_1$ is an independent predictor of a CF person being employed.[28-32] Thus, for the societal perspective we will assume that lung function affects that probability that a CF person is employed, and that changes in lung function increase the chance that a person is employed. Productivity costs will be quantified using average US wage rates.

All costs will be presented in 2017 dollars.

Table 7. Direct costs by disease severity [25]

	$ppFEV_1 \geq 70\%$	$ppFEV_1$ 40%-69%	$ppFEV_1 < 40\%$
Disease management	$10,000	$13,000	$22,000
PEx (age <18)	$21,000	$33,000	$49,000
PEx (age 18+)	$19,000	$30,000	$43,000
Lung transplant	$389,000		
Post-transplant (year 1)	$338,000		
Post-transplant (year 2+)	$128,000		

* PEx = acute pulmonary exacerbation

2.6 Model Outcomes

The model will estimate the average amount of time patients live and their quality of life over time with modulator treatment plus best supportive care vs. other eligible modulator treatments plus best supportive care (when available) vs. best supportive care alone. Utility-adjusted time spent in each health state will be summed to provide estimates of QALYs for each treatment arm.

Model outcomes of interest (for each target population and eligible treatments) will include:

- By intervention:
    - Total health care costs (discounted)
    - Total direct and indirect costs (discounted)

        - Number of acute pulmonary exacerbations
        - Number of lung transplantations
        - Life-years (discounted and undiscounted)
        - QALYs (discounted and undiscounted)
- Pairwise comparisons:
    - Incremental cost-effectiveness (ICER) ratios (cost/life-year and cost/QALY) of modulator treatment plus best supportive care versus best supportive care
    - Incremental cost per acute pulmonary exacerbation avoided
    - Incremental cost per lung transplantation avoided

2.7 Analysis

Sensitivity Analyses

We will run one-way and two-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. We will conduct relevant scenario analyses, including: 1) assumptions about treatment effectiveness beyond the time horizon of trials, 2) variations in duration of treatment effect, and 3) variations in the age of patients eligible for treatment. We will also perform threshold analyses comparing changes in drug price across a range of incremental cost-effectiveness thresholds. We will also conduct a probabilistic sensitivity analysis (PSA), calculating 95% credible range estimates for each model outcome based on the results.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine assumptions and data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. Finally, we will compare results to other cost-effectiveness models in the CF area.

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